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Urologic Oncology

Springer

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Editors

Urologic Oncology

With 148 Figures and 115 Tables

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Preface

Keywords
Urologic oncology, Prostate cancer, Renal cancer, Bladder cancer, Testicular cancer, Penile cancer, Prognosis, Outcome, Imaging

It is with much excitement that we introduce the first edition of *Urologic Oncology*. In an era of "online" medicine, health-care providers are faced with a growing obligation to rapidly and effectively access, understand, and share information relating to diagnostics, treatment planning, and patient care.

Nowadays, there is an incredible amount of dynamic literature surrounding the diagnosis and handling of urologic malignancies. Despite this superfluous information, students, residents, staff member, and chairpersons searching for answers in urologic oncology indicate a need for a reliable, easily accessible, restructured resource for everyday use. *Urologic Oncology* is a collaborative effort that conglomerates the perspectives of expert faculty and fellows in training in the field of urologic oncology.

Divided into seven large parts focusing on general urologic and malignancy-specific information, this textbook is efficiently structured to provide a readily available source of reliable information supported by tables and images. Each disease section details information on the state-of-the-art treatment of urologic malignancies constructed by expert section editors in their specific fields.

This distinct textbook will provide the information needed to care for patients with urologic malignancies appropriately and will promote critical thinking throughout diagnosis and treatment.

We look forward to hearing from you, as we work to improve and build upon this first edition.

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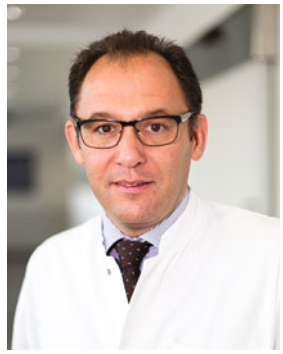
Professor Merseburger is a member of various uro-oncology organizations and serves as an advisor for the European Association of Urology (EAU) Guideline Group for Renal Cancer and was the Chairman of the EAU Guideline Group for Lasers and Technologies. He acts as reviewer and editorial board member for several urology and oncology indexed journals and is associate editor of the *World Journal of Urology* and Editor in Chief of *European Oncology & Haematology* journal.

Professor Merseburger's research activity encompasses both molecular and clinical aspects of uro-oncology, with specific interest in biomarkers and prognostic factors for prostate cancer, renal cell carcinoma, and transitional cell carcinoma. He has authored and coauthored more than 200 peer-reviewed articles, and he is the principal investigator in multiple phase II and III clinical trials.



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Part I

Introduction

Molecular Basics on Genitourinary Malignancies

1

Timothy Hua-Tse Cheng, Wayne Lam, and Jeremy Yuen-Chun Teoh

Contents

Abstract

We constantly face diagnostic and therapeutic challenges in the management of genitourinary malignancies. The lack of highly sensitive and specific cancer markers often results in the need of invasive procedures for both diagnostic and surveillance purposes. Understanding the molecular basics of genitourinary malignancies is essential for personalized and precision medicine. Cancers originating from the same organ could have different biological behaviours and responses towards different types of treatment. An individualized treatment based on molecular features could potentially enhance clinical effectiveness while minimizing treatment-related side effects. In this book chapter, we shall summarize the current knowledge regarding the molecular basics of genitourinary malignancies including prostate cancer, urothelial carcinoma of the bladder and upper urinary tract, kidney cancer, penile cancer and testicular cancer. We hope, by the end of the book chapter, we would be able to provide you insights regarding the next step forward.

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Introduction

For the past decades, localized cancers were mostly treated with surgery and radiotherapy, and metastatic cancers were mostly treated with cytotoxic but nonspecific therapeutic agents (Andre and Pusztai 2006). However, these treatments did not take into account the diversity of genetic profile among the worldwide population (Oliveira-Barros et al. 2017), also the heterogeneity within the tumor itself (Gerlinger et al. 2012). Due to the lack of specificity against cancer cells, these treatments are inevitably associated with adverse events and side effects. The differences in responses toward a particular pharmacological treatment could also be a reflection of the differences in genetic profile and hence the biology of the tumor (Antonarakis et al. 2014).

The concept of neoplasia being attributable to genetic alteration was first introduced in 1911 (Rous 1911, 1973). Progressive and cumulative genetic alteration often leads to the development of neoplasm (Karayi and Markham 2004). Proto-oncogenes code proteins that control and regular cell division, cell differentiation, and programmed cell death (Karayi and Markham 2004; Chial 2008a). When proto-oncogenes are mutated, they become oncogenes which promote the development of cancer cells (Karayi and Markham 2004; Chial 2008a). Tumor suppressor genes, on the other hand, function to restrain inappropriate cell growth and division and enhance programmed cell death (Chial 2008b). Proto-oncogenes and oncogenes are typically dominant in nature, while tumor suppressive genes are recessive (Karayi and Markham 2004; Chial 2008a, b). A deeper understanding of the genetic basis could potentially identify more precise target pathways and allow more effective treatment at the molecular level.

In fact, tremendous advances have been made in the past 15 years in several types of cancers including breast cancer, lung cancer, and colorectal cancer (Tian et al. 2015; Oh et al. 2012; Sorlie et al. 2001). The idealistic approach of personalized medicine has evolved, in the hope of maximizing clinical effectiveness while minimizing unnecessary side effects. It could also help us understand the different biological behaviors of the tumors and decide which treatment is most appropriate. In this book chapter, we shall discuss on a number of genitourinary malignancies including prostate cancer, urothelial carcinoma of the bladder and upper urinary tract, kidney cancer, penile cancer, and testicular cancer. We aim to provide an overview of the molecular basics of the genitourinary malignancies and their potential diagnostic and therapeutic implications in the future.

Prostate Cancer

Prostate cancer is the second most common malignancy in men, with an estimated number of 1.1 million new cases being diagnosed worldwide in 2012 (Ferlay et al. 2013). It has also been shown that the incidence of prostate cancer has been increasing in most countries worldwide (Wong et al. 2016). It is a common disease which carries significant burden to our healthcare system. Family history of prostate cancer and ethnicity of African-American are well-known risk factors of prostate cancer (Jansson et al. 2012; Hemminki 2012; Powell 2007; Tan et al. 2016). These results suggest a possible underlying genetic predisposition to the development of the disease.

About 9% of the men with prostate cancer are considered to have true hereditary disease (Mottet et al. 2016). A previous study was performed to investigate the molecular basis for this association with special interest in the 17q21–17q22 region (Ewing et al. 2012). In this study, youngest patients with presumable hereditary prostate cancer who had available DNA from 94 families were selected. A total of 202 genes were identified in the region of interest, and any presence of nonsense or missense mutations was reviewed. Probands from four families were observed to have the same, rare but recurrent mutation (G84E) in *HOXB13* (rs138213197) (Ewing et al. 2012). *HOXB13* is a homeobox transcription factor gene that is important for prostate development, but the mechanisms by which the G84E mutation could promote prostate carcinogenesis remain to be investigated (Ewing et al. 2012).

Families with germline *BRCA2* mutations were also found to increase risks of prostate cancer (Breast Cancer Linkage Consortium 1999; Thompson et al. 2001). A previous study screened and analyzed the *BRCA2* gene in 1864 men with prostate cancer (Kote-Jarai et al. 2011a). All carriers of truncating mutations were found to have prostate cancer at the age of less than 65 years, with a prevalence of 1.2% in this age group (Kote-Jarai et al. 2011a). It was estimated that germline mutation in the *BRCA2* gene increased risk of prostate cancer by 8.6-fold by the age of 65 years (Kote-Jarai et al. 2011a).

Another study screened 913 men for germline *BRCA1* mutation found that the frequency of deleterious *BRCA1* mutation was 0.45% (Leongamornlert et al. 2012). Three out of the four mutation carriers were found to have prostate cancer at the age of less than 65 years, and the remaining one developed prostate cancer at 69 years (Leongamornlert et al. 2012). It was estimated that the presence of deleterious *BRCA1* mutations increased risk of prostate cancer by 3.75-fold by the age of 65 years.

Although these genetic variants could confer high risk of prostate carcinogenesis, their rarity could only account for a small proportion of the overall familial risk. Alternative models suggest that a person's susceptibility to prostate cancer could occur through multiple loci involving both common and rare genetic variants (Eeles et al. 2014).

Up to date, more than 20 genome-wide association studies (GWAS) on prostate cancer have been published, and a total of 76 single nucleotide polymorphisms (SNPs) have been identified so far (Eeles et al. 2014; Attard et al. 2016). 8q24 was the first region being identified, and it is also the region that has the highest number of independently associated variants (Attard et al. 2016; Amundadottir et al. 2006). However, no significant microRNA transcription was found within the 8q24 prostate cancer risk loci (Pomerantz et al. 2009). Similarly, no association between RNA expression and the risk allele status was detected in normal or tumor tissue (Pomerantz et al. 2009). Since 8q24 is in proximity to the *MYC* proto-oncogene, this raised the question on whether the SNPs could exert long-range tissue-specific control on *MYC* expression (Eeles et al. 2014). This interaction between 8q24 prostate cancer risk loci and *MYC* was subsequently confirmed by chromatin conformation assays (Ahmadiyeh et al. 2010). The underlying functional mechanisms are important issues that remain to be explored.

The SNPs identified could have diagnostic implications. A SNP (rs10993994) located in a region containing the *MSMB* gene on chromosome 10 was found to be closely related to the *MSMB* transcription start site and could have a causal relation to prostate cancer (Eeles et al. 2008; Kote-Jarai et al. 2010). This risk allele was found to be associated with decreased β-microseminoprotein expression which occurs early in prostate cancer development and might serve as a diagnostic biomarker (Whitaker et al. 2010a, b). Genes encoding the kallikreins including prostate-specific antigen (PSA) were found in chromosome 19. A SNP in *KLK3* was found to have associated with prostate cancer, and it could introduce alterations in PSA. Whether this could have any diagnostic implications is another interesting area to be explored. SNPs may also have therapeutic implications. A SNP (rs5919432) located near the androgen receptor gene is of the greatest clinical relevance (Kote-Jarai et al. 2011b), as prostate cell growth relies on androgens, and androgen deprivation therapy has been widely used in treating prostate cancer. Therapeutic agents targeting this pathway could be more clinically effective than suppressing androgens alone.

Tremendous effort has been made in this area, yet the underlying functional mechanisms remain largely unknown. Potential mechanisms include long-range control of gene expression via promoter or enhancer elements, structural rearrangements, and changes in DNA structure or microRNA binding sites (Eeles et al. 2014; Freedman et al. 2011). With more understanding of the molecular basis, important targets for diagnostic and therapeutic purposes might be identified, and they could lead to important clinical implications in the future.

Urothelial Carcinoma of the Bladder and Upper Urinary Tract

Advances in molecular techniques have enabled the study of urological malignancies including bladder and kidney cancer. Understanding the molecular basis of these cancers shed light on the molecular pathogenesis and can also be informative for the diagnosis, prognosis, and response to treatment. The advent of massively parallel sequencing over the past decade has exponentially increased the sequencing data available and has revealed the mutations and differences in expression that can occur in a genome- and exome-wide scale. This is typified by projects such as The Cancer Genome Atlas (2014) and the International Cancer Genome Consortium et al. (2010). However, functional studies are still pivotal in validating some of these findings and shaping our understanding of how genetic changes in linked pathways act in tandem to drive disease progression.

The molecular characterization of bladder cancer has been aided by the fact that most tumors are transitional cell carcinomas that arise from the epithelial surface of a luminal organ. Urothelial tumors in the bladder can be directly visualized via cystoscopy, and tissue can be obtained for histological analysis on multiple occasions. This facilitates the study of early stage disease and disease progression, akin to the adenoma-carcinoma sequence in colorectal cancer.

Twin concordance studies demonstrate that heritable factors have only a modest contribution to bladder cancer predisposition (Lichtenstein et al. 2000). There are no known Mendelian causes of bladder cancer, but relatives of patients with bladder cancer have an increased risk of developing the disease (Kiemeney 2008). This shows that environmental factors play an important role in the development of bladder cancer, and the risk of environmental exposure may be modulated by germline genetic variants.

Various environmental risk factors have been identified including cigarette smoking (Wu et al. 2008), occupational exposure to aromatic amines (Reulen et al. 2008), cyclophosphamides (Vlaovic and Jewett 1999), schistosomiasis (Mostafa et al. 1999), radiation therapy (Suriano et al. 2013), and chronic cystitis (Vermeulen et al. 2015). Schistosomiasis and chronic cystitis have been associated with squamous cell carcinoma. Exposure to cyclophosphamides and radiation therapy has been associated with high-grade and muscle-invasive disease. However, the molecular mechanisms that occur in these environmental risk factors remain largely unknown. Although a significant proportion of bladder cancer cases have been attributed to smoking, there has so far been no correlation found between smoking status and the mutational spectrum from the TCGA data.

Genome-wide association studies (GWAS) and meta-analysis have successfully identified common variants associated with bladder cancer (Kiemeney et al. 2008, 2010; Garcia-Closas et al. 2011; Rothman et al. 2010; Rafnar et al. 2009). As with GWAS of other phenotypes, many of the subjects used for these studies were of European descent. GWAS of bladder cancer in other ancestries have also yielded risk loci (Matsuda et al. 2015; Wang et al. 2016). Bladder cancer risk loci have been identified in 1p13.3 (*GSTM1*), 2q37.1 (*UGT1A*), 3q28 (*TP63*), 4p16.3 (*TMEM129* and *TACC3-FGFR3*), 5p15.33 (*TERT-CLPTM1L*), 8p22 (*NAT2*), 8q24.21, 8q24.3 (*PSCA*), 18q12.3 (*SLC14A1*), 19q12 (*CCNE1*), and 22q13.1 (*CBX6*, *APOBEC3A*). Of interest, some of these variants show a higher level of significance in smokers, suggesting that certain common variants may modulate the risk of developing bladder cancer associated with smoking (Figueroa et al. 2014).

The investigation of somatic changes associated with the development of bladder cancer has been guided by several clinical observations. There appears to be two cancer development pathways. Papillary urothelial cancers tend to be low-grade, superficial, noninvasive protrusions with a high propensity for recurrence, but most are not muscle invasive and do not metastasize. Non-papillary tumors that arise evolve from severe dysplasia or carcinoma in situ. These tumors tend to aggressively invade the muscle layer and have the propensity to metastasize to regional lymph nodes and distant sites. Also, a significant proportion of bladder cancer cases

develop as multifocal tumors with the earliest genetic alterations present in phenotypically normal urothelium. This has been referred to as field cancerization (Braakhuis et al. 2003), where bladder urothelium can be seen as a mosaic, with different patches that behave independently. A part of the urothelium may be susceptible to developing malignant changes, and despite excision of a primary tumor, a second tumor is also more likely to occur at this patch of urothelium. Thus malignant tumors are seen to develop in a particular patch of urothelium with a background of increased susceptibility (Dakubo et al. 2007). However, other studies have demonstrated that metachronous tumors may arise from a single clonal origin (Sidransky et al. 1992; Lamy et al. 2016), and thus there is ongoing debate on clonal origin of urothelial tumors.

Bladder cancers are characterized by the accumulation of somatic mutations. Of the cancers arising from different tissues, urothelial cancers have a high mutation rate of 7.7 mutations per megabase (Lawrence et al. 2013). High-grade muscle-invasive bladder tumors have a mean of 302 exonic mutations per tumor, including 204 segmental copy number alterations and 22 arm-level copy number changes (Cancer Genome Atlas Research Network 2014).

Loss of heterozygosity in loci of chromosome 9 was among the earliest genomic changes found in superficial and muscle-invasive bladder cancer (Ruppert et al. 1993). Its presence in early-stage urothelial cancers has led to the identification of potential tumor suppressor genes that may be involved early in pathogenesis (Chow et al. 2000). These include the p16/ARF locus (Cairns et al. 1998; Williamson et al. 1995), IFNα (Cairns et al. 1994), and TSC1 (Hornigold et al. 1999).

FGFR3 mutations are found in up to 70% of low-grade papillary urothelial tumors and up to 20% of muscle-invasive and metastatic cancers (Sibley et al. 2001; di Martino et al. 2012). These mutations result in the activation of Ras-MAPK signaling pathway and cellular proliferation (L'Hote and Knowles 2005; Castillo-Martin et al. 2010).

High-grade tumors have traditionally been thought to arise from flat urothelial carcinomas or carcinoma in situ and involve mutations affecting P53 and RB. P53 regulates the cell cycle, DNA repair, and apoptosis, while the RB gene encodes a nuclear phosphoprotein, which functions as a negative cell-cycle regulator. Tumors with alterations in both p53 and RB expression tend to have a higher rate of recurrence and progression (Grossman et al. 1998). Transgenic mice studies recapitulate a similar result where those with functionally inactivated P53 and RB develop high-grade CIS lesions progressing to muscle-invasive disease (Ahmad et al. 2012).

Massively parallel sequencing has provided added insight in the mutational heterogeneity of urothelial cancers. Several members of the APOEC family are known to contribute to the hypermutation in multiple cancer types via the enzymatic cytosine deamination (Roberts and Gordenin 2014). Specifically, many urothelial tumors display signs of the APOBEC mutation signature and are associated with increased expression of A3A, A3D, and A3H and PD-L1-positive tumor-infiltrating mononuclear cells (Mullane et al. 2016). Urothelial tumors from TCGA show correlation between APOBEC3B expression, APOBEC mutational pattern enrichment, and overall mutation load. Genome-wide analysis of mutational pathways has also suggested that there may be an overlap between the mutations in genes associated with non-muscle-invasive disease such as FGFR3 and those associated with metastatic disease such as TP53.

The incidence of urothelial tumors in the renal pelvis and ureters is significantly lower than that of the urinary bladder, but there appears to be overlap in the mutational landscape. Urothelial tumors of the upper tract have not been sequenced as extensively as those arising from the bladder. Mutations in HRAS and CDKN2B are more frequently observed in upper tract tumors, while mutations in TP53 and ARID1A are more common in bladder cancers (Sfakianos et al. 2015). Another whole exome sequencing project has demonstrated that FGFR3 mutations and APOBEC-mediated hypermutation are also present in upper tract tumors, but the mutational landscape can be broadly classified into different subtypes based on tumor stage, mutations, and environmental exposures (Moss et al. 2017).

Kidney Cancer

Kidney cancers can arise either from the kidney parenchyma or renal pelvis. The majority of kidney cancers are adenocarcinomas arising from the parenchyma, termed renal cell carcinomas (RCCs). RCC can be further split into histological subtypes such as clear-cell, papillary, and chromophobe tumors. Nearly all tumors arising from the renal pelvis are transitional cell carcinomas which bear similarities with urothelial tumors arising from the ureter and bladder. The molecular basis of RCC was initially guided by the rare germline causes. Germline mutations in VHL (von Hippel-Lindau syndrome), MET (hereditary papillary renal carcinoma), BHD (Birt-Hogg-Dube syndrome), and FH (hereditary leiomyomatosis and RCC) are associated with an increased risk of kidney cancer (Linehan et al. 2009). These familial cancer predisposition syndromes account for only a small proportion of RCC cases. Mechanistically, the kidney cancer genes identified so far are involved with cell metabolism pathways relating to energy, nutrient iron, and oxygen sensing. Though families with germline kidney cancer gene mutations are uncommon, somatic mutations in some of these genes such as VHL have also been found in sporadic RCC and have been important in aiding our understanding and development of targeted drugs (Linehan et al. 2009).

Von Hippel-Lindau (VHL) syndrome is an autosomal-dominant multi-organ neoplastic syndrome that leads to an increased risk of hemangioblastomas, clear-cell RCC, and pheochromocytomas (Kaelin 2007). It is caused by the germline mutations in the tumor suppressor gene VHL, which encodes for pVHL, leading to the overexpression of HIF-1 and HIF-2. Interestingly, there are genotype-phenotype correlations for VHL: deletions and nonsense mutations are associated with a risk of RCC, while almost all families with a predisposition to pheochromocytoma are caused by missense mutations.

VHL is commonly mutated even in sporadic cases of clear-cell RCC (Gnarra et al. 1994). VHL is part of the substrate recognition for E3 ligase complex that marks HIF1α and HIF2α for proteasome-mediated degradation by ubiquitylation (Masson and Ratcliffe 2014; Semenza 2013). HIF-α and HIF-β bind to hypoxia-response elements in gene promoters that regulate angiogenesis, glycolysis, erythropoiesis, iron metabolism, cell proliferation, and apoptosis. The uncontrolled activation of HIF in an adequately oxygenated tissue microenvironment results in transcription of downstream genes including transforming growth factor alpha (TGFα), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), causing tumorigenesis, with tumors that are rich in lipids, glycogens, and vascularity (Semenza 2013; Hakimi et al. 2016). This is an example of how understanding the molecular basis has guided the current target therapies that target genes transcriptionally upregulated by HIF such as vascular endothelial growth factor α (VEGFα), vascular endothelial growth factor receptors (VEGFR), the platelet-derived growth factor receptor (PDGFR), or the mTOR/HIF pathway.

Hereditary leiomyomatosis renal cell carcinoma is caused by mutations in fumarate hydratase (FH) (Tomlinson et al. 2002). Loss of FH leads to the accumulation of fumarate, which in turn leads to the accumulation of HIF-α and the upregulation of HIF target genes (Isaacs et al. 2005). Thus, mutations in VHL and FH can cause RCC by the dysregulation of HIF, via different means.

Hereditary papillary renal carcinoma is caused by mutations in MET as a proto-oncogene that encodes the cell surface receptor for hepatocyte growth factor. Hepatocyte growth factors are involved with mitogenesis, morphogenesis, and motogenesis (Peruzzi and Bottaro 2006). Activating mutations in the tyrosine kinase domain of MET have been detected in familial and sporadic cases of papillary RCC (Schmidt et al. 1997, 1999).

From the familial forms of RCC also present in sporadic RCC, the molecular causes shed light on RCC as a metabolic disease that are disorders of oxygen and energy sensing (Linehan et al. 2010).

Twin concordance studies show only a limited role of heritable factors in the development of kidney cancers (Lichtenstein et al. 2000). However, those with a family history have a twofold

increased risk compared with the general population (Goldgar et al. 1994). In the search of common variants that contribute to the genetic predisposition of kidney cancer, GWAS in European populations have found multiple risk loci including 2p21 (EPAS1, encodes the HIF2α subunit), 2q22.3 (ZEB2), 8q24.21, 11q13.3, 12p11.23 (ITPR2), and 12q24.31 (Purdue et al. 2014; Henrion et al. 2013; Wu et al. 2012). The main risk factors associated with RCC include excess body weight, hypertension, and tobacco smoking (Lipworth et al. 2009). These factors combined may contribute to up to half of all cases of RCC (Benichou et al. 1998).

Massively parallel sequencing has further revealed the somatic mutation spectrum of RCC (Cancer Genome Atlas Research Network 2013; Cancer Genome Atlas Research Network et al. 2016). For clear-cell RCC, copy number aberrations were less frequently observed compared with other tumors, but the commonest CNA was in chromosome 3p which encompassed VHL, PBRM1, BAP1, and SETD2. The most commonly mutated genes were VHL, PBRM1, SETD2, KDM5C, PTEN, BAP1, MTOR, and TP53. The mutational spectrum in papillary RCCs appears to differ based on whether they are type 1 or type 2 tumors. Type 1 tumors are associated with mutations in the MET pathway, whereas type 2 tumors are associated with activation of the NRF2-ARE pathway and CDKN2A loss.

Cells that make up a tumor are not bound by a single set of genetic aberrations, and intra-tumoral heterogeneity has been extensively studied in RCC (Gerlinger et al. 2012). This has particular clinical significance because it raises the question of how representative a single tumor biopsy is of the entire tumor and may also help to explain treatment failure and drug resistance. The comparison of mutations in samples from different parts of the primary tumor and from metastatic lesions enables the construction of a phylogenetic tree and understanding of tumor evolution. While VHL mutations and chromosome 3p loss could be found across different sites (truncal mutations), some driver mutations including SETD2, BAP1, TP53, and PTEN were only present in segments of the tumor (branch mutations). The genetic heterogeneity and tumor evolution may prove to be a challenge in terms of targeted therapy, but approaches may include targeting the truncal mutations.

Penile Cancer

Penile cancer (PeCa) is a rare malignancy, with an incidence of 0.1–0.9 men per 100,000 being diagnosed with the disease in Europe and the USA per year (Parkin and Muir 1992). Squamous cell carcinoma of the penis (SCCp) is the predominant histological subtype, accounting for over 95% of all PeCa (Pietrzak et al. 2006).

Cancer cells typically bear a range of fundamental biological pathways in order to survive and proliferate against the human immune defense system. These pathways are also their weaknesses if identified and potentially enable cancer prevention and the development of targeted therapeutic treatments. Molecular research has, therefore, become an important tool to understand the development of cancers. However, the rarity of PeCa leads to limited clinical and molecular knowledge of the disease, and research into identifying biologically significant molecular pathways in PeCa has been challenging.

There are three key mechanisms of cancer progression which can be targeted for treatment (Protzel and Spiess 2013): first, the molecular mechanism of carcinogenesis which includes the bypassing of human immune defense mechanism of apoptosis and tumor suppression genes; second, pathways involved in tumor progression resulting in tumor invasion and transformation; and third, the ability of cancer cells to develop chemoresistance leading to the development of cancer metastasis.

More specific to PeCa, human papillomavirus (HPV) has been reported to be associated with between 20% and 80% of all PeCa, and correlation between HPV and PeCa subtypes has been established (Muneer et al. 2009). This suggests HPV plays a role in the carcinogenesis of PeCa. As such, both HPV- and non-HPV-induced penile neoplasm pathways have been of research

interests, in particular the potential opportunity to prevent HPV-mediated carcinogenesis of penile cancer using vaccination programs in specific high-risk patient population and to detect precancerous or early-stage disease.

The exact mechanism of carcinogenesis of PeCa remains largely unknown but is generally believed to be multifactorial, associated with DNA damage, genomic instability, cell death resistance, immortalization, and immune-escape (Hanahan and Weinberg 2011). Chronic inflammatory diseases, such as lichen sclerosis et atrophicus and balanoposthitis, are believed to be fundamental risk factors in the development of PeCa, with reactive oxygen/nitrogen species (ROS/NOS) produced by inflammatory cells being potential cause of DNA damage. As a result, mediators of inflammation have been investigated in their roles in penile carcinogenesis, in particular the cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) pathways.

COX-2 is an isoenzyme responsible for formation of prostanoids and has been found to be strongly expressed in PeCa (Golijanin et al. 2004). Overexpression of COX-2 would subsequently cause overproduction of prostaglandins and thromboxanes. The increased release of the potent PGE2 plays a fundamental role in cell proliferation, increased angiogenesis, and the activation of epidermal growth factor receptor (EGFR) (Lee et al. 2013).

Smoking has been suggested to be a risk factor for PeCa, although high-level evidence of this is still lacking and therefore remains controversial. *N*-Nitrosodimethylamine has been postulated to be present in sebaceous glands in smokers, and prolonged exposure of this carcinogen in an uncircumcised penis has been suggested to promote cancer dedifferentiation (Brittebo et al. 1981). Circumcision in childhood is known to be protective against the development of PeCa, perhaps partly due to minimizing risk of development of chronic inflammatory diseases and potentially decreased accumulative exposure to carcinogens such as *N*-Nitrosodimethylamine.

HPV has long been understood to be associated with formation of a genital tumor. Prevalence of HPV in penile cancer ranges between 20% and 80%, with geographical variation (Muneer et al. 2009). HPV serotypes 16 and 18 are the commonest types associated with PeCa and are found in between 60% and 75% of penile intraepithelial neoplasia (PeIN) and invasive tumors (Heideman et al. 2007). Warty and basaloid subtypes of SCC PeCa are in particular associated with HPV. Within the HPV viral genotype is an early (E) region, which encodes proteins required for replication, regulation, and modification of host nucleus and cytoplasm, and a late (L) region, which encodes for capsid proteins. If E6 and E7 viral genes are overexpressed in HPV transformed cells, increased cellular differentiation and proliferation through their interaction with retinoblastoma Rb/E2F and p53 tumor suppressor gene products affect the process of cellular proliferation and apoptosis (zur Hausen 2002). Under normal circumstances, p53 inhibits cell cycle by the p21/Rb cascade. If p53 is inactivated by HPV E6 and E7, carcinogenesis occurs, in particular in the warty and basaloid subtypes (Poetsch et al. 2011). HPV16 DNA has also been found to activate the proto-oncogene *myc*, and *myc* gains and overexpression have been demonstrated in PeCa (Peter et al. 2006). Myc has also been suggested to be associated with risk of tumor progression and has the potential to be a marker for PeCa prognosis.

Limited studies are available in the role of telomerase in PeCa. Telomerase is an enzyme which adds repeated DNA sequences to the 3′ end of the telomere regions of DNA strands to confer stability to the chromosomes. In cancer, telomerase activity has the potential to overcome programmed cell death, leading to indefinite replication capacity. A study conducted by Alves et al. described detectable telomerase activity and its association with invasive PeCa (Alves et al. 2001). However, further studies are required to evaluate its relevance.

Identification of tumor proliferation markers has the potential use to predict PeCa prognosis and metastatic capability. A study by Protzel et al. has been shown Ki67, a proliferation marker, to be strongly expressed in invasive PeCa, and is associated with increased risk of metastasis and poor prognosis (Protzel et al. 2007). However,

another study which included 148 patients found that Ki67 has no prognostic value for cancer-specific survival (CSS) or overall survival in PeCa (Stankiewicz et al. 2012). PCNA, a protein found in the nucleus of cells and is a cofactor of DNA polymerase delta and is essential for DNA synthesis and repair, has been shown to be associated with risk of nodal metastasis in PeCa, but no prognostic value for CSS (Martins et al. 2002).

Epidermal growth factor receptor (EGFR) has been suggested to play a role in tumor progression. Its activation by epidermal growth factor (EGF) or transforming growth factor-α (TGFα) subsequently induces various proliferative pathways such as KRAS-BRAF, HER-3, and HER-4 (Protzel and Spiess 2013). The PI3K/PTEN/AKT pathway has also been found to be altered in PeCa in one of author's previous study (Stankiewicz et al. 2011). It was found that HPV-negative PeCa had increased expression of EGFR, whereas HER3 expression is significantly more common in HPV-positive PeCa. HER receptors are therefore potential receptors that can be used as target for treatment.

For cancer to have metastatic potential, it needs to be invasive and penetrate through the basement membrane. For a cancer to be invasive, a breakdown of the cell-to-cell adhesion is usually required for tumor cells to invade through the basement membrane. E-cadherin, a mediator of intercellular junctions, will need to be downregulated. Epithelial-mesenchymal transition (EMT) is the process which E-cadherin can be downregulated, and various microRNAs and matrix metalloproteinases (MMPs) have been shown to be associated with EMT and subsequent tumor progression (Campos et al. 2006). Studies on EMT are sparse, and further investigation into its role as a marker of tumor progression is required.

Increase in tumor cell mobility and angiogenesis are essential parts of tumor microenvironment in the development of tumor progression and metastasis. In particular, neoangiogenesis plays a very fundamental role for intravasation of tumor cells, which is then followed by its ability to survive within the circulation to spread to other parts of the body. Unfortunately, no circulating tumor cells (CTC) has been identified for PeCa so far. Inhibition of this process has been postulated, with downregulation of metastasis suppressor gene KAI1 appearing to play a role in metastatic seeding in PeCa. It is thought to be associated with nodal metastasis and subsequent poor prognosis (Protzel et al. 2008).

Pathways associated with micro-metastasis have also been postulated to be associated with cancer metastasis, but investigations into its potential associated pathways have been limited. These are pathways required prior to the initiation of macrometastasis and have also been suggested to be associated with chemoresistance. Due to rarity of the disease, initiative to combine worldwide collections of tumors is required to further study these pathways in patients with metastatic PeCa.

The understanding of molecular pathways in PeCa carcinogenesis, tumor progression, and development of metastatic disease give the opportunity to develop therapeutic targeted treatments. In particular, the identification of early invasive and metastatic spread offers the opportunity to provide early aggressive treatment for PeCa which is associated with prognosis once nodal involvement process occurs.

Testicular Cancer

Although relatively rare, testicular germ cell tumors (TGCTs) are the commonest solid malignancy in men aged between 18 and 35 years, with an incidence of 5–10 per 100,000 in developed countries. TGCTs are broadly divided into seminoma and non-seminoma (NSGCT), to guide treatment strategies and prognosis. Its exquisite chemosensitivity makes TGCTs a rare oncological success. Even in patients presenting with advanced disease, the 5-year overall survival (OS) is excellent, with over 80% of patients in developed countries (Siegel et al. 2016).

However, treatment balance to minimize morbidity (such as infertility and future malignancies) while maintaining adequate oncological control for patients with TGCT is yet to be established. Markers for early identification of TGCTs in

advanced disease with chemoresistance may also be able to guide earlier salvage treatment for better oncological control. Further understanding of molecular and genetic basis of TGCT may be able to help identifying testicular tumors with higher metastatic potential in early-stage disease, and nonresponders to chemotherapy in advanced disease, and to develop novel therapeutic agents in chemoresistant patients.

Family history of TGCTs increases risk of development of TGCTs, with a risk of six to ten times higher in patients with first-degree relatives with a history of TGCT. Although hereditary component in the development of the disease therefore appears apparent, no significant genetic linkage has been identified in linkage analysis studies (Crockford et al. 2006).

Studies into the genetics of TGCT usually reflect the tumor's embryonic origin with a low incidence of mutations, loss of parental pattern of genomic imprinting, distinct DNA methylation profiles, and uniparental disomies (Woldu et al. 2017). This makes it different from other somatic tissue-derived tumors. Comparing with other solid tumors, TGCTs are associated with much lower mutation frequency at 0.5 mutations/megabase (Nathanson et al. 2005).

The only consistent chromosomal abnormality on karyotype analysis in patients with TGCT is the presence of isochromosome of the short arm of chromosome 12, 12p [i(12p)] (Atkin and Baker 1982). This has been identified in all histological subtypes and in some carcinoma in situ. The exact mechanism to account for this is yet to be determined. However, a range of genes have been investigated with apparent association, including the proto-oncogenes cyclin D2 (CCND2) and KRAS, the growth factor receptor TNFRSF1A, the glucose transporter GLUT3, the estrogen transporters REA and FLJ22028, and stem-cell-associated genes such as NANOG, STELLAR/DPPA3, and GDF3 (Woldu et al. 2017; Juric et al. 2005; Rodriguez et al. 2003). Unfortunately, the clinical significance of i(12p) chromosomal abnormality has not yet been established, with inconsistent results from previous studies (Bosl et al. 1989, 1994).

On the genetics level in the development of TGCTs, it is believed to be a polygenic, multistep level, starting at the embryonic stage till puberty when spermatogenesis is initiated by further genetic events. Various gene loci related to TGCT tumorigenesis have been identified in genome-wide association studies (GWAS), such as KITLG, SPRY4, BAK1, DMRT1, TERT, and ATF7IP, proposed gene TGCT1 on Xq27, and gr/gr deletion in the AZFc region on Y chromosome (Rapley et al. 2009), with most of them associated with the KIT-KITLG signaling pathway.

Infertility has been found to be a risk factor in the development of TGCTs. The commonest genetic modification associated with infertility was found to be a deletion of 1.6 Mb in the AZF region of the Y chromosome, and this alteration is associated with at least twice the risk of developing TGCTs.

The *KIT* gene, a proto-oncogene receptor tyrosine kinase protein which is partly responsible for cell survival and proliferation, is of particular research interest into its role in TGCT as it has been used for targeted treatment in other malignancy such as gastrointestinal stromal tumor (GIST) (Einhorn et al. 2006). Studies have shown to be relatively more common to be present in patients with seminoma (19%) when compared with NSGCT (Bamford et al. 2004).

Both KRAS/NRAS of the ras pathway are, again, another proto-oncogene receptor tyrosine kinase proteins. They are associated with the activation of pathways such as the Raf/MEK/ERK and PI3 pathways. Defect in both pathways would lead to uncontrollable growth and tumorigenesis. Many compounds are able to inhibit these pathways, and they have already been targets for treatment for other cancers such as Hodgkin's disease. KRAS/NRAS mutations have been detected in up to 7% of seminomas but none in NSGCT (Bamford et al. 2004). Mutations of KRAS/NRAS have also been previously demonstrated to be associated with malignant transformation and are more frequently in tumors with chemoresistance (Feldman et al. 2014). The clinical relevance of such association requires further research for clarity.

TP53 gene is a cell-cycle regulatory protein. It plays an important role in the induction of apoptosis and cell-cycle arrest during stress to help

with DNA repair. It is a gene that encodes p53, and if mutated, aggressive tumor appears to be more profound (Skotheim et al. 2005). An alternative pathway triggered by specific microRNAs has been identified, potentially could be used to target for treatment (Almstrup et al. 2004). TP53 mutation has been reported to be approximately 25% in patients with chemoresistance. However, only 7% of seminomas and none in NSGCT demonstrate TP63 mutations (Bamford et al. 2004). The subsequent alteration of mdm2-p53 binding with the small molecule inhibitors RITA and Nutlin-3 results in cell-cycle arrest and apoptosis in of tumor cells, which has the potential for to be used for targeted treatment (Almstrup et al. 2004).

Targeting BRAF gene mutation has been used in other cancers such as melanoma for targeted treatment. It is yet another proto-oncogene. It is responsible for intracellular signaling pathways in the modulation of cell growth. It encodes a serine/threonine kinase, which in turn regulates the MAP kinase/ERK pathway, playing a major role in cell proliferation and differentiation (Sheikine et al. 2012). BRAF highly correlates with microsatellite instability (MSI), and with the lack of hMLH1 expression, the latter is associated with hMLH1 promoter hypermethylation (which itself is associated with chemoresistance). Although such mutation is not commonly seen in TGCTs, it has been reported to be highly detectable in chemoresistant patients when compared with chemosensitive patients (Honecker et al. 2009). Further research with contemporary sequencing is required to investigate its clinical relevance.

Epigenetic changes in chromosome or its associated protein without alterations in DNA sequences may play a role in the development in many malignancies including TGCT and potentially related to development of chemoresistance. Various studies have been carried out to investigate DNA promoter methylation differences in TGCTs, with higher hypomethylation frequency detected in seminomas over NSGCT (Peltomaki 1991; Smiraglia et al. 2002). In particular, RASSF1A and HIC1 promoter hypermethylation has been found to be associated with cisplatin resistance, while presence of MGMT and RARB promoter hypermethylation is associated with cisplatin sensitivity (Koul et al. 2004). hMLH1 is involved in mismatch repair, and its dysfunction leads to MSI and has also been reported to be associated with chemoresistance (Wermann et al. 2010), and 40 other genes or non-coding RNAs with hypermethylated promoters including RBMY1A have also been identified to be related to the development of TGCT (Cheung et al. 2016).

With regard to miRNAs, which are small non-coding RNA molecules reported to be associated with development of many cancers if deregulated, miRNA-372 and miRNA-373 have been reported to suppress the p53 pathway, leading to cellular proliferation and development of TGCTs in the presence of wild-type p53 (Lize et al. 2010). MiRNA 199a following promoter hypermethylation has been identified to be associated with upregulation of PODXL, leading to cancer invasion and metastasis (Cheung et al. 2011). However, most of the function of miRNAs are yet to be established or validated.

An overall review in the development of TGCT and chemoresistance has been provided. It is a complex, multistep process. Many have been suggested to have the potential as new molecular prognostic marker, but none has yet to be confirmed to be able to predict biological behavior of TGCT or chemoresistance. Future studies concerning the genetics and epigenetics of TGCT will be required and likely will provide significant clinical relevance in the prevention, treatment, and predicting prognosis in patients with TGCT.

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Clinical Aspects and Investigations in Genitourinary Cancer

2

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Abstract

Genitourinary cancer is an important topic in the current era. Understanding the disease is important to tailor the treatment for individual patients. Clinical aspects and investigations are part and parcel in cancer diagnosis. Genitourinary cancer encompasses multiple cancers but five important cancers are discussed in this chapter. This includes renal cell carcinoma, prostate cancer, urothelial cancer, testicular cancer and penile cancer. Other subtypes or variants are beyond the scope of this chapter. This chapter is to encourage the readers to better understand the clinical aspects and investigations that are commonly used in genitourinary cancer.

Investigations play a major role in diagnosis of genitourinary cancer. Understanding the principles of the imaging is important to appreciate and interpret a particular imaging modality. The principles of the imaging are mentioned at the start of the chapter. We have placed the clinical aspects and investigations for individual cancers mentioned above and tailored the topics to include appropriate investigations and salient features to take note in the imaging.

Principles of Common Radiological Investigations

X-Ray

Wilhelm Conrad Röntgen discovered X-rays in 1895. X-rays are generated from X-ray generator, and when this passes through human tissues, tissue attenuation occurs and the X-rays are recorded on a film and reconstructed to form an image.

X-rays are inexpensive and readily available. It is used in urology (X-ray kidney, ureter, and bladder) and in diagnosis and follow-up of urinary stones. It is less sensitive and essentially replaced by IVU or computed tomography (CT).

Intravenous Urography (IVU)

IVU is an inexpensive imaging of the urinary system. It involves injecting IV water-soluble iodinated contrast and capturing series of X-rays of the renal tract at precise time points. The films obtained are:

1. *Plain (scout) film*
   A plain film will give information about the presence of abnormal calcifications along the urinary tract.
2. *Nephrogram*
   This sequence is taken at 1–2 min after IV contrast injection.
3. *Series of films* taken at 5–10 min, 15-min post IV contrast injection. Compression is applied to get appropriate pelvicalyceal imaging unless compression is contraindicated.
4. *Delayed film*
   Appropriate bladder imaging is obtained in delayed phase, and it is useful to diagnose bladder pathologies/tumors.
5. *Post-micturition film* after the patient voids.

Even though IVU is largely replaced by CT, it still has specific roles in urology.

Common uses in urology:

1. Investigation for microscopic hematuria
2. Upper tract urothelial malignancy – seen as filling defect
3. Diagnosis of renal and ureteric stones in select cases
4. Evaluation for congenital anomalies
5. Evaluation of likely ureteric strictures

Ultrasound

Application of short burst of alternating current on an array of crystals within a transducer produces a mechanical wave which travels through a coupling medium to the skin and into the tissues. The transducer acts as emitter and receiver of the sound waves. Some of the waves are reflected back (echoes) to the transducer which converts the sound waves into electrical energy and generates an image. Real-time imaging is possible as the signals are processed and reconstructed in real time. The amplitude of wave reflected gives the pixel brightness in the imaging. The objects which reflect majority of the sound waves appear bright on the gray scale and vice versa. The frequencies of the sound waves used are in the range of 3.5–12 MHz.

Types of transducers:

1. Linear transducer:
   - Piezoelectric crystal arrangement: phased array
   - Frequency: 3–12 MHz (usually 5–7.5 MHz)
   - Beam shape: rectangular
2. Convex transducer:
   - Piezoelectric crystal arrangement: curvilinear
   - Frequency: 1–5 MHz (usually 3.5–5 MHz)
   - Beam shape: sector
3. Sectoral transducer:
   - Piezoelectric crystal arrangement: phased array
   - Frequency: 1–5 MHz (usually 3.5–5 MHz)
   - Beam shape: triangular

Common types of ultrasound study used in urology:

1. Ultrasound KUB – for evaluation of kidney, ureter, and bladder pathologies. It gives information about the renal mass, hydronephrosis, ureteric jets, and bladder mass/stones.
2. Ultrasound scrotum – to evaluate scrotal pathology and testicular pathologies.
3. Contrast-enhanced ultrasonogram (CEUS) – employs microbubbles as contrast medium, and it is useful to evaluate suspicious lesions in those patients who cannot undergo contrasted CT (renal failure or iodinated contrast allergy), usually used for renal lesions.
4. Transrectal US – used as a guide for prostate biopsy but not used as a diagnostic tool for prostate cancer detection. It can be used to evaluate a midline prostatic cyst and for transrectal drainage of prostate abscess.

Computed Tomography

Sir Godfrey Hounsfield invented computed tomography (CT). CT uses X-rays and measures the tissue density, but the beam in the CT scanner is narrower, and this is detected by a detector placed opposite to the beam, and it produces cross-sectional slices as fine as 0.6 mm thick.

The Hounsfield unit (HU) scale is a measurement of relative densities determined by CT. Water is assigned as the reference density (0 units), and other values are measured relative to water. Air is −1000, fat −100, and bone >+200. The kidneys are +40 to +60 and increase to around 150 units after intravenous contrast. CT uses various protocols to accurately image the region of interest. Kidneys are measured with set protocols and gray scale is assigned to each pixel.

Common types of CT scans used in urology:

1. CT KUB – accuracy almost a near perfect 100% for stone detection (once interpretative error accounted for). It will also identify many of the renal colic mimics, such as appendicitis, diverticulitis, etc.
2. CT angiography – used to image status of renal vasculature in renal trauma, arteriovenous fistula.
3. CT kidneys – to evaluate renal mass, pre-op imaging prior to nephron-sparing surgery, and characterization of renal cysts.
4. CT urography – hematuria evaluation, for evaluation of urothelial cancer; it is considered as one of the best modalities for imaging the collecting system.
5. Staging CT scan for other urological malignancies.

Magnetic Resonance Imaging (MRI)

MRI is excellent at imaging the kidneys and locally staging tumors, and we may possibly deduce the likely histology, on the grounds of T2 differences. MRI is also the best imaging modality for assessing zonal anatomy in the prostate and detecting prostate cancer.

The basis of MRI is the directional magnetic field, or moment, associated with charged particles in motion. Because nuclei are charged particles, this precession produces a small magnetic moment. When a human body is placed in a large magnetic field, many of the free hydrogen nuclei align themselves with the direction of the magnetic field. MRI works by manipulating the external magnetic field and by aligning the hydrogen nuclei in the tissues, and the weak radio signals are amplified to create the MR image.

Once the radiofrequency (RF) signal is removed, the nuclei realign themselves. This return to equilibrium is referred to as relaxation. During relaxation, the nuclei lose energy by emitting their own RF signal which is referred to as the free induction decay (FID) response signal.

MR image contrast depends on two tissue-specific parameters:

1. Longitudinal relaxation time, T1
2. Transverse relaxation time, T2

The two basic types of MRI images are T1-weighted and T2-weighted images, often referred to as T1 and T2 images. T1 measures the time required for the magnetic moment of the displaced nuclei to return to equilibrium, and T2 indicates the time required for the FID response signal from a given tissue type to decay.

T1 images show fluid as low signal (dark) and are generally good for anatomy. Blood products, hyperdense renal cysts, and melanin are seen as a high T1 signal. T2 images show fluid as high signal and are useful for showing pathology which is usually associated with edema or for depicting fluid containing structures such as the urinary tract. Fat is usually bright on both sequences.

Current diagnostic MRI scanners use cryogenic superconducting magnets in the range of 0.5 Tesla (T) to 1.5 T. Three Tesla systems are now widely available and are being used regularly. Higher field strength systems provide improved signal-to-noise ratio (SNR), higher spatial and temporal resolution, and improved quantification (Grover et al. 2015).

Common use of MRI in urology

1. MRI kidneys: used to characterize indeterminate small renal lesions, which may be inflammatory or malignant in nature, e.g., AML and in those iodinated contrasts cannot be used
2. MRI abdomen: useful for evaluation of IVC thrombus and its extension
3. MRI (multiparametric) prostate: for potential diagnosis and preoperative staging for prostate cancer
4. MRI testes: rarely done but may be useful in diagnostic dilemma or equivocal findings on ultrasonography

Bone Scans

Bone scans are a nuclear medicine (scintigraphic) study that use Technetium ^{99}m (commonly ^{99}mTc)-methylene diphosphonate as the active agent. The active agent is injected intravenously, and images are captured using a Geiger counter. It has three phases (Mark Thurston 2017):

1. Flow phase – 2 to 5 sec images are obtained for 60 sec after injection.
2. Blood pool phase – image is obtained 5 min after injection.
3. Delayed phase – the bone image is obtained 2–4 hour later.

To note: Superscan is intense symmetric activity in the bones with diminished renal and soft tissue activity on a Tc^{99m} diphosphonate bone scan. It can be seen in prostate cancer with diffuse metastatic disease.

PET (Positron Emission Tomography) Scans

PET scan uses changes in metabolic activities of the tissues to identify/differentiate various lesions. PET can be combined with CT (PET-CT) to get the anatomical information along with the functional information. PET can be combined with MRI (PET-MRI), and this has advantages of PET functional imaging along with MRI's unmatched soft tissue resolution. In this imaging method, the commonly used tracers in urology are 18F-fluoro-deoxy-glucose (FDG), choline, and PSMA (prostate-specific membrane antigen).

FDG-PET – Radiotracer FDG is injected intravenously, and FDG is metabolized by the tumor cells which has high metabolic rate. FDG is metabolized to FDG 6-phosphate. This substrate cannot be further metabolized and gets accumulated in the tumor cells. During imaging, this tracer is quantified.

FDG is excreted by the kidneys and normal physiological uptake is noted in brain, gut, myocardium, and brown fat.

Choline PET – Choline derivatives are used in PET imaging. Commonly used choline derivatives are 11C- or 18F-choline PET. Utility is confined to staging or detecting recurrences in advanced prostate cancer.

^{68}Ga-PSMA ligands are a promising new radiotracer in patients with advanced prostate cancer. Several retrospective studies have shown accurate staging in prostate cancer. It has evolving role in staging, restaging, evaluation of therapy response, and prognostication of high-risk or advanced prostate cancer (Smith and Shetty 2017).

Renal Cell Carcinoma

Clinical Aspects

Many renal masses remain asymptomatic until they are locally advanced, and they are usually diagnosed incidentally on imaging done for other nonrelated clinical problems.

Symptoms associated with RCC are either due to local tumor growth, hemorrhage, paraneoplastic syndromes, or metastatic disease.

Clinical presentation of RCC
• **Incidental**
• **Symptoms of localized disease** – Hematuria – Flank pain – Abdominal mass
• **Paraneoplastic syndromes** – Elevated ESR – Hypertension – Anemia – Cachexia, weight loss – Fever – Stauffer syndrome – Hypercalcemia – Polycythemia
• **Obstruction of the inferior vena cava** – Bilateral lower limb edema – Dilated veins in abdomen – Varicocele – nonreducing
• **Symptoms of systemic disease** – Persistent cough – Bone pain – Loss of weight/loss of appetite – Malaise

Investigations

Laboratory

- Urinalysis – simple and inexpensive, but yield may be low as RCC are parenchymal tumors unlike urothelial tumors.
- Full blood count – to establish a baseline hemoglobin level and platelet count and to look for polycythemia.
- Renal panel (urea, electrolytes, and creatinine) – to assess baseline kidney function which is essential to consider nephron-sparing surgery especially in patients with CKD.
- Calcium panel – to look for hypercalcemia (paraneoplastic syndrome).
- ESR and liver panel, if there is clinical suspicion of paraneoplastic syndrome.
- In metastatic RCC, prognostic markers for Heng's criteria/MSKCC criteria should be done including hemoglobin, corrected calcium

level, neutrophil count, platelet count, and lactate dehydrogenase (LDH).

Imaging

Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are the mainstays of renal mass detection and characterization.

Ultrasound

RCC has varying sonographic appearance. Ultrasonography is useful for distinguishing cystic from solid lesions and can detect lesion vascularity, especially with use of ultrasound contrast agents (Kang et al. 2011). It is not as sensitive or specific when compared to CT or MRI. Ultrasonography is also useful in identification of most renal angiomyolipomas (AML) in view of the significant presence of fat component in majority of AMLs.

Appearance

A standard ultrasonography shows a heterogeneous and solid lesion. If the lesion is cystic, contrast-enhanced ultrasound (CEUS) is a valuable alternative to further characterize renal lesions. It will typically show a lesion which is hypervascular and heterogeneous in the arterial phase with early washout in the delayed phase.

Computed Tomography

CT, with and without intravenous contrast, is the primary imaging test for characterization and staging of renal lesions. CT provides near isotropic acquisition, with three-dimensional reformatting capabilities (Kang et al. 2011). In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HUs) before and after contrast administration.

Small renal mass (SRM): The sensitivity of contrast-enhanced CT for predicting RCC was 79.7%, and the specificity of contrast-enhanced CT for predicting RCC was 44.4% for small renal mass (Kim et al. 2016).

The nephrogenic phase (80–180 sec) is the most sensitive phase for detection of abnormal contrast enhancement (Fig. 1). Excretory phase is important in assessing the collecting system anatomy especially if the patient is a potential candidate for a partial nephrectomy.

MRI

MRI has excellent soft tissue resolution and it may be useful in differentiating doubtful lesions. Renal tumors have certain characteristic appearance on MRI which can possibly help to identify the likely histology (Bott 2012):

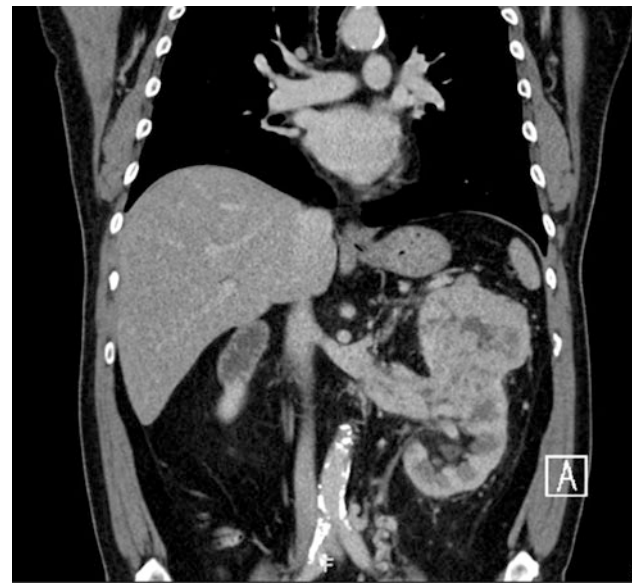

Fig. 1 CT kidneys: portovenous phase showing a left upper pole renal tumor

- **T1:** often heterogeneous due to necrosis, hemorrhage, and solid components
- **T2:** appearances can depend on histology
  - Clear-cell RCC: hyperintense
  - Papillary RCC: hypointense

Tumor pseudocapsule, essentially only seen in low-grade renal cell carcinomas, renal adenomas, and oncocytomas, appears as a hypointense rim between the tumor and the adjacent normal renal parenchyma (Ascenti et al. 2004).

Urothelial Cancer

Clinical Aspects

Urothelial cancer is a cancer of the environment and age; the incidence and prevalence rates increase with age, peaking in the eighth decade of life; and there is a strong association between environmental toxins and urothelial cancer formation (Parkin 2008).

Urothelial carcinomas (UCs) are the fifth most common tumors. They can be located in the lower (bladder and urethra) or upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumors account for 90–95% of UCs and are the most common malignancy of the urinary tract. In contrast, UTUC are uncommon and account for only 5–10% of UCs (Rouprêt 2017).

Presentation

Hematuria is the most common presentation.

Clinical presentation of urothelial cancer
• **Symptoms of localized disease**
– Visible or nonvisible hematuria
– Dysuria, frequency, urgency
– Clot colic
– Acute urinary retention
– Abdominal mass
• **Symptoms of locally advanced disease**
– Colo-vesical fistula
– Per rectal bleed
– Flank pain (with or without fever) due to hydronephrosis or infection
– Chronic pelvic pain

(*continued*)

Clinical presentation of urothelial cancer
• **Symptoms of systemic disease (metastases)**
– Persistent cough
– Bone pain
– Loss of weight/loss of appetite
– Malaise

Investigations

Laboratory

- Urinalysis: to detect microscopic hematuria/sterile pyuria
- Urine cytology: urine cytology has low sensitivity but high specificity. The urine cytology has 84% sensitivity in G3 and high-grade tumors as compared to 16% in low-grade tumors. It is a useful test and is an adjunct to cystoscopy in high-grade malignancy. Cytology is particularly important with patients with carcinoma in situ (CIS) or high-grade disease where cytological changes may be apparent before they are visible at cystoscopy (Brown 2000). Positive urine cytology is suggestive of UTUC when bladder cystoscopy is normal, provided that no CIS is detected in the bladder or prostatic urethra.
- Other urinary markers: (Table 1)

Imaging

CT urography is the investigation of choice. Ultrasonography and MR urography can be used in special conditions. Intravenous urography has largely been replaced by CT urography for evaluating UCs.

CT Urography

This CT contains a non-contrast phase, a portovenous phase, and a delayed/urographic phase. Urothelial carcinoma of urinary bladder appears as either focal regions of thickening of the bladder wall or as masses protruding into the bladder lumen or, in advanced cases, extending into adjacent tissues (Fig. 2). CT will be able to identify T3b tumors (extravesical extension), but it is difficult to identify T1/T2 disease based on CT alone (Hacking et al. 2017). The presence of hydronephrosis indicates obstruction of the

Table 1 Summary of the available urinary markers

Markers (or test specifications)	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumors (%)	Point-of-care test
UroVysion (FISH)[a]	30–86	63–95	66–70	No
Microsatellite analysis	58–92	73–100	90–92	No
Immunocyt/uCyt +[a]	52–100	63–79	62–92	No
Nuclear matrix protein 22[a]	47–100	55–98	75–92	Yes
BTA stat[a]	29–83	56–86	62–91	Yes
BTA TRAK[a]	53–91	28–83	74–77	No
Cytokeratins	12–88	73–95	33–100	No

[a]Reproduced from EAU guidelines on non-muscle-invasive bladder cancer

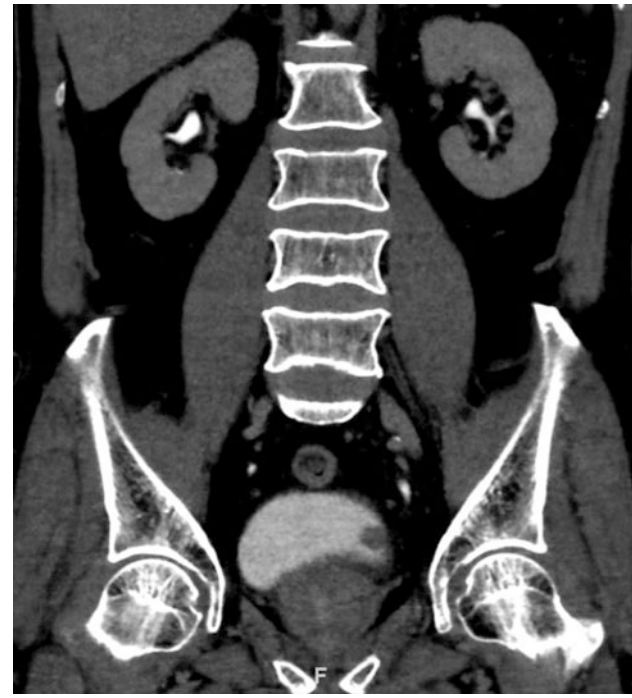

Fig. 2 CT urography: delayed phase showing a filling defect indicating a bladder tumor at the left lateral wall

ureteric orifice by the bladder tumor or muscle invasion at that region. Regional lymphadenopathy can be assessed on CT. Urothelial carcinoma is a field change disease, and it is important to exclude lesions in the upper urinary tract. Delayed phase is important to exclude upper urinary tract urothelial carcinoma (UTUC). UTUC is seen as a filling defect in the pelvicalyceal system or along the ureters. In advanced cases, the lesions can be infiltrating the renal parenchyma. Unlike RCC, UTUC of kidneys will not distort the renal outline, and it is usually centrally located. The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC.

Ultrasonography

It is a useful initial screening tool and bladder tumors are seen as exophytic lesions in the bladder. It is useful for detection of obstruction in patients with hematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

MR Urography

MRI is superior to CT or ultrasonography; however, it is limited by cost and availability. It is a useful modality in patients with allergy to iodinated contrast agents and in people with renal failure. If gadolinium is used as a contrast medium in patients with renal failure, patient should be counseled about nephrogenic systemic fibrosis. In some instances, MRI can distinguish T1 from T2 tumors on T2-weighted images (Hacking et al. 2017):

- **T1:** isointense compared to muscle.
- **T2:** slightly hyperintense compared to the muscle. It is useful in determining the low-signal muscle layer and its discontinuity when muscle wall invasion.

Prostate Cancer

Clinical Aspects

Prostate cancer is the second most commonly diagnosed cancer in men, accounting for 15% of all cancers diagnosed (Ferlay et al. 2015). It is important to know about family history of prostate cancer as the risk of developing prostate cancer is higher with a positive family history. The zones of the prostate were described as peripheral, central, and transition zones (PZ, CZ, and TZ) by John McNeal in 1968, distinguished by microanatomical boundaries, duct drainage, and acinar morphology (McNeal et al. 1988).

Presentation

1. Elevated prostate-specific antigen (PSA) during health screening or evaluation of lower urinary tract symptoms – incidental finding of elevated PSA would usually prompt a urology referral. Other benign causes of elevated PSA, such as benign prostatic enlargement, prostatitis or lower urinary tract infection, and recent urethral instrumentation, should be excluded before further prostate-specific investigations are done. Routine population-based screening with PSA is not recommended in most guidelines, as the evidence of benefit for patient is contradictory. Family history is important where screening is undertaken at earlier age.
2. Abnormal digital rectal examination – a majority of the prostate cancer are seen in the peripheral zone of the prostate, and any hard nodule in the prostate should prompt a urology referral for further investigations and biopsy. If the entire prostate gland feels hard, nodular, and fixed, locally advanced or possibly metastatic prostate cancer needs to be excluded. It is important to note that digital rectal examination does not significantly alter PSA levels.
3. Lower urinary tract symptoms (LUTS) – prostate cancer per se does not cause LUTS unless the prostate cancer is advanced to cause bladder outlet obstruction. However, patients can present with LUTS from concurrent benign prostatic enlargement.
4. Bone pain and constitutional symptoms – this is seen in advanced/metastatic prostate cancer and usually requires urgent intervention. Patients occasionally present with acute neurological deficit due to spinal cord compression from the spinal metastasis.

Investigations

Prostate-Specific Antigen (PSA)

PSA is a serum marker used in diagnosis of prostate cancer. It is organ specific and not cancer specific as it can be elevated in benign causes (BPH, prostatitis, recent instrumentation, etc.). PSA has age-specific reference ranges; however their levels have not been validated in most populations. The upper limit of what is considered "normal," i.e., not warranting further investigation, varies internationally, from 2.5 to 4.0 ug/L.

However, patients with serum PSA <4.0 ugl/L are still at risk of harboring prostate cancer, although the chance of finding significant prostate cancer (Gleason 7 and above/ISUP Group 2 and above) is low as shown in table below (Mottet 2017).

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason ≥7 PCa (%)
0.0–0.5	6.6	0.8
0.6–1.0	10.1	1.0
1.1–2.0	17.0	2.0
2.1–3.0	23.9	4.6
3.1–4.0	26.9	6.7

PSA derivatives and isoforms:

1. **PSA density (PSAD)**
   PSAD = PSA/volume of prostate. If PSAD <0.10, the detection rate of prostate cancer is high when compared to conventional cutoff of <0.15. When a lower PSAD cutoff of 0.10 is used, the detection rate of prostate cancer is higher compared to conventional cutoff of 0.15. Catalona et al. demonstrated that when they accepted a lower PSAD cutoff value of 0.1, they were able to detect 90 percent of all cancer patients and spare 31% of the patients from unnecessary re-biopsies at the same time (Catalona et al. 1997).
2. **PSA kinetics**
   PSA kinetics may be more useful in prognostication rather than diagnosis of PCa.
   A. PSA velocity (PSAV) – annual absolute increase in total PSA. It is expressed in ng/mL/year. In patients with serum PSA levels between 4 and 10 ng/mL, PSA velocity greater than 0.75 ng/mL/year are at increased risk of being diagnosed with prostate cancer. PSA velocity is less commonly used nowadays for prognostication (Ayyıldız and Ayyıldız 2014).
   B. PSA doubling time (PSADT) – exponential increase in PSA over time. It is the time taken to double the PSA level. It has prognostic value in determining the progression or recurrence after a definitive therapy.
3. **Free/total PSA ratio**
   This is useful to differentiate BPH from prostate cancer. This is useful when PSA is between 4 and 10 ng/ml. If F/T PSA is <0.10, the chances of finding a PCa are 56% when compared to 8% if it is >0.25 (Catalona et al. 1998).
4. **Prostate health index (PHI)**
   PHI is derived from a mathematical formula incorporating total PSA, free PSA, and (−2) pro-PSA(p2PSA). The formula for PHI is as below:

$$\text{PHI} = ([-2]\ \text{proPSA}/\text{free PSA}) \times \sqrt{\text{PSA}}$$

US FDA has approved PHI to be used in PSA range of 4–10 ng/ml. Catalona et al. in 2011 published a large study on PHI in 892 men with PSA of 2–10 ng/ml and normal DRE. The study shows an area under curve (AUC) of 0.70 which was better than free PSA or total PSA (Catalona et al. 2011). In NCCN guidelines 2016, PHI >35 provides an estimate of the probability of high-grade prostate cancer in PSA ranges 2–10 ng/ml, and it is informative in patients who have never undergone biopsy or after a negative biopsy (Carroll and Parsons 2016). Lincoln et al. in 2017 validated the use of PHI in Asian population where a biopsy threshold at PHI ≤27.0 would avoid 51% of biopsies, at a 2.5% risk of missing a potentially aggressive cancer (GS ≥7 or more) (Tan et al. 2017).

Other Biomarkers

1. *Prostate cancer gene 3 (PCA 3)*
   PCA 3 is a messenger RNA which was noted to be expressed in urine in patients with prostate cancer, and it is a FDA-approved tool for decision-making in diagnosis of prostate cancer. However, it requires a prostatic massage prior to urine collection for the test.
2. *TMPRSS2-ERG fusion*
   It is a biomarker which represents an androgen-related transcription promoter. It has high specificity but low sensitivity. It is used in conjunction with other biomarkers in view of its low sensitivity (Behesnilian and Reiter 2015).
3. *4 kallikerin (4 K) score*
   The score is obtained from combining free, intact and total PSA and kallikerin like

peptidase 2 (hK2). The test is included in EAU guidelines along with PHI and PCA 3 in risk stratification of patients to reduce unnecessary prostate biopsies.

Imaging

Ultrasonography, MRI, and CT are mainstay in diagnosis. Bone scan is used in patients suspected to have advanced prostate cancer.

Ultrasound

Transrectal ultrasonography (TRUS) is a useful diagnostic modality to determine prostate size and to guide biopsy, usually following an abnormal PSA level or DRE. Transrectal ultrasonography (TRUS) itself cannot be reliably used for prostate cancer diagnosis, as the prostate cancer lesions can be hypoechoic, hyperechoic, or isoechoic. Transrectal ultrasound (US)-guided biopsy is currently the standard of care for diagnosing prostate cancer. A transrectal approach is used for most prostate biopsies, although some urologists prefer a transperineal approach. Cancer detection rates are comparable with both approaches (Mottet 2017).

MRI

Multiparametric magnetic resonance imaging (mpMRI) using a 3-Tesla system, without the need for endorectal coil, is the current standard for prostate imaging. Multiparametric (mp) MRI of the prostate is essentially any functional form of imaging used to supplement standard anatomical T1- and T2-weighted imaging. The functional sequences of choice are dynamic contrast-enhanced (DCE) MRI and diffusion-weighted imaging (DWI), including the calculation of apparent diffusion coefficient (ADC) maps.

Signal characteristics (Verma and Rajesh 2011; Bonekamp et al. 2011):

- **T1:** useful for detection of prostate contour, neurovascular bundle encasement, and post-biopsy hemorrhage
- **T2:**
  - Using an endorectal coil, on T2-weighted images, prostate cancer usually appears as a region of low signal within a normally high signal peripheral zone (Fig. 5).
  - Most significant cancers occur along the posterior portion of the gland abutting the rectum.
- **DWI/ADC:** often shows restricted diffusion
- **Dynamic contrast enhancement (DCE):**
  - Shows enhancement, but it can be difficult to distinguish from prostatitis or benign prostatic hyperplasia (especially in the central zone lesions)
  - More specific than T2 signal
  - Involves post-processing time

Primary indication for MRI is preoperative staging after a prostate cancer is detected on TRUS-guided biopsy of prostate. It is useful to identify extracapsular extension and presence of nodal disease and may aid in the planning of radical prostatectomy, especially with regard to neurovascular bundle sparing and obtaining negative surgical margins. MRI in recent years is increasingly used for primary detection of prostate cancer or after a negative prostate biopsy and persistently elevated PSA levels. It is important to note that MRI has false-negative rate of at least 20%.

MR-fusion biopsy is increasingly being performed and has emerging data for its utility. MRI is useful in targeting suspicious lesions on MRI. Magnetic resonance imaging-targeted biopsies can be obtained through cognitive guidance, ultrasound/mpMRI fusion software, or direct in-bore guidance.

PI-RADS (Prostate Imaging Reporting and Data System) score is given to assess the probability of the lesion being malignant. The score is assessed on 3-Tesla multiparametric MRI. Images are obtained using a multiparametric technique including T2-weighted images, a dynamic contrast study (DCE), and DWI. A score is given according to each variable. The scale is based on a score from 1 to 5 (which is given for each lesion), with 1 being most probably benign and 5 being highly suspicious of malignancy (Weinreb et al. 2016).

The new PI-RADS 2 rather uses stepwise approach to determine a lesion (Fig. 3)

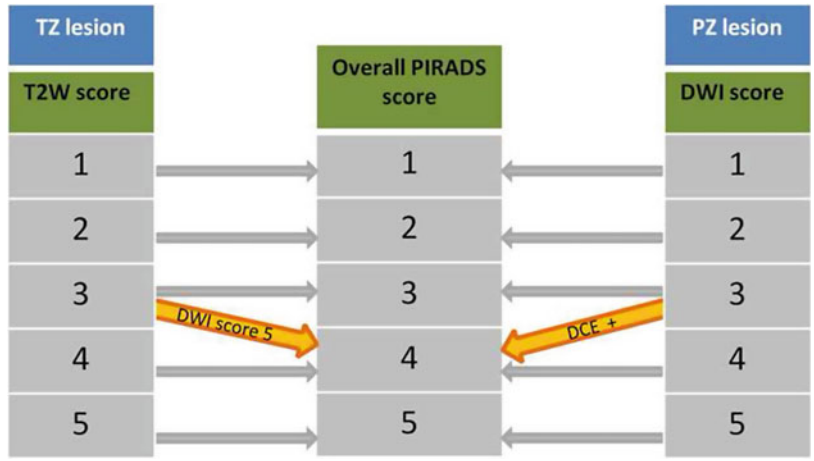

Fig. 3 Data from Abdom Radiol (NY). 2017 Jan; 42 (1): 278–289

CT Scan

It is primarily used in staging for prostate cancer, especially when advanced prostate cancer is suspected (such as CT abdomen and pelvis, with or without CT thorax). It is the investigation of choice to detect enlarged pelvic and retroperitoneal lymph nodes, hydronephrosis, and osteoblastic metastases.

Bone Scan

Osseous bone metastases are detected using Tc^{99} -m bone scan. Prostate cancer metastases are mostly osteoblastic in nature (Fig. 4).

Positron Emission Tomography (PET)

Choline PET is commonly used in prostate cancer; 11C- or 18F-choline Pet/CT has good specificity for lymph node metastases but with a variable sensitivity of 10–73% (Brogsitter et al. 2013).

Afshar et al. report that "^{68}Ga-PSMA ligand PET imaging has been shown to increase detection of metastatic sites even at low PSA-values in comparison to conventional imaging or PET examination with different tracers" (Afshar-Oromieh et al. 2014). ^{68}Ga-PSMA ligand PET is found to be superior to the bone scan in detecting bone metastasis, and it is especially useful for evaluating biochemical recurrence post-radical prostatectomy even at low PSA values (Rauscher et al. 2016).

Testicular Cancer

Clinical Aspects

Testicular cancer represents 1% of male neoplasms and 5% of urological tumors. Its incidence is increasing. Epidemiological risk factors for the development of testicular tumors are components of the testicular dysgenesis syndrome (i.e., cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility), familial history of testicular tumors among first-degree relatives, and the presence of a contralateral tumor or intratesticular germ cell neoplasia (ITGCN) (Albers 2017).

Among the germ cell tumors, there is also stratification according to age, with some tumors being more common in some age groups than others (Jones 2017):

- **First decade:** yolk sac tumor and testicular teratoma
- **Second decade:** choriocarcinoma
- **Third decade:** embryonal cell carcinoma
- **Fourth decade:** seminoma
- ≥**Seventh decade:** lymphoma (usually non-Hodgkin lymphoma) and spermatocytic seminoma

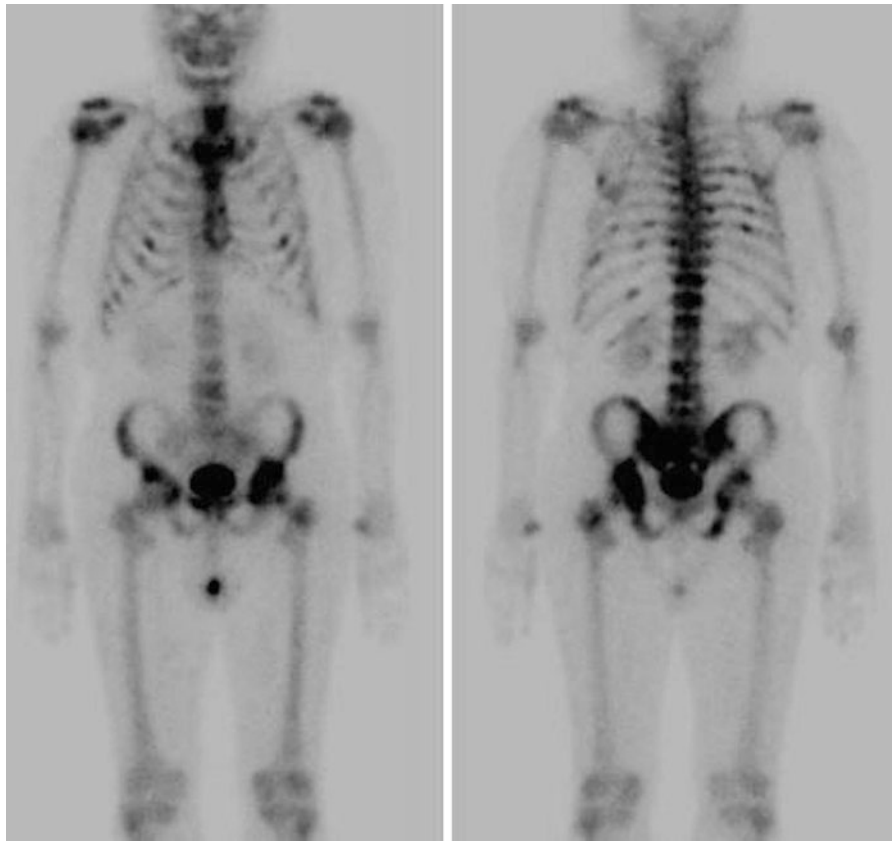

Fig. 4 Bone scan showing multiple osteoblastic metastases noted in bilateral ribs and pelvis

Presentation

The most common presentation is a patient presenting with painless testicular lump. Trauma is not a contributing factor for testicular tumor, but it usually draws attention to the lump.

Clinical presentation of testicular cancer
• **Symptoms of localized disease**
– Painless testicular swelling
– A dull ache or heavy sensation in the lower abdomen
– Trauma with hematoma (rare)
• **Symptoms and signs of disseminated disease**
– Persistent cough, shortness of breath, and/or hemoptysis (mediastinal adenopathy/lung mets)
– Supraclavicular lymph node
– Back pain (bulky retroperitoneal lymph node mets)
– Bone pain (rare)
– Malaise, loss of weight/loss of appetite, diarrhea
– Neurological symptoms (rare)
– Gynecomastia (hCG-producing tumor)

Examination

A solid, firm mass within the testis should be considered testicular cancer until proven otherwise. Prompt diagnosis and early treatment are required.

Unilateral or bilateral lower extremity swelling may be present in patients with iliac or vena caval obstruction or thrombosis. Abdominal mass can be felt in patients with disseminated disease and bulky retroperitoneal disease.

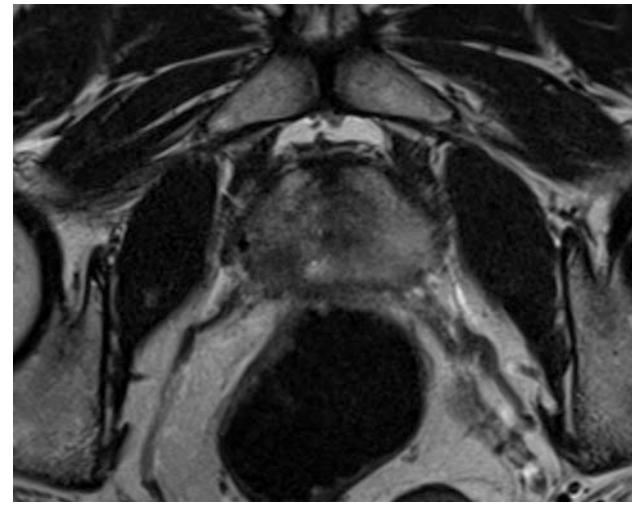

Fig. 5 MRI prostate: T2 axial cut showing a right peripheral zone hypointense lesion

The workup of patients with suspected testicular cancer starts with a complete history and physical examination. Laboratory tests and imaging studies include the following:

- Serum alpha-fetoprotein.
- Serum beta subunit of human chorionic gonadotropin (beta-hCG).
- Lactate dehydrogenase (LDH).
- Chemistry profile.
- Testicular ultrasound study.
- High-resolution computed tomography (CT) scan of the abdomen and pelvis.
- Chest X-ray or CT scan thorax.
- Magnetic resonance imaging (MRI) of the brain should be performed if brain metastases are suspected after clinical examination or presence of neurological symptoms.

Imaging

Ultrasonography

Currently, ultrasonography is used to confirm the presence of a testicular mass and explore the contralateral testis. Ultrasound sensitivity is almost 100%, and it has an important role in determining whether a mass is intra- or extra-testicular. Ultrasound is an inexpensive test and should be performed even in the presence of clinically evident testicular tumor.

Common radiological features suggestive of testicular tumor are:

- Intratesticular mass which may be homogenous or heterogeneous (Fig. 6). An intratesticular mass is suggestive of testicular tumor unless proven otherwise. A paratesticular mass has a higher likelihood of being benign pathology.
- Increased vascularity – can be seen in epididymo-orchitis; however increased blood flow within an intratesticular mass supports the diagnosis of testicular tumor.

Ultrasound appearance of individual germ cell tumors:

(a) Seminoma:
  (i) Seminomas usually appear as a homogeneous intratesticular mass of low echogenicity compared to normal testicular tissue
  (ii) The mass is usually oval and well-defined in the absence of local invasion. It is usually confined within the tunica albuginea, rarely extending to paratesticular structures

(b) Non-seminomatous tumors:

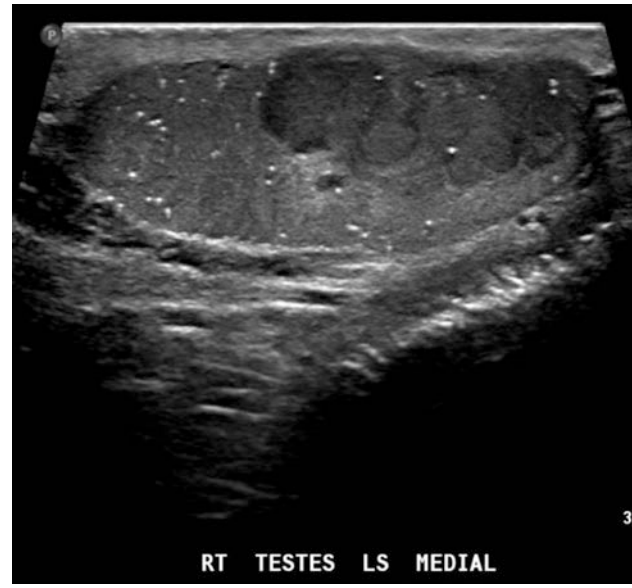

Fig. 6 Ultrasound scrotum showing intratesticular heterogeneous lesion in the right testis

(i) In contrast to seminomas, NSGCTs tend to be more heterogeneous with frequent cystic areas or calcification. They tend to be more aggressive than seminomas, and tunica invasion is common.

(ii) Mature teratomas tend to be cystic with heterogeneous echoes in the fluid representing a mixture of mucinous or sebaceous material with or without hair follicles. Solid components are present of variable echogenicity, including hyperechoic and shadowing fatty components. Immature teratomas tend to be more solid but still heterogeneous on account of areas of hemorrhage and necrosis.

(c) Lymphoma:

Most commonly seen in patients >60 years old.

Tumor Markers

Serum tumor markers are useful for prognostication and staging.

1. Alpha-fetoprotein (AFP)

   Alpha-fetoprotein (AFP) is normally produced by the fetal yolk sac and other organs and is essentially undetectable in the serum in normal men. The half-life for AFP is 5–7 days. AFP is not elevated in pure seminomas. AFP is secreted by yolk sac tumors and to some extent by chorionic tumors. AFP is elevated in HCC and can give false-positive results. If AFP is elevated, the patient should be treated as if he had NSGCT.

2. Beta subunit of human chorionic gonadotrophin (B-hCG)

   Beta subunit of hCG is measured in assays, as alpha subunit is seen in pituitary tumors. The half-life of B-hCG is 1.5–3 days. In seminomas, up to 15% can have elevated serum B-hCG levels. In NSGCT, B-hCG is elevated in 10–20% of CS 1 NSGCTs and 40% in advanced NSGCTs. False-positive results may be seen in patients with hyperthyroidism.

3. Lactate dehydrogenase

   This is a less specific marker and it is an indicator of tumor burden.

CT Scan

Once the diagnosis of testicular cancer is made, a high-resolution computed tomography (CT) scan of the abdomen and pelvis and a chest X-ray are ordered as part of the initial staging workup. Chest CT is recommended if the chest X-ray is abnormal or if metastatic disease in the thorax is strongly suspected clinically (Sachdeva 2017).

MRI and Bone Scan

MRI of the brain and a bone scan are performed if brain and bone metastases are suspected.

PET

^{18}F-Fluoro-2-deoxy-D-glucose (FDG)-PET may contribute to the improvement of diagnosis, staging, and management of patients with testicular cancer. It accurately detects small-volume metastatic disease and plays an important role in characterization of post-chemotherapy residual masses (Gouliamos 2014). PET can be combined with CT to improve the characterization of suspicious lesions. FDG-PET has a high negative predictive value in patient with residual masses after treatment of seminoma (Albers 2017). In patients with residual mass >3 cm, FDG-PET is more useful, whereas in those with residual mass <3 cm, it is optional (De Santis et al. 2004).

Penile Cancer

Clinical Aspects

Penile cancer is usually a disease of the elderly but it can be seen in younger patients too. Incidence increases from 60 years and above (Brosman 2015). The most common cancer type of the penis is squamous cell carcinoma. There is usually a delay in the diagnosis of penile cancer as patients tend to present late. There is considerable anxiety and neglect before the patient seeks medical attention. Neonatal circumcision has been well established as a prophylactic measure that virtually eliminates the occurrence of penile carcinoma. Penile carcinoma is rare in Jewish population where neonatal circumcision is practiced (Licklider 1961).

Presentation

Penile cancer usually presents with painless lesion over the penis. The most common site is the glans (48%) and prepuce (21%). The lesion can be ulcerative, flat, or exophytic. It is important to know the premalignant lesions to understand the relationship with SCC.

Premalignant Lesions

1. *Carcinoma in situ (Tis) of the penis*
   This is named erythroplasia of Queyrat if it involves the glans penis. The lesion appears red, velvety, and well-marginated lesion of the glans penis. Bowen's disease is Tis involving the penile shaft/perineum and characterized by scaly plaques.
2. *Cutaneous horn*
   It is characterized by an overgrowth and cornification of the epithelium. Malignant transformation or association with a malignant tumor may be possible, although this is a rare occurrence.
3. *Balanitis xerotica obliterans (BXO)/lichen sclerosis*
   It appears as a whitish patch over the glans or prepuce, and the meatus is thickened and edematous. It is associated with malignancy and requires closer follow-up even after excision.
4. *Condylomata acuminatum and Bowenoid papulosis* are associated with human papilloma virus (HPV), and malignant transformation has been reported. (Ref: Campbell-walsh urology, 11th edition, p. 846.)

Invasive Cancer

- Penile lesion is the common presenting sign. The lesion can vary from induration to a proliferative growth.
- Symptoms of local invasion or metastasis can be the presenting complaint in patients who present late.

Investigations

1. **Laboratory**
   No specific laboratory tests are diagnostic of penile cancer. Hypercalcemia due to

parathyroid-related substances secreted by penile cancer can occasionally be seen.

2. **Histology**

   Histological diagnosis is the key in diagnosis of penile cancer. Any suspicious lesion should be biopsied to exclude a penile cancer.

3. **Imaging**

   Physical examination is most reliable for accurate staging of the disease.

   Imaging will be essential where proper clinical examination is not possible (e.g., obese patients) or for prognostication/follow-up.

   A. **MRI**

      MRI provides the best soft tissue resolution for local staging of penile cancer. MRI should be performed after artificial erection for accurate staging, and this is critical for proper staging of the cancer.

   B. **CT**

      CT is useful in staging and evaluation for enlarged pelvic and retroperitoneal lymph nodes and distant metastasis.

   C. **PET/PET-CT**

      This may potentially be useful in patients with non-palpable lymph nodes but are suspected to have micrometastasis, although it is not routinely done. This may avoid surgical staging in some patients (Brogsitter et al. 2013).

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Clinical Trials and Their Principles in Urologic Oncology

3

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Abstract

Clinical trials represent a relevant link between cancer research and clinical practice and provide the basis for evidence-based medicine. Trials in uro-oncology are essential for moving new methods of preventing, diagnosing, and treating cancer from the labs to clinical settings with the ultimate goal to improve care and quality of life of cancer patients.

Clinical trials impact the treatment of individual patients by selecting therapies; in addition, they affect also the societies' health systems by evaluating and possibly enhancing the value of provided treatment options. Clinical trial conduction also harbors the potential of posing unknown risks to participants. Additionally, it needs to be considered that potentially biased knowledge retrieved from trials may harm patients. Hence, clinical trial implementation involves a rigorous approach based on scientific, statistical, ethical, and legal considerations.

In this chapter, commonly applied trial designs and relevant aspects of designing clinical studies will be contemplated. The aim is to provide sufficient background needed for proper interpretation of research findings and translating clinical trial results into clinical practice, which will support evidence-based clinical decision-making aiming at the best healthcare for each individual patient. Another objective is to provide basic guidance for the scientific community in the production of reliable evidence. Moreover, ethical principles related to clinical research including the topic of equipoise will be highlighted. Finally, the dilemmas and hurdles encountered in planning and executing trials will be touched. Ultimately one focus will be set on research in uro-oncology surgery which faces specific hurdles different to clinical trials for drug development.

Introduction

Although just a very minor proportion of urological cancer patients (about 3–5%) are enrolled in clinical trials, trials represent a relevant link between basic cancer research and clinical practice and provide the basis for evidence-based medicine. By addressing clinically relevant questions, clinical trial conduction may finally lead to improvements in clinical routine.

Randomized controlled trials (RCT) are the distinguishing mark of evidence-based medicine translating basic research data into clinical practice. RCT and meta-analyses of clinical trials are the gold standard for evaluating efficacy and confirming evidence for medical treatment, medical devices, screening approaches, behavioral modifications, and other interventions and, hence, are the basic requirements for evidence-based therapy. Clinical trials in uro-oncology are essential for moving new methods of preventing, diagnosing, and treating cancer from the labs to clinical settings with the ultimate goal to improve care and quality of life of cancer patients. In addition to exploring new treatment options, clinical trials may also help in determining the best

use of existing interventions or test new approaches for patients seeking care after positive cancer screening tests and identify ways to improve palliative care.

Clinical trials impact the treatment of individual patients by selecting therapies and proving efficacy; furthermore, clinical trial results affect also the societies' health systems by evaluating and possibly enhancing the value of provided treatment options. On the other hand, clinical trials harbor also the potential of posing unknown risks to participants. Additionally, it needs to be considered that potentially biased knowledge retrieved from other trials may harm patients. Hence, the implementation of clinical trials involves a rigorous approach based on scientific, statistical, and legal considerations, and consequently also study oversight guided by strict ethical principles needs to be ensured.

Nonetheless, the quality generated by studies is largely depending on the implementation and rigorous application of accepted and standardized methods at every single stage of study execution, such as randomization to comparably independent groups with regard to known and unknown potential confounding factors. Over many years, however, RCTs have been conducted based on insufficient methodology and empirical evidence rather than scientifically valid and reliable available evidence. Furthermore, the interpretation of RCT data can be impacted by random or systematic errors as well as limited generalizability due to selection bias. Subsequently it is pivotal to choose an appropriate study design to generate reliable data which can be translated into clinical routine (Wunsch et al. 2006; Reith et al. 2013; Spieth et al. 2016). The limitations seen in clinical trial planning and conduction were the main reason why guidelines were developed to provide support to scientists, physicians, authors, reviewers, and editors in evaluating and generating methodological consistency.

Principles of Drug Development

Understanding clinical trials does also include apprehending the main principles of drug development. The general road to drug development and approval has been defined and regulated by the US Food and Drug Administration (FDA) for decades; additionally, also the European Medicines Agency (EMA) and local health authorities have provided guidance on clinical trial conduction. The main focus requested especially by the FDA has always been safety, followed by efficacy. If a drug appears promising in preclinical studies, an investigational new drug (IND) application can be submitted, which contains, besides logistic and manufacturing information, all investigator qualifications and preclinical drug information and data. After IND approval, the drug is being studied in phase 1–3 trials, and if safety and efficacy have been demonstrated in the intended population, the drug sponsor can submit a new drug application (NDA) to the FDA. After FDA review and final approval, the subsequent phase 4 trials may follow for additional monitoring. Over recent years and decades, efforts have been made to harmonize this approval process across the United States, Europe, and Japan through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (Good clinical practice guidelines 1994; Umscheid et al. 2011).

In this book chapter, commonly applied designs of RCT will be summarized; furthermore, relevant aspects of study design and interpretation of RCTs will be contemplated with the aim of providing the clinician with relevant background information, which is needed for the interpreting of research findings and translation of clinical trial results into clinical practice: finally, proper judgment of clinical trial results will support evidence-based clinical decision-making aiming at the best possible healthcare for each individual patient. Another objective of this chapter is to provide basic guidance to support the scientific community in the production of reliable evidence.

In order to critically evaluate clinical research data in uro-oncology, also an overview of the ethical foundations of trial design and trial oversight will be given. **A glossary of relevant terms related to clinical trials is provided in Table 1.** Moreover, we will reflect on the principle of equipoise, an ethical concept that is increasingly

Table 1 Clinical trial glossary

Term	Description
Bias (statistical and operational)	"A partiality that prevents objective consideration of an issue or situation." in statistics it means "a tendency of an estimate to deviate in one direction from a true value." this systematic deviation from the actual value can either result in underestimation or overestimation of the intervention effects. Bias Means a systematic tendency of any factors associated with the design, conduct, analysis, and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value
Blind review	Checking and assessment of data during the conduction of a clinical trial until trial completion and the breaking of the blind, for the purpose of finalizing the planned analysis
Double-dummy	A technique for retaining the blind when administering supplies in a clinical trial, when the compared treatments cannot be made identical. Supplies are prepared for treatment A and for treatment B (for both arms, active and indistinguishable placebo are provided)
Dropout	A subject in a clinical trial who fails (for whatever reasons) to continue in the trial until the last visit or follow-up required based on the study protocol
Equivalency trial	A trial with the primary objective of showing that the response of the compared treatments differs by a clinically unimportant amount only. This is usually shown based on a treatment difference between a lower and an upper equivalence margin of clinically acceptable differences
Full analysis set	The set of subjects that is as close as possible to the intention-to-treat (ITT) principle. The full analysis set is usually derived from the set of all randomized subjects by just minimal and justified elimination of subjects
Generalizability	The extent to which trial findings can reliably be transferred from trial subjects to a broader patient population and a broader range of clinical settings
Independent data monitoring committee (IDMC)	An independent data monitoring committee (IDMC) may be established by the sponsor to assess at predefined intervals the progress of a clinical trial, safety, and efficacy parameters. IDMCs can recommend to the sponsor to continue, modify, or stop a trial
Intention-to-treat (ITT) principle	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating the treatment a patient was assigned to (i.e., the planned treatment regimen) rather than the actual treatment given. Consequently, subjects allocated to a treatment group are followed, assessed, and analyzed as members of that group irrespective of their compliance to the planned treatment course
Inter-rater reliability	The property of getting equivalent assessment results when applying the same methods by different raters on different occasions
Intra-rater reliability	The property of getting equivalent assessment results when applying the same methods by the same rater on different occasions
Interim analysis	Any analysis intended to compare treatment or intervention arms for efficacy or safety at a prespecified time prior to the formal trial completion
Meta-analysis (MA)	Formal evaluation of quantitative evidence from two or more trials assessing the same research question. This regularly involves the statistical combination of summary statistics from various trials. Sometimes the term MA is also used for a combination of raw data
Multicenter trial	A clinical trial conducted at more than one site according to the same study protocol
Non-inferiority trial	A sub-form of equivalency trials. A non-inferiority trial has the primary objective of showing that the response to the investigational product is not clinically inferior to the comparator (in most cases active controls)
Per protocol (PP) set (evaluable subject sample)	The set of data generated by the subpopulation of study subjects who complied with the protocol to ensure that data likely exhibit the treatment effects, according to the underlying scientific model. Compliance covers aspects such as treatment exposure, availability of measurements, and absence of major protocol violations

(*continued*)

Table 1 (continued)

Term	Description
Safety and tolerability	The safety of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests, vital signs, and adverse events. The tolerability of the medical product represents the degree to which evident adverse effects can be tolerated
Statistical analysis plan (SAP)	A statistical analysis plan is a document that contains a detailed technical elaboration of the principal analysis features described in the protocol. The SAP includes detailed procedures for the statistical analysis of study variables and endpoints
Superiority trial	A trial with the primary objective to show a superior response to the investigational product than to the comparator (active or placebo control)
Surrogate variable	A variable that provides an indirect measurement of an effect or endpoint where direct measurement is not feasible or practical (e.g., due to time needed to achieve long-term endpoints)
Treatment effect	An effect attributed to a treatment in a clinical trial. In most clinical trials, the treatment effect of interest is a comparison of two or more treatments
Treatment emergent	An (adverse) event that emerges during treatment or worsens relative to the pretreatment state is defined as a treatment emergent event

important when large multicenter studies are dominating the impact of medical science on clinical practice, and its practical applicability to clinical science. In addition, also the key concepts of clinical trial conduction as well as the dilemmas and hurdles encountered in successful design and execution of a clinical trial will be a relevant part of this article. Ultimately one focus will be set on research in uro-oncology surgery which deals with some hurdles different to clinical trials for drug development.

Finally, it is crucial for physicians and other healthcare providers to understand the basic requirements of well-performed clinical trials in order to maintain a reliable and trustful partnership with patients and industry to develop safe, efficient, and effective treatment options.

Overview of Trial Designs

Types of Clinical Trials

Clinical trials, in their purest form, are designed to observe outcomes of human subjects under experimental conditions. In contrast, noninterventional study designs, e.g., cohort, case-control, and observational studies, are constructed to measure the impact of an intervention without direct influence. From a methodological viewpoint, observational studies are investigating exposure and outcome, whereas experimental studies are observing the outcome of an assigned exposure. Additional nonexperimental research includes case reports, case series, and cross-sectional studies. These types of studies often generate relevant insights without providing any causal inferential value.

Clinical trial designs are mostly favored due to the opportunity to allow randomization of the intervention in order to effectively reduce or completely remove selection bias of patients and unmeasurable confounding parameters. In RCTs, a predefined study sample is built out of the target population (e.g., patients with the relevant diagnosis) and randomly assigned to different groups (e.g., standard-of-care treatment or placebo versus new treatment options). The observed effects of investigational treatments constitute predefined endpoints at specific time points. RCTs may result in high-quality data with the ability to analyze and describe causal relationships. However, besides forming the basis of evidence-based medicine, RCTs still remain subject to limitations (Berkman et al. 2014; Collins and MacMahon, 2001). Misclassification might bias exposure to the intervention or subsequent outcome; furthermore, contamination (e.g., a fraction of patients assigned

Table 2 Clinical trials by phase and characteristics

Phase	Primary goal	Dose	Typical number of participants
Preclinical	Drug is tested in nonhuman subjects (e.g., cell lines, animals) to gather information on efficacy, toxicity, and pharmacokinetics	Unrestricted	Not applicable
Phase 0	Evaluated parameters: Pharmacokinetics, partially oral bioavailability, and half-life of the drug Not regularly done, mostly skipped for phase 1	Very small, sub-therapeutic	Very limited number of healthy subjects
Phase 1	Usually the initial trial for drug testing in humans (when phase 0 is skipped) for dosing, safety, and early efficacy (at this point, it is not presumed that a drug has any therapeutic effect) Testing of different drug doses (dose ranging) in healthy volunteers	Often sub-therapeutic but with ascending doses	About −80 healthy participant or patients with the disease
Phase 2	Subsequent trial of a drug's safety and efficacy in a particular disease setting	Therapeutic dose	N = 100–300
Phase 3	Larger trial comparing a drug with best available therapy to confirm efficacy, effectiveness, and safety, often used for drug approval (1000–3000 patients*) Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect	Therapeutic dose	1000–3000 (depending on disease area; in oncology trials, usually 1000–1500 patients)
Phase 4	Post-marketing surveillance studies to evaluate long-term effects and additional side effects in approved drugs and interventions	Therapeutic dose	Participants are regular patients

to the control arm receive the same intervention outside the trial) and co-interventions (i.e., patients in one arm receive additional interventions more often than patients in the other arm) might reduce the reliability of results. Hence, to assess the efficacy of an intervention, there must be a deliberate control of all known confounding variables including comorbidity in a clinical trial, which requires first a homogeneous group of study participants. On the other hand, the evidence provided by a well-designed and accordantly executed trial has no clinical value if the real-world patient population looks quite different, and thus results cannot be transferred to the general patient population. Accordingly, subjective judgment including clinical, epidemiological, and biostatistical reasoning has to be applied in order to decide which and to what extent curtailments can be accepted to create internal validity on the one hand and generalizability of a clinical trial on the other.

Phases of Clinical Trials

Clinical trials to test new cancer treatments are commonly classified into phases with each phase being characterized by a specific design and sample size. If a new treatment is successful in one phase, it will typically proceed to additional testing in the next clinical trial phase.

Trial designs might also be combined to two phases (e.g., phase 1/2 or phase 2/3 trials) in a single protocol, which may allow more quickly answering research questions with fewer patients, partially based on an adaptive trial design for seamless transition between trial phases.

Table 2 provides an overview on the main characteristics of clinical trial phases.

Preclinical, Phase 1, and Phase 2 Trials

During the early phases (phases 1 and 2), it is assessed whether a new treatment is safe and what its side effects are; furthermore, the evidence of activity or optimal dosage is evaluated.

Phase 1 trials usually test interventions in healthy volunteers or treatment-refractory patients aiming to address potential safety issues, pharmacokinetics, and characteristics related to dose-response. In oncology trials, also reduction of tumor growth as a treatment effect is measured. Prior to phase 1 studies, unfrequently also phase 0 clinical trials may be conducted, which are very small trials conducted for decision-making whether or not a new agent should proceed to phase 1.

Preclinical investigations include animal studies and evaluations of drug production and purity. Animal studies explore (1) the drug's safety in doses equivalent to the estimated exposure in humans, (2) pharmacodynamics (i.e., mechanisms of action and the relationship between drug levels and clinical response), and (3) pharmacokinetics (i.e., drug absorption, distribution, metabolism, and potential drug-drug interactions). This data must be submitted for IND approval if the drug is planned to be further studied in human subjects.

Phase 1 trials (synonym: dose escalation human pharmacology studies) are the first instance in which the new investigational agent is studied in humans; they are usually performed in an open-label manner in a small number of healthy and/or diseased participants. The FDA emphasizes "safety first"; hence, consequentially this trial phase is designed to test the safety and maximum tolerated dose (MTD) of a drug, human pharmacokinetics and pharmacodynamics, and drug-drug interactions. The MTD, or the drug dose before a dose-limiting toxicity, is determined by different statistical designs. Dose escalation is based on strict criteria, and subjects are closely followed for potential toxicities over a sufficient period (Umscheid et al. 2011). For participants in phase 1 trials and the physicians enrolling patients, it has to be made sure that they understand the objective of early trial phases, as there is a considerable risk of misinterpreting it as therapeutic. Despite strong evidence that objective response rates in phase 1 trials of chemotherapeutic drugs are very low (about 2.5%), patients may still have a misconception and consider receiving a direct medical benefit from trial participation (Umscheid et al. 2011).

Phase 2 trials (synonym: therapeutic exploratory trials) usually enroll a higher number of participants than phase 1 studies and are conducted in volunteers with the disease of interest. They are designed to test safety, pharmacokinetics, and pharmacodynamics but may also be designed to answer questions essential for the planning of phase 3 trials, including the determination of dose and dosing frequencies, route of administration, and trial endpoints. Phase 2 clinical trials may provide the possibility to evaluate evidence for drug efficacy by (1) examining different dosing arms, (2) comparing the study drug with historical patient controls retrieved from published series, or (3) randomizing subjects to different arms, potentially already a control arm. The small number of patients and primary safety concerns within a phase 2 trial usually limit its power to establish efficacy. Even under the consideration of proper phase 2 trial results, there is still the necessity of a subsequent phase 3 trial.

At conclusion of the initial trial phases, a meeting between the sponsor, investigators, health authorities (EMA, FDA), and governmental agencies may occur to review the study data and IND, in order to ascertain the viability of progressing to a phase 3 trial. These conversations usually include plans for trial design, sample size, data collection, endpoints, safety concerns, analyses, case report forms, as well as potential manufacturing concerns.

Phase 3 Trials

Phase 3 trials are usually pivotal studies designed to provide data for approval by health authorities by testing new treatments against a control, either placebo or standard of care; outcome might be assessed with regard to superiority or non-inferiority. They are usually conducted based on prior studies having demonstrated safety and potential efficacy. Besides efficacy, safety of the new treatment is compared to the comparator. Phase 3 trials in uro-oncology usually include regularly 1000–1500 patients and a more diverse patient population than in phase 2 to make sure that results are valid to confirm efficacy and identify the incidence of common side effects. For drug development studies, phase 3 trials are

often additionally classified as phase 3a (before submission to health authorities for approval) and 3b (after approval).

Based on the vast combination of strategies applicable to the design of a phase 3 studies, the Consolidated Standards of Reporting Trials (CONSORT) guideline was established to improve the quality of trial reporting and assist with evaluating the conduct and validity of trials and their results (http://www.consort-statement.org/). By employing flow diagrams, readers can identify at which stages subjects withdraw from a study (e.g., due to ineligibility, lost to follow-up, missing evaluation for the primary endpoint). As exclusion of missing data reduces the power of studies considerably and results in accordant bias, the best way to avoid such challenges is to implement such tools, thereby enrolling eligible patients only and ensuring that they remain on-study.

Phase 4 Trials and Post-Marketing Assessment

Given that phase 3 trials usually include 1000–1500 of strictly selected subjects, the limited statistical power to establish adverse event rates generally represents one main limitation with regard to transferring results to the real-world patient population. This highlights the significance of phase 4 trials in identifying less common adverse drug reactions and assessing long-term safety data, which is also requested by health authorities and governmental authorities. In addition, phase 4 trials are partially conducted to receive approval for expanded indications after an initial approval and market access in a different indication or target patient population (Umscheid et al. 2011).

Once a drug is approved, the FDA or EMA as well as local health authorities and governmental agencies may require that a sponsor conducts a phase 4 trial. Phase 4 trials (synonym: therapeutic use study, post-marketing study) are observational studies on approved drugs to (1) identify less common adverse reactions or additional adverse reactions in the real-world patient population and (2) evaluate health economy-related questions such as cost and/or drug effectiveness in diseases, populations, or doses similar to or different from the original study population. About 20% of approved drugs acquire new black box warnings, and approximately 4% are finally withdrawn for safety reasons after marketing which again demonstrates the limitations of pre-marketing studies. The situation of pre-marketing studies focusing on a selected patient population on the one hand and post-marketing studies after approval in a broader patient population on the other reflects "a deliberate societal decision to balance delays in access to new drugs with delays in information about rare adverse reactions" (Strom 2004). Over the recent decades, there has been a steady rise in voluntarily reported serious adverse drug reactions submitted directly by physicians or consumers or indirectly by manufacturers to health authorities and programs such as the FDA's MedWatch program (Administration USFaD 2010). Nonetheless, some weakness of such surveillance strategies to detect serious adverse events remains. Common criticisms of post-marketing surveillance strategies include the reliance on voluntary reporting which results in incomplete data, partially unreliable information, and the difficulty to calculate a realistic event rate. Furthermore, there is always some concern that drug safety reporting by manufacturers may compete with their financial interests, and finally also the dependence on governmental bodies to approve a drug and afterward seek evidence potentially leading to marketing withdrawal is partially considered suspicious (Strom 2004; Fontanarosa et al. 2004). The establishment of a national health data network might be one solution to oversee post-marketing surveillance independent of health authorities (Maro et al. 2009); further possibilities could be preplanned meta-analyses of related trials to assess less common adverse events (Berlin and Colditz 1999) and large-scale simple RCTs with limited eligibility and treatment criteria and a broader real-life patient population (Hennekens and Demets 2009).

There is a considerable variability in timing and number of patients enrolled in the different study phases; however, in uro-oncology, there is a thumb rule that phase 1 studies enroll between 30 and 100 healthy volunteers over a period of

1–2 years, phase 2 usually between 200 and 300 patients in a time period between 2 and 3 years, and phase 3 trials around 1000–1500 patients for 3–5 years.

Design of Clinical Trials

When designing a clinical trial, it is important to define a number of relevant parameters for generating clinically meaningful results. These include the patient population, study treatment, trial endpoints, and trial conduction (e.g., randomized vs nonrandomized) (Spieth et al. 2016).

The two standard designs for RCT are parallel and crossover designs (Berkman et al. 2014; Wellek and Blettner 2012). Following randomization, subjects will be assigned either to a defined intervention throughout the treatment period (parallel design) or first receive with one intervention followed by another after reaching an (intermediate) study endpoints. Crossover trials are generally considered powerful as they provide the possibility that study participants serve as their own control, thus excluding variability due to interindividual differences (Wellek and Blettner 2012; Hollis and Campbell 1999). Nonetheless, this argument is not overall valid for oncology trials, where individual characteristics and baseline criteria might change from one interaction to the next. Furthermore, while randomization is powerful to ensure validity in parallel-designed studies, special precautions have to be considered in crossover studies to account for possible carry-over effects. Carry-over effects are effects that "carry over" from one condition, e.g., exposure or treatment, to another. Randomization of the treatment sequence and appropriate wash-in and washout periods are consequently commonly used to avoid carry-over effects (Wellek and Blettner 2012).

To test for treatment effects of combined interventions, also factorial study designs have been developed where individuals are randomized to receive two or more interventions (Hollis and Campbell 1999; Whelan et al. 2012). This study design increases the study efficiency because it allows for assessment of multiple interventions within one single trial. Factorial designs allow for testing the effects of each factor on the response variable as well as the effects of the interacting factors on the response variable (Spieth et al. 2016).

Research Question and Hypothesis

Designing an RCT starts with addressing a clinically relevant research question. As outlined previously, depending on the research question, the study hypothesis will subsequently either aim at superiority or non-inferiority (Zhang et al. 2014; Akobeng 2008). The most common type of phase 3 trials are comparative efficacy trials (synonym: superiority trials, placebo-controlled trials, pivotal trials) and compare the intervention of interest with standard of care or placebo.

Even in the best-designed placebo-controlled trials, it is not uncommon to demonstrate a placebo effect, in which subjects exposed to the inert substance exhibit an unexpected improvement in outcomes compared with historical controls or patients outside a clinical trial. The placebo effect may be attributed to a general improvement in care in subjects enrolled in a clinical trial; another explanation might be that study volunteers are mainly acutely symptomatic and will naturally improve or regress to the mean as the trial progresses (Cahana and Romagnioli 2007; Foddy 2009; Wilcox 2008). Such considerations further highlight the uniqueness of study participants and why a trial may lack external validity.

Another type of phase 3 trials, the equivalency trial (synonym: positive-control study), is designed to confirm whether the experimental treatment is similar to the comparator within prespecified margins, which subsequently also means that a placebo is almost never included in this design. The intervention is estimated equivalent to the comparator, when the differences between intervention and comparator for a defined endpoint are within a defined range (Walker and Nowacki 2011). The predefined margins are usually retrieved from external evidence, statistical basic calculations, and clinical experience, and there is little to no guidance for such setting how to define acceptable margins (Umscheid et al. 2011).

Non-inferiority trials are variants of equivalence studies excluding the possibility of a less effective experimental intervention and designed to prove that a new treatment is at least as good as the standard therapy in terms of efficacy. Potential advantages of tested treatments are, e.g., lower costs, lower toxicity, improved side effect profile, or improved forms of administration compared to the standard of care (Spieth et al. 2016). However, although generally straightforward, the validity of non-inferiority trials might be jeopardized by the lack of efficacy of the standard treatment and the appropriate choice of non-inferiority margins. The non-inferiority margin has to be defined a priori and determines the sample size of the trials as well as the objective of the trial. Hence, in clinical practice, one needs to be cautious in interpreting the results of non-inferiority trials, as they are frequently designed and analyzed incorrectly based on statistical designs relevant for comparative efficacy studies but not for equivalency trials. Non-inferiority trials are also more susceptible to false-positive results than other study designs (Fleming 2008).

The Patient Population

In the earlier phases of drug development, the choice of subjects for a clinical trial may be mainly influenced by the wish to maximize the chance of observing specific clinical effects of interest, and, hence, just a narrow subgroup of the actual patient population in the accordant indication is selected for trial participation. In the further course of drug development, latest when confirmatory trials are undertaken, the study patients more closely mirror the actual target population by applying inclusion and exclusion criteria reflecting as much as possible the target population. On the other hand, it needs to be considered that the patient population should be sufficiently homogenous to precisely estimate treatment effects. An individual clinical trial can never totally represent future patients also due to further possibly influencing factors such as geographical location, medical practice, clinical routine, and treatment patterns including availability of other drugs. The impact of such factors should be reduced wherever possible and subsequently be reflected and discussed when finally interpreting study results.

Hence, robust trial design requires first the selection of an appropriate study population. In order to study a patient population of the appropriate disease state and level of diversity, investigators define inclusion and exclusion criteria that determine the eligibility of a patient for a clinical trial. These criteria can include patient characteristics (e.g., age, performance status) as well as disease- and treatment-specific characteristics (e.g., tumor stage, localization of metastasis, number and type of prior therapies).

One basic requirement is that participants voluntarily consent for trial participation and interventions. Due to voluntariness and other parameters impacting patient selection, the enrolled cohort may potentially and partially substantially differ from the actual target population for which the medication may later be approved. This type of selection bias is called “volunteer bias” and may arise from eligibility criteria and inherent subject attributes including factors such as geographic location, patients’ attitude, health status, education, marital and socioeconomic status, and race. Also subjective exclusion by investigators due to anticipated study compliance or expected overall prognosis can impact patient selection considerably (Gravetter and Forzano 2009). Furthermore, predefined characteristics and narrow inclusion and exclusion criteria may limit the generalizability of trial results to a broader patient population especially for patients with prevalent comorbidities not included in clinical trials. This consideration underscores why experimental treatment’s efficacy (i.e., a measure of success of an intervention in a clinical trial setting) may not necessarily translate into treatment effectiveness (i.e., a measure of its value in the real world).

When selecting the patient population to be studied in a clinical trial, investigators should include patients who are likely to benefit from the intervention being tested. Additionally, the population should be selected under the consideration that the results of the trial should be generalizable to patients in clinical practice. With increasing diversity of the patient population,

study results may to a broader patient population be more generalizable.

Definition of a Comparator

In controlled trials, the agent or regimen being investigated is compared to a control. The control may be either a placebo or a standard treatment – one in wide use and considered effective at the time the trial is designed (Umscheid et al. 2011; ClinicalTrials.gov). Although placebo is sometimes used as a control in clinical trials, it is rarely used in oncology trials, where there may be ethical issues with this approach. It is important to note that because some clinical trials take months or even years to complete, the standard treatment may no longer be in wide use by the time results from the trial are reported.

Calculating the Right Sample Size

The estimation of sample size is a key issue in RCTs. Its purpose is to enroll an adequate number of subjects with a given confidence on the number that may be affected by sampling error (Arya et al. 2012; Flecha et al. 2016). Thus, the researcher will get the data in a shorter period, cost-effectively and following ethical principles. A proper estimation of the sample size is essential to avoid the occurrence of errors Types I and II. The size can be estimated using a mathematical formula which will depend on the purpose, nature, and parameters investigated in the RCT. However, the decision to choose the appropriate values of the parameters required for calculation is not always simple (Naing et al. 2006). It is, therefore, crucial that study authors present the estimated sample size through statistical principles.

To adequately address the "primary question (s)" of interest, a sufficient sample size is required to have enough power to detect a potential statistical difference. Traditionally, power is defined as having at least an 80% chance of finding a statistically significant difference between the outcomes of two interventions when a clinically meaningful difference exists. The outcomes or endpoints of the investigation can be objective (e.g., death) or subjective (e.g., quality of life) and must always be reliable and meaningful measures. Statistical analyses commonly used to analyze outcomes include logistic regression analysis for dichotomous endpoints (e.g., event occurred or did not occur), Poisson regression for rates (e.g., number of events per patient or years), Cox regression analysis for time-to-event endpoints (e.g., survival analysis), and linear regression for continuous measures (e.g., weight).

Planning Statistical Analysis

The importance of the correct use of statistical analysis lies in the researcher's interest to better interpret, organize, and analyze research data. In addition, through statistics, it is possible to draw conclusions and make predictions for the population as well as assist in decision-making. In a clinical trial, after identifying the groups to be compared, it is necessary to define the dependent variable response that will be applied to test the hypothesis.

It is usual to set as the hypothesis of interest the lack of difference between groups, known as the null hypothesis. The alternative hypothesis is a second statement which contradicts the null hypothesis, that is, that there is no equality between the groups. These two cases cover all possible values (0–1) for the statistical hypothesis test with finally one of the two statements being true. The null hypothesis is rejected if the p-value enhances the specifically defined limit, which is usually set as 0.05 in the medical field indicating that there are significant differences between the groups when the calculated p-value is less or equal to 0.05. The p-value indicates the probability that Type I error has occurred. The calculation of p-values is useful either to support the evaluation of a specific difference of interest or as a flagging device applied to a large number of safety variables to highlight differences worth further attention. It needs to be considered that this statistical significance does not necessarily imply clinical significance (Pagano and Gauverau 2012).

An alternative to statistical analyses that are based on the *p*-value is the size effect analysis that aims to determine the clinical significance of the detected effect, which is not limited to dichotomous outcomes (significant or not significant). In other words, this statistical model is an appropriate measure to determine the clinical

significance of the clinical procedure proposed by the RCT. In addition, it will enable to determine whether the sample size was adequate to get enough statistical power (Flecha et al. 2016; Naing et al. 2006). Thus, through the use of size effect analysis, it is possible to identify whether the observed differences are small, medium, or large (Steinberg and Thissen 2006).

The most common approach in analyzing phase 3 trials is the intention-to-treat (ITT) analysis, in which subjects are assessed based on the intervention arm to which they were randomized, regardless of the treatment they actually received. This is commonly known as the "analyzed as randomized" rule. A complementary or secondary analysis is an "as-treated" or "per-protocol" analysis, in which subjects are evaluated based on the treatment they have actually received, regardless of whether they were randomized to that treatment arm. ITT analyses are preferable for the primary analysis of RCTs, as they eliminate selection bias by preserving randomization; any difference in outcomes can therefore be attributed to the treatment alone and not confounders (Umscheid et al. 2011). In contrast, an "as-treated" or "per-protocol" approach may eliminate any benefit of random treatment selection in an interventional trial, as it estimates the effect of treatment received. The study thereby becomes similar to an interventional cohort study with the potential for treatment selection bias. If adherence in the treatment arm is poor and contamination in the control group is high, an ITT analysis may fail to show a difference in outcomes. In contrast, a per-protocol analysis takes these protocol violations into account.

The investigation of safety and tolerability is a multidimensional problem. Although some specific adverse effects can usually be anticipated and specifically monitored for any drug, there is a wide range of possible adverse effects, and new and unexpected side effects are always possible. Furthermore, an adverse event experienced after protocol violation, such as the use of a prohibited medication, may introduce a bias. In addition, there might be geographic variations in the reporting of adverse events. Finally, it should be outlined again that adverse events do not necessarily represent side effects of the treatment tested but events occurring in patients while enrolled on the trial regardless of the underlying causality. Considering these aspects, statistical difficulties associated with the analytical evaluation of safety and tolerability of drugs are obvious. Finally, conclusive information from confirmatory clinical trials in this regard is the exception rather than the rule. In most trials, the safety and tolerability implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this supports interpretation. It is also valuable to make use of graphical presentations in which patterns of adverse events are displayed both within treatment groups and within subjects.

Endpoints of Clinical Trials

Primary and Secondary Endpoints

Efficacy and safety in clinical trials are measured by predetermined endpoints or outcomes (ClinicalTrials.gov). In uro-oncology trials, these include clinical endpoints, such as overall survival or cancer-specific survival, as well as surrogate endpoints, which are expected to predict a clinical outcome by assessing short-term or intermediate-term endpoints (Brenner 2008).

The primary endpoint is the key measure from which clinical benefit is assessed and has to be selected prior to defining the study sample size (Stanley 2007). The primary endpoint or target variable should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. Mostly there is just one single primary variable, but combined or co-primary endpoints are selected increasingly. In uro-oncology, especially in trials in the field of advanced prostate cancer (PCA), e.g., overall survival (OS) and radiographic progression-free survival (rPFS) are used as co-primary endpoints.

The primary endpoint will usually be an efficacy variable, as the primary objective of most confirmatory trials is to provide strong evidence with regard to efficacy. Less frequently in uro-oncology trials, also safety and tolerability are selected as primary variables; nonetheless, their application as secondary and exploratory

endpoints reflects their importance. Measurements relating to quality of life and health economics are further potential primary variables depending on the primary objective of the trial. For selection of the primary variable, it should be considered that it needs to reflect accepted norms and standards in the relevant field of research. Additionally, it is recommended to use reliable and validated variables with previous experience retained from earlier studies. Sufficient evidence needs to be available that the primary variable provides a valid and reliable measure of a clinically relevant and important treatment benefit in the defined patient population. The primary variable is used when estimating the sample size.

In summary, the selection of the primary endpoint in a clinical trial requires the consideration of several factors:

(a) Which endpoint reflects the most clinically meaningful measure of benefit?
(b) Which endpoint could guide treatment decision-making in this disease state and patient population?
(c) Can the trial be conducted in a reasonable time frame when using a specific endpoint? For example, some endpoints require longer follow-up than others which lengthens the time required to complete trials and obtain meaningful results (Lebwohl et al. 2009).
(d) Can a sufficient number of patients be recruited to complete the trial? This consideration is especially relevant in trials where surgical procedures are tested and recruitment generally may be compromised. Some endpoints necessitate larger trials in order to demonstrate statistically significant differences between arms, which potentially results in recruitment and enrollment challenges. Furthermore, treatment environment might change during the enrollment period with other drugs coming to the market (Lebwohl et al. 2009).

Next to primary endpoints, secondary endpoints are chosen to provide additional and potentially valuable information about the treatment being tested. The trial protocol should prespecify secondary endpoints to increase the likelihood that statistical analysis of those endpoints will be valid (Chin and Lee 2008). Secondary variables are either supportive measurements related to the primary objective or measurements related to the secondary objectives. Their predefinition in the protocol is important, as well as an explanation of their importance for interpretation of trial results. The number of secondary variables should be limited and should be related to a limited number of clinically relevant questions (Umscheid et al. 2011).

Composite Variables and co-Primary Endpoints

If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine multiple measurements into a composite variable by using a predefined algorithm. The primary variable sometimes arises as a combination of multiple clinical measurements (e.g., rating scales which are mainly used in psychiatric disorders). This approach addresses the multiplicity problem without requiring adjustment to the Type I error. The method of combining multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit. Is a co-primary endpoint applied as primary variable, the components of this variable may be analyzed separately, where clinically meaningful and validated. This has been done, e.g., in clinical trials in metastatic castration-resistant prostate cancer (CRPC) where rPFS and OS were used simultaneously as primary endpoints. When a rating scale is used as a primary variable, it is especially important to address such factors as content validity, inter- and intra-rater reliability, and responsiveness for detecting changes in the severity of disease.

Surrogate Endpoints (SEP)

When direct assessment of the clinical benefit to the subject through observing actual clinical efficacy is not practical, indirect criteria may be considered. Commonly accepted surrogate variables are used in a number of indications where they are believed to reliably predict clinical benefit. A surrogate

endpoint is often chosen in place of a primary endpoint to enhance study efficiency (i.e., less cost and time, improved measurability, and smaller sample size requirement). Ideally, the surrogate should completely capture the effect of the intervention on the clinical endpoint, as formally proposed by Prentice. Based on the definition by Prentice, there are four criteria defining an endpoint as SEP based on statistical validation purposes (Prentice 1989; Ellenberg and Hamilton 1989):

- The intervention has a significant impact on the SEP.
- The intervention has a significant impact on the actual endpoint.
- There is a significant association between the SEP and the actual endpoint independent from the intervention.
- The effect of the intervention on the actual endpoint can be explained by the use of the SEP.

However, several endpoints and markers pretended to represent SEPs have mistakenly been named SEP as Prentice criteria were finally not entirely met. One must be cautious when relying on surrogates, as they may be erroneously implicated in the direct causal pathway between intervention and true outcome (Strom 2004; Temple 1999).

As surrogates are commonly employed in phase 1–2 trials, it is highly likely that a high proportion of clinically effective therapeutics are warped due to false-negative results using such endpoints. It is important to validate surrogates as reliable predictors of clinical endpoints using meta-analyses and observational studies including large population cohorts; in conjunction, biological plausibility should be ensured.

Finally, there are two main concerns with proposing surrogate variable. First, surrogates may not truly predict the clinical outcome of interest. For example, it may measure treatment activity associated with a specific pharmacological mechanism while not providing full information on the ultimate treatment effects. There have been many instances where treatments showing a highly positive effect on a proposed surrogate have been shown to be detrimental to clinical outcome; conversely, there are cases of treatments conferring clinical benefit without measurable impact on proposed surrogates while impacting the outcome of interest in a positive way. For example, in trials testing vaccination (Sipuleucel-T) in the indication of early mCRPC, OS was significantly improved, while there was no significant impact on PFS which would reflect the surrogate (Kantoff et al. 2010). Such scenarios also reflect that there may be a detrimental effect by negatively judging a putative surrogate marker, when patients are subsequently taken off treatment. Second, proposed surrogate variables may not yield a quantitative measure of clinical benefit that can be directly weighed against adverse effects. Statistical criteria for validating surrogate variables have been proposed, but the experience with their use is relatively limited. In practice, the strength of the evidence for surrogacy depends upon the biological plausibility of the relationship, the demonstration of the prognostic value for the clinical outcome in observational studies, and the evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome. Furthermore, a relationship between clinical and surrogate variables for one drug does not necessarily apply to drugs with different mechanisms of action even if applied in the same disease.

The problem of defining SEPs for clinical trials and clinical routine represents also a considerable hurdle in the field of PCA, mainly (m)CRPC. Despite some recent successful attempts in addressing this issue, there is still limited evidence for short- and intermediate-term endpoints which could serve as SEPs for OS. Approved compounds in the field of advanced PCA and CRPC are increasingly applied also at earlier disease stages and in a sequential manner; it is thus increasingly difficult to attribute significant OS improvement to a single compound (De Wit et al. 2014). For clinical trials and clinical decision-making alike, appropriate early surrogate markers for clinical benefits due to a specific treatment are warranted. Furthermore, early proof of efficacy would imply a potential health

economy benefit. To date, however, none of the parameters currently considered as potential SEP in the CRPC setting was able to fulfill all the Prentice criteria for the endpoint OS. One example for a potential SEP is PSA decline during treatment, which is often considered to mirror treatment effects (Scher et al. 1996). On the one hand, PSA is a proper biomarker for screening purposes and an excellent marker for detecting biochemical recurrence subsequent to radical prostatectomy. However, in later tumor stages and later lines of treatment, the correlation between changes in PSA values, clinical failure, and survival is controversially discussed (Vicini et al. 2005). Correlation with OS has even been questioned in earlier stages, e.g., after salvage treatment in patients with recurrent disease (Simmons et al. 2007; Aus 2007). Especially non-cytotoxic compounds may impact PSA expression independently from their effects on tumor progression and survival (Thuret et al. 2008). Another potential surrogate marker is imaging, e.g., technetium Tc99m bone scans. However, also rPFS could not be proven to reflect OS reliably, which may be related to reduced specificity due to osteoblastic activities in reparatory or inflammatory processes. Furthermore, especially in trials with the newer hormonal compounds (but also for docetaxel) as well as in clinical routine, bone scan flares are regularly reported, which may lead to potential misinterpretation of results as tumor progression (Thuret et al. 2008; Ryan et al. 2011; Berthold et al. 2008). Impressive results have also been reported for treatment with cabozantinib (c-met/VEGF-TKI); however, the most recent reports on clinical benefit and OS improvement question the value as surrogate markers (Hussain et al. 2011). In addition, different definitions of PFS applied in clinical trials (based on PSA, radiographic progression, or as composite endpoint) impact outcome assessment, an effect which is increased by the use of compounds with different mechanisms of action including immunotherapy with limited impact on PFS as compared to OS (Hussain et al. 2011; Scher et al. 2007, 2008; Halabi et al. 2009; Kelly et al. 2010; Michaelson et al. 2014). Finally, also the mechanism of action impacts SEPs. Accordant criteria which could represent SEPs with a strong correlation to OS are currently assessed in most phase 2/3 trials in advanced PC.

In addition to the general hurdles related to SEP development, there are several requirements for acceptance of SEPs for regulatory purposes and health authorities, e.g., a treatment benefit has to be proven. Furthermore, surrogate markers need to be prospectively validated and confirmed in a couple of phase 3 trials and ideally reflect effects of different mechanisms of action in the same disease setting. Currently OS and in addition skeletal-related events (SREs) are accepted to reflect this in PCA. Besides these, also continuous quality of life and prolongation of the time until reduction of quality of life are considered additional endpoints coming on top of OS improvement. Particularly robustness and accuracy of predictive and surrogate biomarkers have to be confirmed in different settings and trials before considered reliable during the approval and benefit assessment process of new compounds. Characteristics of accepted endpoints are, e.g., defined in the National Cancer Institute, FDA, and Centers for Medicare and Medicaid Services' Oncology Biomarker Qualification Initiative, which is part of the FDA Critical Path Initiative (US Food and Drug Administration Website 2000; Altar 2008).

Recently joint efforts have been made especially by the Development of Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) Working Group. ICECaP is an international collaboration to identify valid surrogates for OS when assessing the efficacy of new therapies for localized PCA. One meta-analysis analyzed data from early-stage disease randomized trials and confirmed that metastasis-free survival represents a valid and reliable surrogate for OS in this disease setting (Xie et al. 2016). Furthermore, the group performed a decision analysis on the cost and health effects of implementing approval of an adjuvant therapy for PCA based upon disease-free survival as a surrogate endpoint for OS.

Patient-Reported Outcomes (PROs) and Endpoints and their Increasing Relevance in Clinical Trials

There are several more potential endpoints identified (and partially validated). This aspect will be outlined in this subchapter for patients with advanced PCA and CRPC. Particularly markers considering the individual and subjective patient status are becoming increasingly relevant, especially with regard to assessing the efficacy of new compounds regarding PRO and patient-relevant endpoints in clinical trials. Ostensibly, the trust in tumor-associated parameters such as Gleason score or tumor stage and objective parameters such as laboratory parameters is lower than the trust in putative subjective PROs. However, on a second view and based on the current evidence, one should be aware that PROs might better predict OS and other intermediate endpoints than standard laboratory values (Cella 2014).

The Eastern Cooperative Oncology Group (ECOG) performance status and tumor-related pain also constitute prognostic variables. Pain is the most established PRO in the CRPC patient population and is associated with inferior survival and diminished quality of life (Halabi et al. 2008; Fisch et al. 2012; Autio et al. 2016; Armstrong et al. 2007). When pain is selected as important component or primary endpoint of a study, the Prostate Cancer Working Group 3 (PCWG3) recommends a baseline assessment using serial measurements, including pain intensity, pain interference, and opiate intake over several days before treatment starts, using methods described by the FDA (Basch et al. 2014). Physical functioning should also be assessed and can be measured at baseline and during treatment using an established multi-item questionnaire such as the physical function measure of the European Organization for Research and Treatment (EORTC) of Cancer Quality of Life Questionnaire C30 or Patient-Reported Outcomes Measurement Information System (PROMIS) instruments. Also collection of patient-reported adverse events should be considered at baseline and during treatment using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (Basch et al. 2017).

Adverse Event and Patient-Reported Outcomes (PROs) Reporting in Clinical Trials

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses (Scher et al. 2016; Cohen 1992).

All clinical trials have the potential to produce AEs. AEs are classified as serious or nonserious, expected or unexpected, and study related, possibly study related, or not study related. A serious adverse event needs to fulfill one of the following criteria: death, life-threatening event, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly/birth defect, and other important medical events. Relationship to study treatment would be assessed by the local researcher based on his/her medical judgment to determine whether the death could have been related to the study device. An adverse event can also be declared in the normal treatment of a patient which is suspected of being caused by the medication being taken or a medical device used in the treatment of the patient.

Researchers participating in a clinical trial must report all adverse events to the drug regulatory authority of the respective country where the drug or device is to be registered [e.g., FDA in the United States]. Serious AEs must be reported immediately; minor AEs are bundled by the sponsor by collecting AE reports from the local researchers and are submitted later to health authorities. Both the local investigators' and the sponsors' judgments of the seriousness of the AEs will be used to finally assess the relationship of the AE to the study drug.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the general guideline displayed in Table 3.

Table 3 Guidance for adverse event severity grading

Adverse event severity grading	Description
Grade 1	Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care activities of daily living
Grade 4	Life-threatening consequences, urgent intervention indicated
Grade 5	Death related to AE

Collection of patient-reported symptoms related to adverse events from treatment should be considered using the National Cancer Institute's PRO-CTCAE (http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/9781405132664/9781405132664_4_003.pdf). PRO-CTCAE is a measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials and designed to be used as a companion to the CTCAE. It includes an item library of 124 items representing 78 symptomatic toxicities for the assessment of symptoms related to AEs categorized to frequency, interference, severity, and presence/absence/amount. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials.

Conducting the Trial in the Best Possible Way: How to Avoid Bias

The gold standard in clinical research is a scientifically rigorous, randomized, and well-controlled trial. When the trial population, the treatment, and the study endpoints have been identified and defined, the trial design is not yet complete. In phase 3 and some phase 2 trials, the patient population may be randomized and stratified.

According to Pannucci and Wilkins, bias can occur in the planning, data collection, statistical analysis, and publication phases of research. Understanding research bias and how it affects study results allows readers to critically and independently review the scientific literature and avoid treatments which are suboptimal or potentially harmful (Pannucci and Wilkins 2010a).

Bias is defined as "a partiality that prevents objective consideration of an issue or situation." In statistics it means "a tendency of an estimate to deviate in one direction from a true value." This systematic deviation from the actual value can either result in underestimation or overestimation of the intervention effects. As it is usually more appreciated to show that a new intervention works than to showing that it does not, biases in clinical trials most often result in an overstatement in the importance of effects of new interventions. Bias may occur at different stages of a clinical trial and based on various reasons. Most discussions on bias focus on biases that can occur during the trial, from the allocation of participants to study groups through the assignment to interventions and outcome measurements. However, several more types of bias can arise, even before the trial is carried out or after the trial has been finished (Good clinical practice guidelines 1994).

Below we will focus on a number of selected types of bias occurring prior, during, and after the trial.

Bias During Study Planning:

- **Selection bias:** Selection bias can occur both in the way that individuals are accepted or rejected for participation in a trial and in the way that the interventions are assigned to individuals after acceptance to a trial. Randomization is one way to reduce or eliminate selection bias (http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/9781405132664/9781405132664_4_003.pdf).

- **Ascertainment bias:** This type of bias occurs when the results or conclusions of a trial are systematically distorted by the knowledge of the intervention each individual participant is receiving. Ascertainment bias can be introduced by the person administering the interventions, the participants, the investigator assessing or analyzing the outcomes, and even the people who write the clinical study report (http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/9781405132664/9781405132664_4_003.pdf).
- **Choice-of-question bias:** One of the least recognized types of bias is hidden in the choice of the question that the trial intends to answer. This would not necessarily affect the internal validity of a trial but may have profound effects on its external validity or generalizability. There are many forms of this bias, e.g.:
  - *Hidden agenda bias*: This bias occurs when a trial does not aim at answering a question but demonstrating a pre-required answer.
  - *Vested interest bias*: Conversely to the hidden agenda bias, this bias may occur under the unspoken consideration "Don't do a trial if it won't show you what you want to find" (Fries and Krishnan 2004).
  - *Self-fulfilling prophecy bias*: This type of bias occurs when the study is carried out in a way to ensure the desired result.
  - C*ost and convenience bias*: This bias can seriously compromise what investigators choose to study. When it studies what can be afforded or what is convenient rather than answer those questions which are relevant from a clinical perspective, resources relevant for important research are dissipated.
  - *Funding availability bias:* This bias occurs, where studies tend to concentrate on questions that have (for various reasons) a higher chance of receiving funding.
- **Regulation bias (also institutional review board bias, bureaucracy bias)**: When institutional review boards are overly restrictive and block studies addressing important questions, this results in accordant bias (http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/9781405132664/9781405132664_4_003.pdf).
- **Wrong design bias**: The perceived value of an RCT may sometimes induce researchers to use this design for questions that may be better answered with a different design (Berkman et al. 2014). The wrong research design can produce misleading answers.

Biases Occurring During the Trial:

- **Population or sample choice bias**: The sample population studied can have a major effect on the generalizability of study results. If the sample is overly restricted by not including women (*gender bias*) or people belonging to specific age groups (*age bias*), the results may not be generalizable to people who do not belong to the groups. Recruitment bias may occur when population choice is restricted due to specific approached to potential participants.
  - *Severity of illness bias* is an important subgroup of the sample choice bias, occurring when patients with mild forms of diseases may not respond in the same way as those at a more severe stage (http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/9781405132664/9781405132664_4_003.pdf).
- **Intervention choice bias**: The nature of the intervention chosen can have a major effect on the results obtained; also the stage at which an intervention is studied can be very important. The *too early bias* and the *too late bias* can determine the detected effects (Lilford et al. 2000). This holds particularly true for surgical trials where there can be a *learning curve bias* or improvements (or regression) in the techniques.
- **Comparison choice (or control group) bias**: If an intervention is compared to a poorly chosen control group, it can erroneously appear to be more (or less) effective than it really is. If a study compares an experimental intervention with a placebo control, the results will only tell us whether the intervention has a specific effect

or not, but it will not imply that the experimental intervention has a different or better effect than existing alternatives (http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/9781405132664/9781405132664_4_003.pdf).

- **Outcome choice bias**: Sometimes RCTs evaluate outcomes that are easy to measure rather than relevant outcomes (*measurement bias*) (http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/9781405132664/9781405132664_4_003.pdf).
- **Performance bias**: This bias may occur if additional treatment interventions are provided preferably for a group. Blinding of patients and of those involved in the application of interventions prevents this bias and also protects against placebo differences in responses between the groups.

Biases Occurring During the Reporting of a Trial:

- **Withdrawal bias**: This bias is introduced by inappropriate handling of withdrawals, dropouts, and protocol violations. Ideally, all trial participants should complete the study, follow the protocol, and provide data on all the outcomes of interest at defined time points. In reality, most trials have missing data, e.g., as participants drop out before the end of the trial, because participants do not follow the protocol deliberately or accidentally or because outcomes are not measured correctly.
- **Selective reporting bias**: A major and common source of bias is selective reporting of results, by describing outcomes with positive results or which favor the studied intervention. The investigator may even unconsciously be attracted more to certain outcomes than others. Variants are the *social desirability bias* in which the items that are desired, or the *optimism bias* in which the items hoped for, are more likely to be reported.
- **Detection bias**: This bias type arises if the knowledge of the patient's name influences the evaluation of the results. This is avoided by blinding those who assess the results (Jüni et al. 2001).
- **Fraud bias**: Even if hopefully rarely, intentional fraud is perhaps the most important, most serious, and most difficult-to-detect source of bias. The extent to which fraudulent results are reported may be underestimated especially under the pressure to produce results.

Biases Occurring During the Dissemination of the Trials:

- **Publication bias**: Investigators and sponsors are more likely to write and submit, and peer reviewers and editors are more willing to accept manuscripts with positive results for publication.
- **Language bias**: Recently, a variation of publication bias has been described as *language bias*, to indicate that manuscripts may be submitted to and published by journals in different languages depending on the direction of their results. More studies with positive results may be published in English (Moher et al. 2003).
- **Country of publication bias is a variant of this bias**: That is, the tendency by some countries to publish a disproportionate number of positive trials (Vickers et al. 1998).
- **Time lag bias**: This bias type occurs when the speed of publication depends on the direction and strength of the trial results. It seems that trials with negative results take twice as long to be published as trials with positive results (Ioannidis 1998; Stern and Simes 1997).
- The most important design techniques for avoiding bias in clinical trials are blinding and randomization, and these should be regularly intended to be included in most controlled clinical trials in a marketing application. Most such trials follow a double-blind approach where treatments are prepacked in accordance with a suitable randomization schedule and supplied to the study sites labeled only with the subject number and the treatment period so that no one involved in trial conduction is aware of the specific treatment allocated to

individual subjects. Bias can also be reduced at the design stage by specifying procedures in the protocol to minimize anticipated irregularities that might impair a satisfactory analysis, including protocol violations, withdrawals, and missing values. The protocol should consider actions both to reduce the frequency of such problems and also to handle the problems that occur in data analysis (Flecha et al. 2016).

Randomization

A hallmark of the phase 3 trial design is the balance in treatment allocation for comparison of treatment efficacy. When properly designed, conducted, and reported, RCTs represent the gold standard in the evaluation of health interventions since the randomization of different groups can provide results without bias between groups exposed to different treatment conditions (Jüni et al. 2001). The random assignment to treatment groups aims to ensure that the characteristics of the participants which may affect the results are balanced and treatment groups are produced with similar distribution of known or unknown prognostic factors (Flecha et al. 2016; Polit and Gillespie 2010). This clinical trial practice attempts to eliminate imbalance of confounders or any systematic differences or biases between treatment groups. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects.

The statistical tool of randomization, first introduced to clinical trials by Sir Austin Bradford Hill, was born out of the necessity (and ethical justification) of rationing limited supplies of streptomycin in a British trial of pulmonary tuberculosis (Doll 1992; Hill 1963). Fifty years after the publication of the first RCT, the technical meaning of the term randomization still confuses some researchers. Finally, randomization depends on two processes: generation of an unpredictable designation sequence and the confidentiality of this sequence until the intervention starts. Random allocation presupposes that each patient has a known and usually equal chance of receiving a treatment option as other participants, but the treatment to be given cannot be predicted. The generation or allocation of the sequence is appropriate if the sequences can prevent selection bias, for example, randomized computer-generated numbers, random number table, envelope drawing, coin flipping, card shuffling, dice throwing, etc. (Polit and Gillespie 2010; Altman and Bland 1999). A common approach is also to simply randomize treatments according to the dates of birth, the hospital registration numbers, or the enrollment dates. Although all these approaches are basically unbiased, since they are not related to patient characteristics, problems arise from the accessibility and knowledge of the allocation system. When the treatment is known when a patient is considered for participation in the clinical trial, this knowledge may influence the decision to recruit that patient and thereby produce incomparable groups (Altman and Bland, 1999; Pannucci and Wilkins 2010b).

Randomization based on a single sequence of random assignments is known as simple randomization. Simple randomization can be trusted to generate similar numbers in the two trial groups and to generate groups that are roughly comparable in terms of known (and unknown) prognostic variables. Simple randomization randomly allocates each subject to a trial arm regardless of those already assigned (i.e., a "coin flip" for each subject). Although easy to perform, major imbalances in treatment assignments or distribution of covariates can ensue, making this strategy less than ideal. To improve on this method, a constraint can be placed on randomization that forces the number of subjects randomly assigned per arm to be equal and balanced after a specified block size ("block randomization"). Blocking is used to ensure that comparison groups will be of approximately the same size. For example, in a trial with two arms, a block size of four subjects would be designated as two positions in arm A and two positions in arm B. Even though the positions would be randomly assigned within the block of four subjects, it would be guaranteed that, after randomization of four subjects, two subjects would be in arm A and two subjects would be in arm B. Restricted randomization describes any

procedure to control the randomization to achieve balance between groups in size or characteristics. Stratified randomization is achieved by performing a separate randomization procedure within each of two or more subsets of participants (e.g., those defining age, smoking, or disease severity). Stratification by the center is common in multicenter trials (Altman et al. 2001).

Different trial designs require also different procedures for generating randomization schedules with the randomization schedule being reproducible. Although unrestricted randomization is an acceptable approach, some advantages can be gained by randomizing subjects in blocks. This helps to increase the comparability of the treatment groups, particularly when subject characteristics may change over time, for example, due to changes in the recruitment policy. It also provides a better chance that the treatment groups will be almost equal of size. In crossover trials, it provides the possibility of obtaining balanced designs with their greater efficiency and easier interpretation.

In multicenter trials, the randomization procedures should be organized centrally. It is advisable to have a separate random scheme for each center, i.e., to stratify by center or to allocate several whole blocks to each center. More generally, stratification by important prognostic factors measured at baseline (e.g., severity of disease, age, sex, etc.) may be valuable in order to promote balanced allocation within strata. Such an approach has potential greater benefit especially in small trials. The use of more than two or three stratification factors is rarely necessary and less successful at achieving balance and is logistically troublesome. Factors on which randomization has been stratified should be accounted for later in the analysis (Flecha et al. 2016).

Assessing the quality of randomization of 250 controlled trials and 33 meta-analyses and analyzing the association between these evaluations and the estimated effects of treatment, Schulz concluded that trials in which the allocation sequence was inadequately concealed produced higher estimates of treatment effects than trials in which authors reported adequate concealment (odds ratio exaggerated, on average, by 30–40%) (Schulz 1996). Nonetheless, trials with improper generation sequence led to an estimation of treatment effects similar to those of trials with adequate generation. Thus, the procedure for generating sequence has a lower overall impact on preventing bias than the procedure for concealment (Schulz 1996). This observation makes sense, since having an unpredictable random sequence should make little difference without an adequate concealment.

According to the Acceptance Program Guidelines, clinical trials should include a randomized selection of individuals, should apply a parallel or a crossover design, and should be double-blind (American Dental Association, Council on Scientific Affairs 2012). In combination with blinding, randomization helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

Blinding

The phase 3 trial design often dictates the interventions to be blinded or masked to minimize assessment bias of subjective outcomes. Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial. Such bias arises from the knowledge about treatment and may have an impact on the recruitment and allocation of subjects, the subsequent care, the attitudes of patients to the treatments, the handling of withdrawals and assessment of endpoints, and the exclusion of data from analysis.

Specific blinding strategies include “single blinding” (subject only), “double-blinding” (both subject and investigator), or “triple blinding” (data analyst, subject, and investigator). The double-blind trial represents the optimal approach, where neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of patients are aware of the treatment. This includes anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. This requires that the treatments applied during the trial cannot be distinguished by appearance,

taste, or other parameters and that the blind is maintained appropriately during the whole trial. This level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality, appropriate personnel will be unblinded.

Unfortunately, not all trials can be blinded (e.g., the method of drug delivery cannot be blinded). Also the development of established drug toxicities may lead to inadvertent unmasking and raise ethical and safety issues (Umscheid et al. 2011). The double-blind nature of some clinical trials may be partially compromised by apparent treatment-induced effects. Difficulties in achieving the double-blind ideal can arise: the treatments may be of a completely different nature, e.g., surgery and drug therapy; two drugs may have different formulations, and, although they could be made indistinguishable by the use of capsules, changing the formulation might also change the pharmacokinetic and/or pharmacodynamic properties and hence require that bioequivalence of the formulations be established; the daily pattern of administration of two treatments may differ. In such cases, blinding may be improved by blinding investigators and relevant sponsor staff to certain test results (e.g., selected clinical laboratory measures). One way of achieving double-blind conditions under these circumstances is to use a double-dummy technique. This technique may sometimes force an administration scheme that is sufficiently unusual to influence adversely the motivation and compliance of the subjects. Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the subject's physician for the subject's care. Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence. When appropriate, additional strategies can be applied to enhance study efficiency, such as assigning each subject to serve as his/her own control (crossover study) or evaluating more than one treatment simultaneously (factorial design) (Umscheid et al. 2011).

If a double-blind trial is not feasible, the single-blind option should be considered. In a single-blind trial, the investigator and site staff are aware of the treatment, but the subject is not or vice versa. In an open-label trial, the identity of treatment is known to all. In some cases, only an open-label trial is practically or ethically possible. Single-blind and open-label trials provide additional flexibility, but it is particularly important that the investigator's knowledge of the next treatment should not influence the decision to enter the subject; this decision should be made prior to the knowledge of the randomized treatment. For these trials, consideration should be given to the use of a centralized randomization method. In addition, clinical assessments should be made by medical staff who are not involved in treating the subjects and who remain blind to treatment. In single-blind or open-label trials, every effort should be made to minimize the various known sources of bias, and primary variables should be as objective as possible, and steps taken to minimize bias should be outlined in the protocol.

Blinding (or masking) should not be confused with allocation concealment. The allocation concealment is intended to prevent selection bias, protecting the designation sequence before and until allocation occurs. It can always be successfully implemented. However, blinding seeks to avoid determination bias and protects the sequence after allocation, which cannot always be implemented (Moher et al. 2003).

In their review, Schulz et al. concluded that studies that were not double-blind yielded larger estimates of effects than double-blind trials (odds ratio exaggerated, on average, by 17%) (Schulz 1996). Double-blinding and avoidance of exclusions after trial entry are the most important methods for reducing bias. Although the strength of this effect falls short of that for allocation concealment, double-blinding appears to prevent bias (Schulz 1996). Finally, randomization controls the selection bias, and the double-blind design controls the observer bias.

Stratification

Another feature of phase 3 trial design is stratification, which is commonly employed in

combination with randomization to further balance study arms based on prespecified characteristics. Stratification is the division of the study population into subgroups, also referred to as "strata" or "blocks" with each stratum representing a particular section of the patient population. This measure facilitates analysis by ensuring that specific prognostic factors of presumed clinical importance are properly balanced in the trial arms (Scott et al. 2002). For example, patients could be divided up according to age, gender, ethnicity, social background, medical history, or any other factors that are considered relevant. Groups of subjects are then included in the clinical trial to match each of these groups within the patient population. In PCA clinical trials, patients might, e.g., be stratified according to Gleason score, risk classification, N/M stage, and additionally non-tumor-related parameters such as geographical region which might have a considerable impact on treatment patterns.

Clinical Trial Oversight

Historic abuses and recent calamities highlight the importance of institutional review boards (IRBs) and independent data monitoring committee (IDMC) in ensuring that human research goes conform with national and international standards of safety and ethics (Mello et al. 2003; Steinbrook 2002).

IRBs are charged with protecting the rights and welfare of human subjects involved in research conducted or supported by federal departments (Umscheid et al. 2009). In order to ensure compliance with strict and detailed guidelines, IRB members are authorized to approve and request modifications or reject research activities. General criteria for IRB approval include (1) risks to subjects are minimized and are reasonable in relation to benefits, (2) selection of subjects is equitable, (3) informed consent is sought, (4) sufficient provisions for data monitoring exist to maintain subjects' safety, (5) adequate mechanisms are in place to ensure subject confidentiality, and (6) rights and welfare of vulnerable populations are protected (Umscheid et al. 2009).

IDMC boards may be established by the sponsor to assess at prespecified intervals the progress of a clinical trial, safety data, and efficacy parameters; further, recommendations to the sponsor whether to continue, modify, or terminate a trial can be provided. The independence of the IDMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The IDMC should include clinical trial scientists knowledgeable in the appropriate disciplines including statistics. Besides safeguarding the interests of study subjects and preserving the integrity of the trial, IDMC also ensures that definitive and reliable trial results are made available in a timely fashion to the medical community (Ellenberg et al. 2002). Specific responsibilities include monitoring data quality, study conduct (including recruitment rates, retention rates, and treatment compliance), drug safety, and drug efficacy. Outcomes from IDMC activities can include, e.g., an extension of recruitment strategies, if the study is not meeting enrollment goals; changes in study entry criteria, procedures, treatments, or study design; and early closure of the study due to safety issues (external or internal), slow recruitment rates, poor protocol compliance, or clinically significant differences in drug efficacy or toxicity between trial arms (Ellenberg et al. 2002).

The role of the IDMC should be clearly defined in the operating procedures of the committee. Furthermore, the IDMC should maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. IDMC members ideally should be free of significant conflicts of interest and should be the only individuals to whom the data analysis center provides real-time results of treatment efficacy and safety.

Finally, the complexity and expense of monitoring human research have prompted the establishment of contract research organizations to oversee clinical trials. They are commonly commercial or academic organizations hired by the study sponsor "to perform one or more of a sponsor's trial-related duties and functions," such as organizing and managing an IDMC or managing and auditing trial data to maintain data quality

(Umscheid et al. 2011; Guidance for Industry 1996).

The Ethical Foundation of Clinical Trials

Principle of Equipoise

Depending on the predefined clinical research question and statistical considerations, RCTs are frequently designed to determine superiority, non-inferiority, or equivalence of an experimental intervention relative to established standard of care or placebo (Zhang et al. 2014; Akobeng 2008). Before randomly assigning patients to one or more of the competing study arms, investigators involved in design and conduction of clinical trials need to be free of any treatment preferences, which means there is genuine uncertainty about the best treatment regimen for the disease of interest (Fries and Krishnan 2004; Freedman 1987). This so-called principal of equipoise represents an ethical prerequisite for conducting an RCT. However, clinical investigators commonly face the dilemma where emerging data (e.g., arising from preceding phase 2 trials) provide a strong signal of efficacy for an experimental treatment. Additionally, the existing standard-of-care treatment, even if considered efficacious, is normally in need of improvement due to minor impact on an otherwise unfavorable course of a disease (Spieth et al. 2016). Once there is no longer clinical or personal equipoise, continuation of and contribution to an RCT should be reconsidered; otherwise serious biases may be introduced (e.g., selection bias) (Fries and Krishnan 2004).

Preplanned interim analyses at certain time points or recruited sample sizes during an ongoing RCT aid in maintaining clinical equipoise (Fleming et al. 2008). Trial data are analyzed for benefit, harm, or futility, and decisions on continuation or termination of the trial will be made by an IDMC board according to clinical equipoise (e.g., large effect size suggests superiority of one treatment over the other, and clinical equipoise no longer exists) and further considerations. However, it should be noted that repeated significance testing on accumulating data results in the need to adjust the hypothesis in order to maintain the overall significance level.

Ethical Considerations Within Clinical Trials in Urology

Modern investigators must be aware of the ethical aspects surrounding clinical trials and should aim to exceed the expectations and requirements from their review boards. Given the characteristics of the urological patients in oncology, significant issues are frequently encountered.

First of all, an important clinical question needs to be formulated. Researchers need to think about their research question ensuring that it is based on solid scientific principles enhancing the knowledge within the field. Patients enrolled in a clinical trial should be confident that their participation should result in a valuable scientific contribution. Secondly, in order to best protect the rights of individual patients, investigators should adhere to the principles of autonomy, beneficence, and justice based on the Belmont Report (The Belmont report 2000). Autonomy implies that the individual should make important decisions intentionally and free of external influence. Beneficence hints at the responsibility of the investigator to maximize positive outcome of the trial for each patient. This is a fundamental principle of the Hippocratic oath along with the responsibility to "do not harm" and thereby minimize the potential negative outcomes of the trial. Justice dictates that the design and implementation of a clinical trial need to be fair to the participants. Patient selection needs to be free of bias and drawn from a relevant patient population (The Belmont report 2000).

The Council for International Organizations of Medical Sciences (CIOMS) and the World Medical Association (WMA) have both published guidelines for the ethical management of biomedical research. The CIOMS provides 21 guidelines related to ethical justifications and scientific validity of research, informed consent, and equity regarding burden and benefit among other issues.

The CIOMS guidelines were updated in 2016 with special emphasis on the scientific and social responsibility (van Delden and van der Graaf 2016).

The WMA Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) was first adopted in 1964 and has undergone several revisions, the most recent in 2013. The last revision highlights the need to disseminate research results, including negative and inconclusive studies. It also includes a requirement for treatment and compensation for injuries related to research. Moreover, the updated version is felt to be more relevant to limited resource settings – specially addressing the need to ensure access to an intervention if it is proven effective. Some publications have evaluated the discontinuations and nonpublication rates of surgical clinical trials in the United Kingdom. Out of 395 surgical clinical trials registered (18 in urology), almost 25% were discontinued early (44% of them due to poor recruitment); 66% had a completed publication at a median of 5 years from study completion. Industry funding (over 60% of RCT in surgery) was clearly associated with a decreased likelihood of publication (OR 0.43; 95% CI 0.26–0.72; $p = 0.001$) (Chapman et al. 2014).

Overall, both sets of guidelines provide an excellent framework for the ethical conduct of biomedical research and are of benefit when preparing research proposals for institutional review.

Any clinical trial that aims to be ethically formulated needs to provide a freely given informed consent. The consent must be legalized according to the nation's law system and should also conform the principles stated by the Declaration of Helsinki and CIOMS. Additionally, in the event that pertinent information becomes available during the course of a trial, it is the investigator's responsibility to advise the participants of any information that pertains to the informed consent. The potential study subjects should be provided with an overview of the rationale for the proposed research in order to decide on their participation. This includes informing subjects of their responsibilities during the trial (i.e., taking the medications, follow-up appointments) as well as any procedures that will be performed. There should be an honest and open communication between the person recruiting and the subject. No fear of reprisal should exist if subjects decline participation. Patients need to be explained the inclusion and exclusion criteria. Participants require to obtain detailed explanations of risks and benefits of participation in the trial at the time of consent. Risks refer to the potential mental and physical injury as a result of the participations in the study. An explanation of the solutions to tentative issues should also be provided. The benefits of the inclusion should also be part of the consent including an improvement in the symptoms or condition. It is mandatory to explain alternative treatments as well as potential benefits for society. Additionally, patients recruited to surgical trials are to be informed about the risk of early termination or nonpublication.

Confidentiality is also an important part of the written informed consent. It needs to be maintained from consent till the study conclusion. Personalized information including subject's name, date of birth, and ethnicity along with any other personal identifiers must remain confidential. Study participants should be notified at the time of consent if any personal identifiers will be disclosed during the course of the trial and what measures will be taken to maintain confidentiality. If the trial implies photography or video, the participants need to be aware that they have the right to access such files any time.

The information regarding the informed consent, confidentiality, compensations and costs, voluntary participation, as well as contact information needs to be provided in a written material in lay language in a clear and understandable manner. The informed consent has to be signed and dated by both the participant and the individual obtaining the consent, although verbal consent is allowed by some review boards in some instances.

Precision Medicine, Genomics, and Molecular Testing in Clinical Trials

The practice of clinical trials is evolving to keep pace with these advances in the scientific understanding of cancer. Already less very large trials

are conducted in which all patients with the relevant disease stage regardless of the underlying biology of their cancer are randomly assigned to receive the experimental or control treatment. Such large trials require a large number of patients to detect an effect as often a limited number of patients respond to the experimental therapy to draw a definitive conclusion.

Hence, understanding the need to include selected patients only for trial participation based on a very specific patient profile and an enhanced chance for treatment response was the first step for precision medicine and the development of personalized clinical trial conduction and patient selection based on underlying molecular and genetic testing. Over the last decades, biomedical researchers have begun to unravel cancer's immense complexity, drilling down to the molecular level to better understand the genetic and biological changes that drive how cancers develop, grow, and spread. The greater understanding of cancer and how tumors behave at the molecular level has allowed scientists to develop a new generation of targeted drugs and immune-based therapies, identify biomarkers that can be used to guide therapy and select patients who are most likely to respond to a drug, and develop novel strategies to detect difficult-to-treat cancers early.

The consequence is that clinical trials need to be adapted to build on new research insights that target molecular alterations and only test the experimental therapy in the selected population which can increase the speed and efficiency of clinical trials, as only the patients most likely to benefit are included in the trial.

The Relevance of Genomic Research for Urological Cancers and for Clinical Trials in Uro-Oncology

Precision medicine has the highest potential to impact the care of patients. The study of cancer genomes has revealed abnormalities in genes that drive the development and growth of many types of cancer. This knowledge has improved our understanding of the biology of cancer and led to new methods of diagnosing and treating the disease. Over the past decade, large-scale research projects have begun to survey and catalog the genomic changes associated with a number of types of cancer. These efforts have revealed unexpected genetic similarities across different types of tumors. For instance, mutations in the *HER2*gene have been found in a number of cancers, including the breast, bladder, pancreatic, and ovarian. Researchers have also shown that a given type of cancer may have several molecular subtypes. For several cancer types, the existence of certain subtypes had not been known until researchers began to profile the genomes of tumor cells, and for several tumors, the amount and genomic specifics of subtypes are still not known yet.

Whereas the discovery of cancer-causing genetic and epigenetic changes in tumors has not yet enabled the approval of drugs specifically for defined genomic alterations or diagnostic tests in uro-oncology, this is the case already in other oncology diseases, such as melanoma. For example, vemurafenib (Zelboraf®) was approved by the FDA in 2011 for the treatment of patients with melanoma who have a specific mutation in the *BRAF* gene detected by an FDA-approved test. For the near future, however, genomic target-specific diagnostics and treatment have to be expected for urological tumors as well. For example, in PCA, clinical trials are now conducted selecting patients based on the presence of specific markers, including BRAC1 and BRAC2 genes.

Opportunities and Challenges in Cancer Genomic Research in Urological Tumors

Also for other urological cancers, there is a diverse landscape of genetic alterations which needs a proper foundation for understanding the molecular basis of this group of diseases. The recent advances in molecular profiling have led to a rapid expansion of biomarkers and potential predictive information for patients with urologic malignancies. Across disease states, distinct molecular subtypes have been identified, with

the potential to inform choices of management strategy. Biomarkers predicting response to standard therapies (such as platinum-based chemotherapy) are emerging. In several malignancies particularly renal cell carcinoma (RCC) and CRPC, targeted therapy against commonly altered signaling pathways has emerged as standard of care. Finally, targeted therapy against alterations present in rare patients (defined as less than 2% of the patient population) across diseases has the potential to drastically alter patterns of care and choices of therapeutic options.

However, actively conducted molecular or genomic precision medicine in clinical trials is still in the fledgling stages and needs further development overcoming some hurdles.

Although mutations that drive the development and progression of cancer types have been identified in large-scale research studies, urological tumors have not yet been deeply characterized. New technologies and knowledge gained from previous genomic studies could be used to define the full set of driver mutations in many cancers. For example, the ability to compare tumor and normal DNA from the same patient may allow discovery of potential driver mutations for tumors.

Comprehensive analysis of cancer genomes has revealed a great diversity in the genetic abnormalities within one single type of cancer. Moreover, recurrent genetic alterations within these cancers are often involved in only a small percentage of cases. Discovering rare genetic alterations is therefore an ongoing challenge.

Another hurdle is represented by the need to acquire high-quality biological samples, particularly for uncommon or tumor types or those not primarily treated by surgery.

Another need is to expand the current use of genomic methods to investigate the molecular basis of clinical phenotypes. This approach could help to identify genetic changes which may distinguish aggressive and indolent cancers. Similar approaches could be used to study the molecular basis of a specific treatment response as well as mechanisms of resistance to treatment.

- The wealth of data emerging from cancer genome studies will be increasingly integrated with patients' medical histories and clinical data. Such information could be used to develop more tailored approaches to diagnosis and treatment, as well as to improve methods of predicting cancer risk, prognosis, and treatment response.
- Developing cell lines and animal models capturing the diversity of human cancer is still an unmet need. Models of rare cancer subtypes may be underrepresented or do not even exist.
- Genomic tools will also be essential for analyzing results from precision medicine clinical trials. Managing and analyzing the vast amount of data involved in genomic studies are additional challenges for the field. This area of research requires an efficient bioinformatic infrastructure and a strong expertise provided by cross-disciplinary teams.
- Further prospective studies in the setting of clinical trials including patients under study treatment and standard of care are needed and will help define reliable predictive biomarkers and new therapeutic targets leading to real improvement in patient outcomes.
- Finally, cancer genomic research comprises chances and opportunities but also adds further ethical responsibility to researchers and physicians, when genomic data are generated including putative, but not yet proven value related to disease risk, progression, and treatment response prediction. Not only benefit but also harm may result from haphazard use of genomic information inside and outside clinical trials, considering also the dilemmas patients and their relatives may face alongside with specific knowledge about (insufficiently validated) genomic markers.

Specific Considerations Related to Clinical Trials in Uro-Oncology

Medical Tumor Treatment

Generally, the principles for clinical trials in uro-oncology are the same as for all other clinical trials as outlined in this book chapter. On the other hand, there are some disease-related specifics to

the single diseases which need to be considered when planning a clinical trial. Such considerations mainly relate to the individual patient population, the disease state, the treatment sequence, and the overall treatment landscape present at the time point of trial planning and start. In the framework of a book chapter, it might be difficult to reflect all possible scenarios of individual clinical trial design and conduction.

The authors will focus mainly on PCA in this subchapter, as over the recent years, most clinical trials in uro-oncology have been conducted in this disease. Hence, also the experience in conducting clinical trials including identification of hurdles and recommendations for proper execution might serve as an example for other uro-oncology diseases. Furthermore, the most comprehensive guidance for clinical trial conduction and outcome measurement is provided by the PCWG3 (Scher et al. 2016).

In their recent update, new recommendations have been provided for clinical trial planning and conduction in PCA patients, mainly related to the fact that the treatment landscape has considerably changed over the past years alongside with an improved understanding of the disease biology. These aspects made it even necessary to redefine disease and treatment stages in a different way (Scher et al. 2016). One additional consideration for the recently amended recommendation of the PCWG3 was also to move drug development closer to the unmet needs in clinical practice by focusing on those disease manifestations most likely to affect prognosis adversely.

PCWG3 has reworked the conceptualization of the disease, which means that the disease-state model has been revised in order to define trial objectives on the basis of state-specific clinical needs (Fig. 1) (Scher et al. 2016).

The decision milestones in PCWG3 were based on disease states defined by the status of the primary tumor, presence or absence of distant disease on imaging (metastatic versus non-metastatic), testosterone levels, and prior chemotherapy exposure. Further emphasis has also been placed on designing clinical trials within a biomarker context and focusing on biomarker development for outcome prediction, management guidance, and enhanced clinical decision-making (Table 4). The revised model aligns with the indications and actual uses of currently approved drugs and provides the framework for a decision tree that closely follows contemporary clinical practice. Key recommendations included the differentiation of adenocarcinomas from other histological types such as pure small-cell carcinomas and variants with neuroendocrine differentiation. Furthermore, the pre- versus post-chemotherapy treatment setting has been replaced by treatment sequences, the order in which treatment was administered, and the sensitivity of the tumor to each. In addition, trial designs were developed for the different CRPC phenotypes defined by the pattern of tumor spread as well as for trials in the nonmetastatic CRPC state. Ultimately, the importance of serial biologic profiling of the disease using blood-based assays of tumor material, imaging, or biopsy of metastatic tumor sites has been emphasized with the aim to identifying mechanisms of primary or adaptive resistance and to better select treatment based on disease biology (Scher et al. 2016).

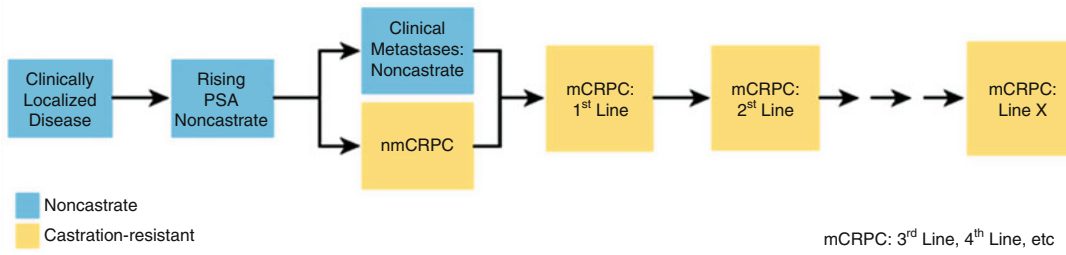

Fig. 1 Redefined prostate cancer clinical states model (Copyright from Prostate Cancer Clinical Trials Working Group 3; Scher et al. 2016)

Table 4 Relevant aspects in clinical trial planning and conduction (Adapted from PCWG3 recommendations 2016)

Trial aspects	Relevant considerations and actions
Clinical tumor states	1. mCRPC should be considered in terms of prior treatment lines rather than in relation to docetaxel treatment 2. Specific systemic treatments should be recorded in the order they were administered, including start and stop dates and response (if available) 3. Different PCA histologies (i.e., small-cell carcinomas, pure neuroendocrine carcinoma) should be distinguished from adenocarcinomas 4. Serial biologic profiling of the disease is important both at the start of a new therapy and time of progression
Principles of trial conduct	1. Posttreatment outcomes reflecting patient benefit or serving as surrogates of benefit for use in regulatory submissions should be discovered and qualified to accelerate drug approvals 2. Consistently report measures of progression in a trial versus the clinical need to continue a particular therapy beyond progression as long as the patient is benefiting from the treatment beyond needs to be distinguished
Eligibility for enrollment	1. Eligibility criteria using clinical and biologic parameters intended to homogenize patients' prognosis while enriching for tumor biomarker profiles most likely to respond to treatment should be applied 2. Testosterone assays that accurately measure levels in the 1–2 ng/dL range performed in a central laboratory should be applied 3. Lymph node size should be assessed on the basis of the short axis. The requirement to be 2 cm in size for measurable disease was eliminated 4. Specific trial designs are needed based on different clinical phenotypes defined by location and distribution of radiographic metastases
Treatment: Defining dose, schedule, and pharmacodynamic markers	1. Pharmacodynamic outcome measures that confirm the mechanism of action and determine a dose and schedule specific to the effect of a particular agent on the malignant process are required 2. Greater focus should be placed on pharmacodynamic biomarkers that establish proof of mechanism and can also be used to determine dose and schedule on the basis of biology and safety rather than safety alone 3. Posttreatment biomarker measurements to assess antitumor activity should be tailored to each agent's mechanism of action at fixed intervals
Baseline disease assessments	1. Baseline assessments should include tumor histology, timing, duration, and response (if available) for all prior systemic treatments and a standardized assessment of blood-based, PRO-based, and imaging-based biomarkers and the molecular characterization of the tumor 2. Information on molecular/biologic subtypes of CRPC in addition to the five clinical subtypes (defined by extent and location of metastases) should be included. Type of progression at trial entry is defined as PSA-only progression, radiographic progression by site of disease spread, or both; for radiographic progression, it should be recorded whether progression was caused by growth of existing lesions, appearance of new lesions, or both
Measuring outcomes and reporting: Blood-based and molecular measures	1. When there are progressing lesions, re-biopsy with histology and biomarker assessment is recommended of the progressing metastatic site 2. PSA outcomes should be interpreted within the context of a drug's mechanism of action, and the anticipated timing of a potential favorable/unfavorable effect on PSA should be considered 3. Definitions have been suggested on how to define and report outcomes related to CTC enumeration (using CellSearch platform)

(*continued*)

Table 4 (continued)

Trial aspects	Relevant considerations and actions
Measuring outcomes and reporting: PROs	1. The patient perspective in prostate cancer clinical trials is important; there is the need to further optimize the assessment, collection, analysis, and presentation of PRO data 2. Disease-related symptom measurement is recommended including pain intensity and interference and physical functioning by validated tools 3. Patient-reported AEs using NCI's PRO-CTCAE should be collected
Measuring outcomes and reporting: imaging and clinical measures	1. It should be considered that there might be a mixed response designation as a manifestation of disease heterogeneity 2. It should be recorded whether disease progression represents growth of preexisting lesions, development of new lesions, or both; separate recording needed whether progression is occurring in a single organ or disease site versus multiple sites 3. First posttreatment bone scan is suggested to be used as the baseline scan to be compared with all future scans; the response in bone, caused by the advent of novel bone-targeting agents, should be noted 4. Location of nodal disease (pelvic versus extra-pelvic) and visceral disease (lung/liver/adrenal/CNS) should separately be recorded for prognostic implications 5. Up to five individual lesions per site (e.g., nodes, lung, liver as separate sites) should be recorded and followed to address disease heterogeneity 6. New criteria are defined for the first occurrence of metastatic disease in men with nmCRPC at enrollment 7. Bone-related outcomes, SREs, and SSEs (with the suggestion to focus on SSEs) represent a more direct clinical benefit to patients 8. The concept of treatment beyond progression has been introduced where clinical benefit by one or more disease manifestations is being observed, thus defining an objective of NLCB

There is also an increased recognition of disease heterogeneity and emerging resistance; hence, additional considerations have been included in the PCWG3 recommendations. Intratumoral heterogeneity (ITH) with separate cancer subclones has been identified in urological cancer diseases, including PCA and bladder and renal cancer (Gerlinger et al. 2015). Considering the heterogeneity in prognostic and predictive markers, one can imagine that there are also functional differences between individual tumor subclones (Gerlinger et al. 2015; Aziz et al. 2015). As mentioned above, serial biopsies from metastasis are in the focus; however, when ITH is not related to the distribution of different cell clones in the primary tumor only but is also displayed in metastatic distribution, multiple biopsies from several metastatic lesions would need to be taken to account for this. Furthermore, minority clones which are potentially not even recognized when biopsies are taken from the primary tumor may be the only origin of metastasis, which further challenges traditional prognostic biomarker approaches for tumor profiling. Besides, phenotypic expression markers such as RNA and proteins vary between different tumor cell types and over the course of disease. Further, several assessable genetic alterations were identified as subclonal in individual tumors. This raises the question whether patients would actually benefit from a specific treatment targeting such single alteration, a scenario which needs further evaluation in clinical trials (Gerlinger et al. 2015). Especially PCA is furthermore characterized by mutations in several oncogenes and tumor suppressor genes, such as PTEN, BRAF, EGFR, FGFR3, KRAS, and several more (Gerlinger et al. 2015; Mitelman et al. 2007; Tomlins et al.

2005; Agarwal et al. 2012). These include insertion, deletion, or substitution of nucleotides and chromosomal gains, losses, or rearrangements such as fusions involving members of the E twenty-six (ETS) family of transcription factor cancer (Gerlinger et al. 2015; Mitelman et al. 2007; Taplin et al. 2012). Accounting for ITH probably represents the biggest hurdle in genomic biomarker assessment. Gerlinger recently concluded that the impact on overall outcome of the absolute and relative abundance of subclones positive for a specific biomarker also needs to be assessed to foster the development of algorithms for the integration of results from multiple biopsies (Aziz et al. 2015). Repeated analysis during treatment may allow for adjustment of therapy, keeping in mind that prognosis and prediction of drug sensitivity may be based on the most aggressive subclone of a tumor. The degree of ITH may also correlate with genomic instability, and ITH itself should probably be considered as a novel biomarker for prediction of treatment resistance as well (Gerlinger et al. 2015).

Another specific and increasingly relevant need is to define the point of treatment discontinuation when the patient is not benefiting anymore from treatment. The term of no longer clinically benefiting (NLCB) has been introduced as potential endpoint as well, finally preferred over waiting for the first evidence of progression.

Caveats for Randomized Clinical Trials in Urologic Oncology Surgery

As mentioned previously, properly designed RCT endeavors to offer the highest level for evaluating the efficacy of certain intervention. The quality of design and reporting of RCT are key determinants that ensure medical progress on behalf of the patients. In the early 1990s, the shortcomings in the transparency of RCT enforced the scientific community to standardize the reports according to CONSORT criteria. Initial CONSORT recommendations were published in 1996 and updated later in 2001 (Shamseer et al. 2016). These guidelines have been consequently adopted by several medical journals, and they appear to have resulted in improved quality of RCT. However, several areas such as reporting of trial methods continue to meet CONSORT criteria in less than half of the urology trials (Scales et al. 2007).

Urology is a surgical specialty; thus, the massive application of RCT for future research is truncated. Surgical RCT faces special challenges regarding feasibility, acceptability, methodology, and ethics. Specifically, blinding is practically impossible.

Major obstacles to RCT in surgical uro-oncology are (but are not limited to):

(a) **History**: Several surgical treatment options were introduced far in advance **before the concept of clinical trials was designed and improved medical** outcomes from death to cure. Once a treatment is established and becomes standard of care, it is very difficult to test it against placebo. Benefits of new surgical treatments are relatively minor so that it might be considered unethical to conduct randomized clinical trials with comparison to placebo.

(b) **Impact of commercial competition on data objectivity about new procedures**: Currently about 50% of RCT are funded and conducted by industry which may affect outcome statements. A recent study analyzed the publication agreements between industry partners and researchers, and a majority of physicians mentioned the right of industry partners to approve or disapprove the proposed manuscripts (Kasenda et al. 2016).

(c) **Surgeon's equipoise**: One of the most relevant common surgeon's traits is the capacity for taking important clinical decisions in short time as required in the operating room. This quality might result in an uncertainty with regard to the capacity to evaluate the pros and cons of two different treatment options. This state of equipoise is a requisite for RCT.

(d) **Lack of funding, infrastructure, and experience in data collection**: In a publication examining four major urological journals, major deficits in the quality of reporting were noted, involving the description of the

randomization process, blinding, and description of study withdrawals.

(e) **Lack of education in clinical epidemiology**: A recent analysis of RCTs in urology underscored the need for further training in methodological reports. A total of 82 RCTs were analyzed within the urology literature, 23% of them reported as oncological with almost 50% being industry funded. Moreover, among the oncology subgroup, the mean CONSORT reporting was 15.9, having increased 4 points since last scan in 2004 (Narayan et al. 2016).

(f) **Rare conditions, life-threatening, and urgent situations**: Application of informed consent and randomization are challenging in those environments.

(g) **The surgical learning curve**: Urological oncology procedures might be complex and imply certain repetition in order to reach mastery. During the learning curve, errors and occurrence of side effects and adverse events are more likely, which represents another hurdle in developing and performing clinical trials in the operating field. For example, strong data supports that laparoscopic radical prostatectomy is a skilled procedure with a slower learning curve than the open procedure. Recurrence rates clearly decrease down to less than 9% after 750 laparoscopic procedures have been performed (Vickers et al. 2009).

(h) **Surgical definitions of procedures**: Surgical techniques are described within protocols; however, every single surgeon performs similar procedures in a different manner. When comparing operations, clear definitions are needed regarding the limits and acceptable variations in the technique, as those might imply differences in outcomes. Conversely, in trials comparing drugs, this issue does not apply. SWOG is currently enrolling patients in a RCT regarding the use of limited vs extended pelvic lymph node dissection during cystectomy for invasive bladder cancer (NCT# 01224665); in order to enroll patients, it is mandatory that the surgeon provides proof of approved lymph node dissection (images); moreover, each patient that is enrolled requires graphic imaging on its procedure, which underlines the difficulty of standardization of surgical procedures within clinical trials.

(i) **Quality control monitoring**: Delivering poor-quality surgery clearly impacts oncological outcomes; thus ensuring minimum quality standards is a requirement for any RCT in surgery. Herr et al. reported surgical factors as the most relevant to influence bladder cancer outcomes (Herr et al. 2004). The authors analyzed data from the neoadjuvant chemotherapy trial on muscle-invasive bladder cancer (SWOG 8710) reporting that the strongest predictor of positive surgical margins was the specialized training of the urologist with a urological oncology fellowship.

(j) **Development versus research**: RCTs consume substantial resources and are therefore not justified for some questions about minimal modifications to techniques to treatments. Surgery generally progresses through those modifications that collectively provide progress. During the historical progression through handwashing via the use of antiseptics to aseptic surgical environment, the change in morbidity from surgical infections was huge, but the increment with each step was small enough to allow skepticism. For example, the topic of preoperative antiseptics to prevent surgical site infection is a hot question in the surgical environment. Several RCTs have been performed regarding the superiority of povidone vs chlorhexidine to prevent SSI. Results are controversial and contradictory. A higher level of evidence was recently added by providing a Cochrane meta-analysis on RCT within the issue being unable to provide a clear answer (Park et al. 2016; Dumville et al. 2015).

(k) **Patient's equipoise**: Three types of RCT are commonly described as surgical. Type 1 trials are standard RCT comparing medical treatments in surgically treated patients. Type 2 compares surgical techniques and Type 3 non-surgical versus surgical treatments. The last subtype provides particular difficulties regarding the equipoise of patients. Patients

often reject RCT because they don't want their treatment to be decided by a randomization system. Type 3 trials increase this concern as adverse effects differ enormously and the surgical options are irreversible. An example of this is the trials evaluating cytoreductive nephrectomy (CNx) in the tyrosine kinase inhibitor era for metastatic RCC (mRCC). Two RCTs in the immunotherapy era demonstrated a clear survival advantage for CNx performed prior to immunotherapy. The introduction of oral targeted therapies (VEFG inhibitors and TKI) against mRCC raised the question of the best timing for CNx in the new scenarios. Another two RCTs were launched: the French CARMENA trial (CNx plus sunitinib vs sunitinib alone) and the European SURTIME trial (sunitinib plus CNx plus sunitinib vs CNx plus sunitinib). SURTIME trial was closed in early 2016 due to poor recruitment, and CARMENA is slowly recruiting in France. The main reason for poor recruitment is related to lack of equipoise regarding the treatment options. Out of 34 scenarios on mRCC exposed to British urologists and medical oncologists, only 8 scenarios according to the medical oncologists would be eligible for CARMENA (Stewart et al. 2016).

(l) **Missing awareness of hurdles in clinical trial conduction (patient recruitment and retention) and lack of expertise in statistical planning and clinical trial development**: Another recent example for the hurdles with regard to patient equipoise but also for the missing awareness of potential hurdles and proactive management in clinical trial conduction might be transferred from the experience with the German PREFERE study (https://clinicaltrials.gov/ct2/show/NCT01717677?term=prefere&rank=1). The PREFERE trial started recruitment in 2013 and was just recently stopped due to poor enrollment. This study proposed to randomize men with low- or early intermediate-risk PCA to one of the four different management options, i.e., radical prostatectomy, external beam radiation, brachytherapy by permanent seed implantation, and active surveillance. Patients had the additional option to choose to be randomized between 1, 3, and 4 of these options, which overall resulted in 11 sub-studies within 1 RCT. The primary endpoint was cancer-specific survival; secondary endpoints included OS, disease progression, toxicity, and quality of life. The study design was based on the expectation that the outcomes in the treatment arms would be similar; the statistical design was therefore developed to confirm non-inferiority between the four arms. The recruitment was expected to take 4 years for overall 7600 participants with a 13-year follow-up. Finally, until the end of June 2016, 384 patients only had been recruited, and subsequently enrollment and funding of the trial were stopped in November 2016 (https://clinicaltrials.gov/ct2/show/NCT01717677?term=prefere&rank=1; Zu wenig Probanden Krebsforscher). Based on the experience retrieved from unsuccessful clinical trials, several conclusions and learnings can be drawn which should be taken into consideration for future trial planning:

(i) Patient equipoise is one major point for comparative studies testing surgical and nonsurgical management options. Hence, a thorough trial planning considering different recruitment scenarios is definitely needed.

(ii) Physicians tend to overestimate recruitment in clinical trials; realistic expectations for enrollment might be reduced to 10–25% of physicians' expectations and even more depending on the specific environment and disease stage.

(iii) New studies should focus on questions which are not already being tested in comparable trials. PEFERE focused on questions which had already been addressed by more major RCTs (e.g., Scandinavian study, PIVOT and START studies, ProtecT study); other trials in this field had completed accrual focusing on quite related questions (with the exception of not including brachytherapy), albeit with less restrictions on PCA risk category.

(iv) Realistic expectations are needed with regard to the clinical relevance of the addressed questions and the statistical power to answer these questions. Based on the non-inferiority design, just small differences in outcome between the arms were expected with very few participants dying of PCA, so that even under the consideration of proper enrollment and analysis, no change to clinical practice should have been expected (Expertise Ian Tannock).

Measuring Outcome and Reporting in Uro-Oncology Trials

When talking about reporting of clinical trial results in uro-oncology, it is recommended to use control/relieve/eliminate endpoints to assess antitumor effects of therapies that are anticipated to kill tumor cells, particularly in the early phases of clinical development. For therapies not expected to kill tumor cells, delay or prevent endpoints should be used. Thereby, endpoints estimating activity in early-phase trials (such as declines in PSA, changes in circulating tumor cells (CTC), and time to progression) with the aim to demonstrate sufficient antitumor activity to decide about further study need to be distinguished versus endpoints used in registration trials where the aim is regulatory approval and clinical benefit needs to be shown. Generally, consultation with regulatory authorities is strongly recommended when selecting and defining endpoints for clinical trials intended to support drug approval, as the suitability of efficacy endpoints to demonstrate clinical benefit is context dependent (Food and Drug Administration 2007). Although demonstrating OS may be challenging as a primary endpoint, it is assumed that all trials, particularly RCT, will continue to follow patients for survival to report survival results. If possible, all therapies administered subsequent to the intervention, including start and stop dates when available, should be recorded until death. This reflects an essential point since the availability and use of life-prolonging treatments post protocol may reduce the ability to demonstrate the OS benefit of an effective treatment.

On-treatment evaluations should include physical examinations, symptom assessments, and laboratory studies to assess safety, with appropriate attribution to the disease or therapy. Imaging should include cross-sectional imaging of the chest, abdomen, and pelvis, as well as bone scintigraphy or other methods to assess potential advanced disease, regardless of whether patients have involvement of those sites at baseline. Imaging strategies should be restricted to known sites of disease risk missing disease progression at new sites.

As also recommended by PCWG3 for PCA trials, disease assessments should be performed at fixed intervals in uro-oncology trials to better understand when the antitumor effects occur, to minimize patient exposure to ineffective treatment, and to better assess the timing of the antitumor effects of an agent. For PCA trials, the recommendation is to have an 8- to 9-week assessment interval for the first 6 months and every 12 weeks thereafter, which has been based on the findings of several trials (Fizazi et al. 2015; Beer et al. 2014; Ryan et al. 2013). This relatively short interval also helps clarify bone scan flare (the development of new lesions on a first follow-up scan that may not represent progression but instead favorable treatment response). For other diseases such as RCC or UCB, the recommendation could be similar but has not been standardized overall yet; for testicular or penile cancer depending on stage and risk categorization, additional considerations will have to be taken into account to define assessment intervals.

Using a short interval of disease assessment including imaging will also inform the optimal assessment interval in subsequent trials, which is particularly important for biologic therapies who may have delayed antitumor effects. Notably, the applicability of the immune-modified RECIST criteria to PCA has not been established, in particular, whether an early increase in the size of a nodal or visceral lesion represents the recruitment of immune effector cells or tumor growth (Gerlinger et al. 2012). It is also noteworthy that

neither the RECIST criteria nor the immune-modified RECIST criteria address changes in osseous disease (Scher et al. 2016).

The main recommendations for uro-oncology clinical trial conduction include (adapted from PCWG3 recommendations for PCA and relevant also for other uro-oncology diseases) (Scher et al. 2016):

1. Baseline patient assessment should include tumor histology, detailed records of prior systemic treatments and responses, and a detailed reporting of disease subtypes based on the anatomic pattern of metastatic spread. The percentage of patients with a specific disease pattern should be described, and stratification for a specific pattern of disease may be indicated.
2. New recommendations of PCWG3 for trial outcome measures include the time-to-event endpoint of symptomatic skeletal events (SSE) to be used beyond time to first metastasis and time to progression.
3. The concept of NLCB should be considered to underscore the distinction between the first evidence for progression and the clinical need to change treatment. Progression in existing lesions should be reported distinct from the development of new lesions.
4. Focusing PROs on core concepts of disease-related symptoms, physical functioning, and AEs is advised, with the goal of improving the standardization of PRO in uro-oncology clinical trials.
5. Consultation with regulatory authorities is recommended if a trial is intended to seek support for drug approval.
6. Detailed molecular assessments of tumors including biologic profiling using serial tumor samples should be incorporated in clinical trial strategies to better understand the disease biology, to gain insight into mechanisms of resistance, and to identify predictors of sensitivity to a specific therapy. This requires the molecular characterization of an individual patient's tumor at the time treatment is considered. To establish clinical significance, the strength of the association between early changes in individual outcome measures and molecular or genetic determinants should be evaluated.
7. Molecular biomarkers in metastatic lesions can be assessed through a directed biopsy (or by using blood-based assays such as CTCs in PCA) or cell-free nucleic acids (RNA or DNA or proteins), recognizing that the biologic profiles of different lesions and blood-based assays in the same patient may not be the same (Gerlinger et al. 2012; Spritzer et al. 2013).
8. The number of tumor cells within a single metastatic site that harbor a specific alteration may also vary, and, as such, simply detecting its presence at a low frequency may not predict sensitivity.
9. Histological subtypes should be distinguished, and eligibility of patients for clinical trials should also be based on the basis of prior therapies received. This should result in a greater focus on developing specific protocols for the distinct clinical phenotypes.
10. Standards for the interpretation of outcomes for therapies that affect the immune system are still needed. Although improvements in symptoms and/or functional status can be clinical benefits in their own right, determining the clinical significance of a statistically significant change in a PRO measure is another area of focus.
11. Distinction between the need to consistently report progression and the need to terminate a treatment because the patient is NLCB from the therapy he/she is currently receiving is required.
12. The drug development process should come more closely to common clinical scenarios encountered in routine practice. It also aims to allow a more complete characterization of the host and his/her disease both at treatment start and over time, which may help establish the value and the benefit of continuing a therapy beyond progression.

Final Considerations and Summary

To offer patients the most effective and safest therapies in the field of uro-oncology, it is important to understand the key concepts involved in

performing clinical trials dealing with medical tumor treatment and surgical interventions. The attention by the mass media to safety-based drug withdrawal emphasizes this point. Understanding the ethical precepts and regulations behind trial designs may also help key stakeholders respond to future research dilemmas. Moreover, well-designed and executed clinical trials can contribute significantly to the effort to improve the effectiveness and efficiency of healthcare. Through rigorous practices applied to novel drug development as well as to the evaluation of advanced surgical techniques and further interventions, physicians and patients can maintain confidence in the prescribed therapies and interventions, recommended by their physicians.

Take-Home Messages

- Emphasizing safety first, the most common route of studying a new therapeutic is from the establishment of the MTD in humans (phase 1) to pharmacodynamic and pharmacokinetic studies and exploration of therapeutic benefit (phase 2), followed by comparing its efficacy to standard of care or placebo in a larger population of volunteers (phase 3), and ultimately post-market evaluation of adverse reactions and effectiveness when administered to the general population (phases 3b and 4).
- Structured study design and performance as indicated in the Consolidated Standards of Reporting Trials statement should be employed as well as registration in a public trial database.
- The internal validity that results from the selective inclusion criteria and the artificial setting within a clinical trial must be balanced with the intent to translate study findings to the real world in clinical practice (i.e., generalizability or external validity).
- Enrollment and treatment allocation techniques, endpoints, methods of comparison, and statistical analyses must be carefully chosen in order to plausibly achieve the intended goals of the study. Clinically relevant endpoints should be defined a priori, and an unbiased analysis and report of the study results should be warranted.
- In the comparison of experimental treatment with standard care, preplanned interim analyses during an ongoing RCT can aid in maintaining clinical equipoise by assessing benefit, harm, or futility, thus allowing decision on continuation or termination of the trial.
- Inclusion of PRO-CTCAE should be considered in both early- and late-phase clinical trials. Results from PRO-CTCAE analyses can help determine optimal dosing and tolerability and can inform the risk-benefit evaluation of treatments.
- There is a need to further identify and validate predictive and surrogate markers, on the one hand, for efficacy assessment of compounds in clinical trials despite sequencing of several efficient drugs and on the other hand also to allow for early assessment of treatment efficacy, sensitivity, or resistance to a specific treatment and accordant treatment decisions in clinical routine.
- Major hurdles for appropriate biomarker development are (i) limited incorporation of conclusive biomarker assessment and validation in clinical trials, (ii) the assessment of the right markers in the wrong setting or attributed to a discordant stage of disease, and (iii) the considerable tumor heterogeneity in uro-oncology tumors lacking process from theory to practice in order implement a marker in clinical routine and make it clinically utile. Clinical trials including tumor specimen assessment and biopsy of metastasis are required, preferably with serial biopsies taken.
- There is a risk that subjects who volunteer (or the actual physicians who enroll patients) for phase 1 studies will misinterpret its objective as therapeutic. Improvements to the process of informed consent could help in reducing these misconceptions while maintaining adequate enrollment numbers.
- Both significant and nonsignificant results should be objectively reported and published. Potential conflicts of interest and funding sources should be disclaimed in study report or publication.

- Joint efforts between industry, academia, investigators, regulatory agencies, and health authorities are required to conduct clinical trials in the best interest of patients and to generate reliable results based on rigorous implementation of high-quality criteria for clinical trial conduction.
- The major principle and basic requirement of clinical trial conduction in uro-oncology is to ensure the safety of subjects who volunteer for clinical trials. Justifiably, modern clinical trials are founded on numerous and continually evolving ethical principles and practices that guide the investigator in performing human research without violation of the Hippocratic oath. Preserving the integrity and credibility of clinical trial data reported is an ethical precondition and necessity.

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Bone Target Therapy in Urologic Malignancies

4

Simone Bier, Tilman Todenhöfer, and Arnulf Stenzl

Contents

Abstract

Almost 90% of patients with advanced prostate cancer and only 30% of patients with urothelial and renal cell carcinoma develop bone metastases. Patients with bone metastases have a high risk of skeletal-related events such as fractures and spinal cord compression. These events have a significant impact on quality of life as well as tumor progression. Both bisphosphonates and the RANKL-targeting antibody denosumab have shown to have a significant positive impact on skeletal-related events. Whereas for metastatic castration-resistant prostate cancer, phase III randomized

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trials have confirmed positive effects of denosumab and zoledronic acid on bone-related morbidity, only little evidence is present for application of these agents in bladder or renal cell carcinoma. Whereas denosumab has proven to delay onset of bone metastases in CRPC patients without bone metastases, zoledronic acid failed to prove a bone metastasis-preventing effect. The application of this agent in castration-sensitive PC is discussed controversially after a clinical trial has shown no benefit of zoledronic acid in this setting.

In patients with advanced prostate cancer and multiple bone metastases, therapy with radiopharmaceuticals is of utmost importance. Especially treatment with the alpha-emitter radium-223 chloride causes a significant delay of symptomatic skeletal-related events as well as a significant improved overall survival both in the initial phase III trial and the data of the early access program. Data on the use of radium-223 in other urologic malignancies is limited.

Introduction

While most urological malignancies are localized at the time of diagnosis, patients with advanced disease frequently present with bone metastases. Exemplarily, up to 90% of patients presenting with prostate cancer in advanced stages (Bubendorf et al. 2000) and up to one third of all patients with advanced urothelial bladder cancer and renal cell carcinoma (RCC) develop bone metastases (Jemal et al. 2006; Wang et al. 2013; Table 1).

Whereas patients with prostate cancer most commonly develop osteoblastic bone lesions, lesions in patients with renal cell carcinoma or urothelial carcinoma most commonly have a mixed osteoblastic/osteolytic phenotype (Bubendorf et al. 2000; Wood and Brown 2012). Both osteoblastic and osteolytic lesions lead to decreased bone stability. Thus, pathological fractures in weight-bearing bones are often the result of metastatic lesions. In patients with bone metastasis from solid tumors, approximately 20% develop pathological fractures (Coleman 2006).

Table 1 Rate and type of bone metastases in patients with advanced urological malignancies (Bubendorf et al. 2000; Wood and Brown 2012)

Tumor	Rate of bone metastasis in patients with advanced malignancies	Type of bone metastasis
Prostate cancer	85–90%	Mainly osteoblastic
Urothelial carcinoma of the bladder	35–40%	Mixed osteoblastic/osteolytic
Renal cell carcinoma	20–35%	Mainly osteolytic

In addition to pathological fractures, patients with bone metastases have an increased risk for other complications such as spinal cord compression and pain leading to surgery of the bone or radiation therapy. These complications are summarized collectively to "skeletal-related events." Skeletal-related events come along with a decreased quality of life, an impaired mobility, and an increased mortality as well as higher healthcare costs (Oster et al. 2013). A patient with bone metastases will suffer a skeletal-related event every 3–6 months on average (Coleman 2006).

Bone metastases deriving from prostate and kidney tumors are commonly responsible for secondary involvement of the spinae. In 20% of the patients with metastases of the vertebral column, spinal cord compression can be diagnosed. Due to neurological abnormalities, like motor weakness, sensory disturbance, and sphincter malfunction, these bone metastases become symptomatic (Coleman 2006; Healey and Brown 2000).

Hypercalcemia is a common problem in patients with bone metastases due to increased bone turnover at times leading to severe complications including neurological dysfunctions and cardiac arrhythmias (Coleman 2006).

Table 2 Variation of the localization of bone metastasis in dependence of the quantity of the metastases (Wang et al. 2013)

Localization of the bone metastasis	Patients with few bone metastasis	Patients with moderate bone metastasis	Patients with extensive bone metastasis
Thoracic vertebrae	17.2%	24.2%	13.9%
Lumbar vertebrae	39.7%	13.7%	6.5%
Ileum	10.3%	13.7%	13.9%
Ribs	8.6%	13.7%	30.9%

Bone Metastases in Patients with Prostate Cancer

Epidemiology

At the time of diagnosis, 4–7% of the patients already have bone metastases, and every sixth patient with prostate cancer develops bone lesions within 15 years after radical prostatectomy (Popiolek et al. 2013). More than 50% of patients with bone metastases develop skeletal-related events over time (Oster et al. 2013). Additionally, prostate-specific cancer treatment induces bone loss that may impair bone stability and increases the risk for fractures. Both, bone metastases and therapy-induced bone substance reduction, may lead to immobility, pain, and significant decrease of quality of life (Todenhofer et al. 2013).

Pathophysiology

In prostate cancer, even before development of bone metastases, a reduced bone density as well as varied biochemical markers in blood and bone marrow can be observed (Hussain et al. 2003; Todenhofer et al. 2013).

In dependence of the quantity of the bone metastases, the distribution pattern varied, but predominantly involved sites of bone metastases are the thoracic and lumbar vertebrae, as well as the ilium (Table 2; Wang et al. 2013). One important reason for the primary and frequent location of bone metastases is to the vertebral system of veins (Batson's plexus), which contains blood out of the prostate and which is in close proximity to the spine (Batson 1967). Another important factor is the high content of hematopoietic/"red" bone marrow in these locations. This hematopoietic stem cell niche is known to be competitively invaded by disseminated prostate tumor cells (Carlin and Andriole 2000).

It has been shown that disseminated prostate tumor cells are able to compete with hematopoietic stem cells for occupancy of the hematopoietic stem cell niche (Shiozawa et al. 2011). In 20% of the patients with prostate cancer, these disseminated tumor cells (DTCs) can be detected. However, the prognostic value of these DTCs is still unclear and a topic of current investigations (Todenhofer et al. 2015a; Weckermann et al. 2001).

The development of bone metastases is based on an interaction of tumor cells with the microenvironment of the bone marrow (Roodman 2004). Osteoblastic metastases, which are common in prostate cancer, have an abnormal microstructure and therefore reduce mechanical stability of the bones. On one hand, the development of these osteoblastic metastases is induced by secretion of osteoblastic stimulation factors, like VEGF (vascular endothelial growth factor), PDGF (platelet-derived growth factor), and endothelin 1 (Logothetis and Lin 2005; Nelson et al. 1995); on the other hand, increased activation of osteoclasts induces the development and supports progression of the metastases. This leads to an increased evidence of bone turnover markers. It therefore follows that bone turnover markers are higher in osteoblastic metastases than in osteolytic ones (Demers et al. 2000).

Another important pathway is the RANKL pathway. In patients with prostate cancer, an increased receptor activator of NF-κB ligand (RANKL) expression either by tumor cells or

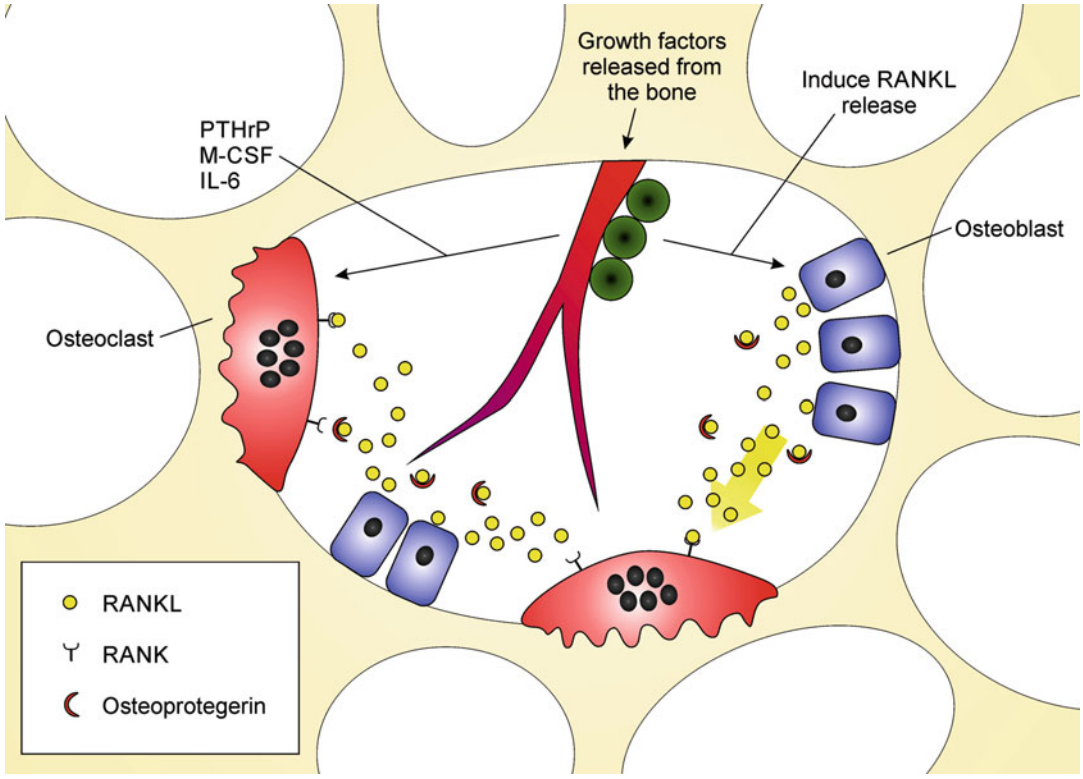

Fig. 1 Metastatic bone disease – the pathophysiology: the release of RANKL from osteoblasts is introduced by tumor cells. RANKL activates osteoclasts. The activation of osteoclasts also passed by the promotion of secret factors (PTHrP, M-CSF, IL-6), which are secreted by tumor cells. The bone resorption leads to an activation of bone morphogenetic proteins as well as a releasing of factors by osteoclasts. These factors stimulate the proliferation of the tumor cells

osteoblasts can be detected. RANKL is a member of the TNF receptor family. The binding of RANKL on osteoclast precursor cells results in osteoclastogenesis and increased bone turnover (Odero-Marah et al. 2008). The increased activity of osteoclasts leads to release of cytokines (including RANKL) that further stimulate osteoclasts. This mechanism represents the so-called vicious cycle of bone metastases (Fig. 1).

Diagnosis of Bone Metastases

Serological Findings and Clinical Examination

In patients with newly diagnosed prostate cancer, several factors exist that indicate an increased risk for presence of bone metastases. These factors include Gleason score, local tumor stage, and PSA serum concentration. A PSA value of 100 ng/ml has been shown to have a negative predictive value for bone metastases of 100% (Rana et al. 1992). Current guidelines indicate that only patients with a predominant Gleason 4 pattern or higher or patients with a PSA $>=20$ require further diagnostic workup for bone metastases (Mottet et al. 2016).

In patients with disease relapse after primary curative treatment (radiation, surgery), several factors indicate the presence of distant metastases. These include a short time interval between treatment and PSA relapse, a short PSA doubling time, and a high Gleason score at time of diagnosis (Pound et al. 1999).

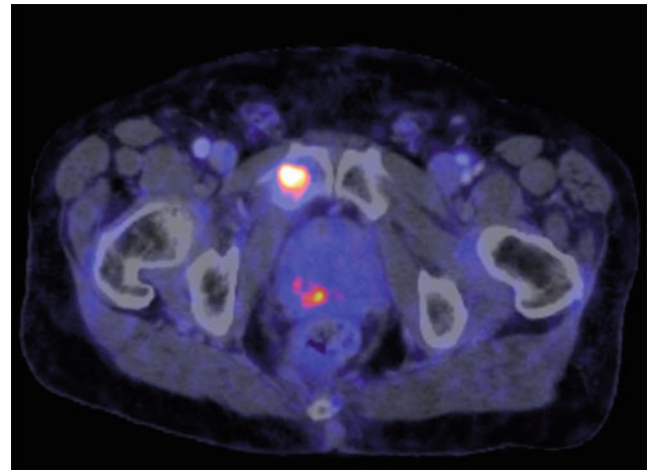

Fig. 2 PSMA-PET/CT: Uptake of PSMA in a bone metastases and prostate cancer

Bone Scan

For primary diagnosis, the negative predictive value of the bone scan is estimated between 87% and 100% (Miller et al. 1992; Oesterling et al. 1993). As mentioned above, its diagnostic application depends on PSA value, Gleason score, and clinical stage, but in symptomatic patients, the performance of a bone scan is obligatory.

The interpretation of a scintigraphic bone scan is challenging, especially for response monitoring. This is due to the fact that discrimination between therapeutically induced bone substance alterations and progression in size can appear similar (Eisenhauer et al. 2009). However, a quantitative evaluation of the tumor load is possible. Therefore, the *Prostate Cancer Clinical Trials Working Group 3* has defined that the detection of at least two new lesions on the first follow-up bone scan requires a confirmation >6 weeks, while treatment is continued. If there are two or more lesions in this confirmation, progression is documented (Scher et al. 2016).

MRI

For detecting bone metastases in patients, whole-body MR imaging has a higher sensitivity than bone scan (82% vs. 71%; $p < 0.05$). But the sensitivity of whole-body MR imaging is less than of FDG-PET (82% vs. 90%) (Daldrup-Link et al. 2001).

Pet-Ct

Compared to the choline metabolism, prostate-specific membrane antigen (PSMA) is over-expressed in most patients with prostate cancer. Therefore, it was expected that ^{68}Ga-labeled PSMA ligand as a tracer for positron emission tomography (PET) was superior to 18F–choline-based PET. A study showed a significant better detection rate of lesions by using PSMA-PET/CT than using FDG-PET/CT ($p = 0.04$) especially in patients with lower PSA (Fig. 2; Afshar-Oromieh et al. 2014).

Also the sensitivity of PET/CT and F-PET is superior to the sensitivity of bone scan. However, as with MRI, cost-effectiveness and availability are important factors for determining a radiographic option (Brogsitter et al. 2013).

Serum Markers for Bone Metastases

There is no clear recommendation for the assessment of serum bone turnover markers in patients with prostate cancer due to a limited sensitivity and specificity.

Bone alkaline phosphatase (AP) is a frequently used marker to evaluate the burden of bone metastases (Lorente et al. 1996), and it is also suitable for the assessment of therapy response or risk stratification for skeletal-related events (Izumi et al. 2012; Sonpavde et al. 2012).

Another important bone resorption marker is N-telopeptide (NTx). Study could show that a

Table 3 Specification of antiresorptive agents (Todenhöfer et al. 2015b)

	Bisphosphonates	Denosumab
Target	Osteoclast	Osteoclast
Mechanism of action	Inhibition of mevalonate pathway	Antibody against RANKL
Route of administration	Intravenous/oral	Subcutaneous
Contraindication	Renal insufficiency	Hypocalcemia
Adverse effects	Osteonecrosis of the jaw, acute-phase reaction, gastrointestinal (in case of oral administration)	Osteonecrosis of the jaw, hypocalcemia

reduction of urinary NTx during therapy of patients with androgen-dependent as well as castrate-resistant prostate cancer comes along with an improved overall survival (Som et al. 2012).

Another trial of 1824 patients with solid tumors receiving bisphosphonates were subdivided in patients with a high, a moderate, and a low level of NTx. Both in patients with prostate cancer and in patients with other solid tumors, the first SRE was significant earlier in patients with a high level ($p < 0.001$ and $p < 0.001$) compared to patients with a low level of NTx. The trial also showed a significant decreased progression-free survival in patients with prostate cancer and a high ($p < 0.001$) as well as a moderate NTx level ($p = 0.015$) compared to patients with a low level of NTx. A high or moderate NTx level also comes along with an increased risk of death in patients with prostate cancer ($p < 0.001$ and $p < 0.001$) as well as in patients with other solid tumor ($p < 0.001$ and $p < 0.001$) (Coleman et al. 2005).

Increased bone turnover markers can be a result of bone metastases as well as of androgen deprivation treatment. The bone formation marker "pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen" (ICTP) and the bone resorption marker "amino-terminal procollagen propeptide of type I collagen" (PINP) are discussed to indicate the presence of bone metastases before it can be detected by radiographic diagnostic regardless of an androgen deprivation therapy. In a small study of 64 patients with prostate cancer, the predictive value of both tests was evaluated. Increased PINP levels could be detected 8 months before the first positive bone scan (Koopmans et al. 2007).

Treatment of Bone Metastases

Antiresorptive Therapy

The goal of antiresorptive therapy is the prevention of skeletal-related events (SRE). Moreover, antiresorptive therapy has been shown to reduce tumor-associated skeletal pain in patients with bone metastases. Therefore, in patients with tumorous bone involvement, antiresorptive therapy should be considered (Table 3).

Bisphosphonates

Bisphosphonates represent a major drug class for the treatment of patients with bone metastases. The main goal of antiresorptive drugs in bone metastases is to inhibit bone turnover by interacting with osteoclasts. However, it has been also discussed that antiresorptive therapies directly interact with tumor cells. Different studies were able to show an anticancer effect of bisphosphonates on different types of tumor cells, including prostate cancer cell lines (Clezardin et al. 2005; Green 2004; Roelofs et al. 2006). The most potent member of the new-generation bisphosphonate family is zoledronic acid. The particularity of zoledronic acid is its capacity to bind and inhibit farnesyl pyrophosphate in the mevalonate pathway, which are needed for the posttranslational prenylation of different GTPases. GTPases are important for the survival pathways, so overall the binding of zoledronic acid leads to cell death and apoptosis (Benford et al. 1999; Raikkonen et al. 2010; Rondeau et al. 2006; van Beek et al. 1999).

Several studies have focused on the use of bisphosphonates in patients with metastatic CRPC (mCRPC). In a phase III trial leading to approval of zoledronic acid in patients with

mCRPC, 643 patients with mCRPC and bone metastases were randomized into three groups – one receiving 4 mg, one 8 mg of zoledronic acid intravenously, and the third a placebo every fourth week. Unfortunately, an increased rate of renal toxicity was assessed in the 8 mg group, so the dosage was consecutively reduced to 4 mg, as well. Nonetheless, the treatment groups showed a significantly increased time span to the first on-study skeletal-related event (321 days (placebo) vs. 363 days (8 mg zoledronic acid) vs. 428 days (4 mg zoledronic acid)), and the total rate of skeletal-related events were significantly reduced (49% vs. 41% vs. 38%) (Saad et al. 2004). Based on these results, zoledronic acid has been introduced as standard of care for treatment of prostate cancer patients with bone metastases.

In patients with metastatic castration-sensitive PC (CSPC), however, there is no benefit for the treatment with zoledronic acid.

In a large phase III trial with 645 patients with castration-sensitive prostate cancer and bone metastases, the treatment with zoledronic acid, compared to placebo, couldn't lead to a significant prolonged time to the first skeletal-related event (31.9 vs. 29.8 months) or significant increased overall survival (Smith et al. 2013).

The results of an adaptive, multiarm, multistage, platform randomized controlled trial were published in 2016. In this study, 2962 men with prostate cancer were randomized in four different treatment arms: standard of care vs. standard of care + docetaxel vs. standard of care + zoledronic acid vs. standard of care + zoledronic acid + docetaxel. Primary endpoint was overall survival. In this study, zoledronic acid had no effect of the overall survival (HR 0.94, 95% CI 0.79–1.11; $p = 0.450$). Median overall survival was 71 months in the group treated with standard of care, 81 months in the group treated with standard of care and docetaxel (HR 0.78, Cl 0.66–0.93; $p = 0.006$), and 76 months in the group treated with standard of care + docetaxel + zoledronic acid (HR 0.82, Cl 0.69–0.97; $p = 0.022$) (James et al. 2016).

Another effect that has been frequently discussed in the context of bisphosphonates and PC is a potential prevention of the development of bone metastases. In preclinical models, an eradication of disseminated tumor cell bone has been demonstrated (Banys et al. 2013). However, this effect has not been shown in clinical trials. A phase III study aimed to assess the preventive effect of zoledronic acid on the development of bone metastases. In this study, 1433 patients with localized prostate cancer were treated with standard PC therapy alone vs. standard PC therapy in combination with zoledronic acid 4 mg/3 months. Neither the time to development of bone metastases nor overall survival could be improved by administration of denosumab (Wirth et al. 2015).

Bisphosphonates are associated with typical side effects. Acute-phase reaction is a frequent and bothersome side effect associated with intravenous bisphosphonates (18%). Osteonecrosis of the jaw occurs in less than 2% but can be long lasting and very painful for the patients. Due to its renal excretion, the dose of zoledronic acid has to be adjusted to renal function.

Other bisphosphonates do not play a major role in the management of bone metastases due to PC. Clodronic acid is an oral bisphosphonate, which has shown to reduce metastases-associated skeletal pain significantly in gynecological tumors. However, the treatment with clodronic acid does not have a preventive value regarding skeletal-related events but interestingly has shown to improve the overall survival time. This apparent contradiction has led to a reduced use clodronic acid therapy (Ernst et al. 2003).

Denosumab

Denosumab is a monoclonal antibody binding RANKL (receptor activator of NF-κB ligand) that is applied subcutaneously (s.c.). This application form has the advantage, compared to the i.v. infusion of zoledronic acid, that there is no rapid serum concentration peak with an immediate concentration decreases after i.v. injection but rather a long-term serum conservation of denosumab (5–21 days after injection) (Chen et al. 2004).

Denosumab has been demonstrated to have significant effects in patients with mCRPC. In a phase III trial, denosumab was compared to

zoledronic acid: 1904 patients with mCRPC were treated with 4 mg zoledronic acid or with 120 mg denosumab for 4 weeks. The first endpoint of the study was the appearance of the first skeletal-related event. The time span to the first skeletal-related event was significantly improved by denosumab (20.7 vs. 17.1 months) (HR 0.82, 95% CI 0.71–0.95; $p = 0{\cdot}0002$ for non-inferiority) (Fizazi et al. 2011). Regarding quality of life and progression of pain in patients with advanced prostate cancer, the treatment with prostate cancer leads to a decreased time till the development of moderate pain (4.7 vs. 3.7 months; $p = 0.05$) and a decreased pain worsening, which comes along with a better quality of life (Henry et al. 2014).

The effect of denosumab on SREs in patients with mCSPC is unclear, as no data from clinical trials in this context is available.

Denosumab is the first drug that has been able to prevent the development of bone metastases in a clinical phase III trial in patients with CRPC. In this trial, 1432 patients with a castration-resistant prostate cancer and high risk for developing bone metastases were randomized to receive either denosumab 120 mg/4 weeks group or placebo. The treatment with denosumab led to a significant prolonged time to the first bone metastases. Especially, patients with a brief PSA doubling time showed an extraordinary benefit of a treatment with denosumab (Smith et al. 2012, 2013).

Denosumab has also an important role in the management of patients with cancer treatment-induced bone loss (CTIBL). In patients with non-metastatic prostate cancer and ongoing androgen deprivation therapy, the treatment with denosumab has been shown to provide a significant prolonged time to new vertebral fractures as well as an increased bone mineral density (Smith et al. 2009).

Similar to the treatment with zoledronic acid, osteonecrosis of the jaw is a significant adverse effect of the treatment with denosumab. Another significant side effect physicians should be aware of is hypocalcemia, which occurs more frequently in patients undergoing denosumab therapy than in patients treated with zoledronic acid (Table 4). Therefore, a supplementary application of calcium and vitamin D is necessary. Moreover, the calcium serum level has to be checked regularly (Todenhofer et al. 2015b).

Table 4 Negative side effects of zoledronic acid and denosumab (Fizazi et al. 2011)

Negative side effects	Zoledronic acid [%]	Denosumab [%]
Acute-phase reaction	18	8
Infection	43	40
Bone pain	26	25
Peripheral edema	18	20
Osteonecrosis of the jaw	1	2
Hypocalcemia	6	13
New malignant disease	1	2

External Radiation Therapy

Bone metastases often cause pain and thereby reduce the quality of life. In patients with solitary bone metastases, external beam radiotherapy is highly effective for pain management (Dy et al. 2008; Hartsell et al. 2005).

Moreover, in patients with spinal cord compression, external beam radiation therapy is an essential rescue therapy for prevention of pronounced spinal cord damage: if spinal cord compression is suspected, high-dose corticosteroid therapy is obligatory and should be initiated immediately. After radiological diagnosis of spinal cord affection, decompressive surgery should be discussed and followed by irradiation. If a surgical decompression is not feasible, external beam radiotherapy combined with systemic therapy is the treatment option of choice (Marco et al. 2000).

In patients with multiple bone metastases, external beam radiotherapy could be a theoretical treatment option but is potentially associated with fulminant adverse effects. So far, only limited data from studies using radiation therapy in patients with multiple bone metastases is available.

Table 5 Adverse effects of radium-223 treatment compared to place controlled cohort (Parker et al. 2013)

	Radium-223	Placebo
Hematologic adverse effects		
Anemia	31%	31%
Thrombocytopenia	12%	6%
Neutropenia	2%	3%
Nonhematologic adverse effects		
Diarrhea	25%	15%
Fatigue	26%	26%
Bone pain	50%	62%

CyberKnife Stereotactic Radiosurgical Treatment

Radiosurgical treatment has been shown to provide high efficacy in the treatment of solitary metastatic lesions. In patients with bone metastases from different solid tumors, radiosurgical treatment provided pain control and improved quality of life after treatment of spine tumors or spine bone metastases (Degen et al. 2005). In patients with prostate cancer, only limited data is available on the use of CyberKnife radiosurgical treatment. In a small trial of 40 patients with one or two metastases and prostate cancer, the image-guided robotic radiosurgery was evaluated. The treatment was associated with a reasonable local tumor control indicated by freedom of local tumor recurrence (Muacevic et al. 2013).

Radiopharmaceuticals

In patients with multiple bone metastases, the intravenous application of radionuclides is another treatment option. It causes a sufficient reduction of pain and improves quality of life. Especially in patients with osteoblastic metastases, increasingly positive effects of radionuclides are documented. A key disadvantage of the treatment with radionuclides is the high rate of hematologic side effects: the hematotoxicity can cause leucopenia and thrombocytopenia. As part of these hematotoxicity effects, leucocytes and thrombocytes are verifiable lowered to 30–70% of their initial value (Table 5). This is usually reversible within 3 months after end of the therapy and should therefore not be considered in patients with severe pre-therapeutically bone marrow depression (Todenhofer et al. 2015b).

Most of the used radiopharmaceuticals are beta-emitter: strontium-89-chrloride, samarium-153-EDTMP, rhenium-186-HEDP, and renium-188-HEDP. The only alpha-emitter, which is used, is radium-223 chloride. Interestingly, all radionuclides bind to a ligand, which then accumulates in areas of increased bone turnover (Jong et al. 2016).

Beta-Emitter

In patients with prostate cancer and symptomatic bone metastases, the response rate to beta-emitters is estimated between 65% and 80% (Schoeneich et al. 1998). Furthermore, the treatment with beta-emitters can lead to complete pain reduction in 15–30 percent of the patients, and this positive effect can endure up to 6 months (Kraeber-Bodere et al. 2000). Beta-emitters can be combined with cytotoxic drugs or targeted drugs. A phase II trial with 72 patients showed that a combined therapy of doxorubicin and strontium-89 chloride leads to a significantly increased overall survival compared to chemotherapy only (Tu et al. 2001). Yet another trial revealed a significant pain reduction caused by docetaxel-based chemotherapy regimens combined with samarium 153. However, the latter trial could not demonstrate a beneficial effect on the progression-free survival (Fizazi et al. 2009).

Unfortunately, the possible negative hematologic side effects of a beta-emitter therapy have led to a decreased application of this treatment option, especially in patients under add-on chemotherapy. Interestingly, recent studies have shown that these side effects are probably overestimated. Moderate adverse effects were still present but could be managed properly (Morris et al. 2009).

Alpha-Emitter (Radium-223)

Radium-223 is an alpha-emitter. In a phase III trial, its therapeutic value was investigated in a large cohort of patients with metastatic castration-resistant prostate cancer. The trial included 921 patients with symptomatic castration-resistant prostate cancer with two or more bone metastases. The application of radium-223 led to a significant prolonged overall survival compared to placebo (14 vs. 11.2 months). However, patients with visceral metastases were excluded from this trial. The beneficial effect on survival was observed in patients with previous chemotherapy with docetaxel as well as in patients without previous chemotherapy. In addition, the time to symptomatic SREs was significantly prolonged in the radium-223 arm in comparison to the placebo arm (13.6 vs. 8.4 months). However, subgroup analysis yielded that this positive effect only occurs in patients with additional bisphosphonate therapy (Sartor et al. 2014).

In comparison to other radionuclides, the grade of hematotoxicity was lower. Moreover, this reduced myelotoxic effect is accompanied by a higher cytotoxic effect and therefore a reduced particle dose for induction of cell death. This fact is especially important for small bone metastases, with reduced capacity for radionuclides (Sgouros et al. 2010).

Moreover, the increased cytotoxicity of high-energy alpha-emitter loaded particles leads to a more pronounced effect in hypoxic and therefore more radiation-sensitive tumor cells compared to beta-emitters (Wenzl and Wilkens 2011).

Bone-Related Effects of Other Drugs Approved for mCRPC Treatment

To address the importance of bone metastases in patients with CRPC, recent studies in mCRPC patients have include bone-related endpoints such as time to first skeletal-related events. It could be demonstrated that the application of abiraterone and enzalutamide has positive effects on complications related to bone metastases.

Abiraterone

Abiraterone acetate potently blocks cytochrome P450c17 (CYP17) which is an important mediator of testosterone synthesis. Hence, it is a selective inhibitor of androgen biosynthesis (de Bono et al. 2011). The treatment with abiraterone combined with prednisolone leads to a prolonged progression-free survival as well as a prolonged overall survival, both in patients with previous chemotherapy and in patients without previous chemotherapy. Moreover, patients without previous chemotherapy but abiraterone acetate have a longer time span until final chemotherapy induction (Ryan et al. 2013).

Concerning bone metastases, a large clinical trial evaluated the effect on skeletal-related events in 1195 patients with castration-resistant prostate cancer and previous docetaxel-based chemotherapy. In this trial, patients were randomized in a group treated with abiraterone and prednisolone and a group treated with prednisolone and placebo. There was a significant prolonged time to the first skeletal-related event in the abiraterone group (25.0 vs. 20.3 months; HR: 0.61, $p = 0.0001$) (Logothetis et al. 2012).

Noteworthy negative side effects of the treatment with abiraterone and prednisolone are hepatic dysfunction and edemata.

Enzalutamide

Enzalutamide is a selective inhibitor of the androgen receptor. In large clinical trials, the treatment with enzalutamide led to a prolonged progression-free survival, as well as a prolonged overall survival in patients with and without previous chemotherapy (Scher et al. 2012).

In the phase III trial with previous chemotherapy, 1199 patients with castrate-resistant prostate cancer were treated with enzalutamide or placebo. There was found a significant prolonged time to the first skeletal-related event in the group treated with enzalutamide (16.7 vs. 13.3 months; HR: 0.69, $p = <0.001$). In addition, radiographic progression-free survival (8.3 vs. 2.9 months; HR: 0.4, $p < 0.001$) as well as overall survival was prolonged (18.4 vs. 13.3 months; HR: 0.63, $p < 0.001$) (Scher et al. 2012).

Bone Metastases in Patients with Urothelial Carcinoma of the Bladder

Epidemiology

At primary diagnosis, 75–80% of patients with urothelial carcinoma have disease confined to the mucosa or submucosa. These patients have a negligible risk of having primary bone metastases. In patients with advanced/metastatic BC, the risk of having metastatic disease is as high as 30–40%.

Large trials showed that 30–50% of the patients with bladder cancer, who were treated via radical cystectomy, presented with recurrence within 5 years after treatment. 75% of these patients developed distant metastases in the course of the disease, whereof 33% were metastases to the bone (Yafi et al. 2011, 2012). Interestingly, most bone metastases after radical cystectomy develop within 2 years after surgery (Yafi et al. 2012). Altogether, 30–40% of patients with metastatic urothelial carcinoma of the bladder have bone metastases.

Diagnosis

Due to the fact that bone metastases of urothelial cancer of the bladder are very rare at the time of diagnosis, a bone scan is not primarily necessary. Sole exceptions are patients with specific symptoms that are suggestive for the presence of tumorous bone involvement (Stenzl et al. 2011).

After cystectomy, up to 50% of the patients showed distant metastases, in dependence of T-stage and lymph node involvement. The bone is one of the most likely sites of distant metastases of bladder cancer (Ghoneim et al. 2008). The value of periodic monitoring after radical cystectomy is still discussed. One of the reasons is that more than 50% of the distant metastases are diagnosed after being symptomatic (Stenzl et al. 2011).

Antiresorptive Therapy of Bone Metastases in Patients with Bladder Cancer

By inhibition of bone resorption, bisphosphonate derivatives are able to defer skeletal-related events. In a small trial of 40 patients with bladder cancer-related bone metastases and previous palliative radiotherapy to the effected bone, patients were randomized into two groups, one treated with zoledronic acid (4 mg) and one treated with placebo. In this trial, patients in the zoledronic acid arm had a significantly prolonged median time span to the first skeletal-related event compared to patients in the placebo arm. Additionally, patients treated with zoledronic acid showed an improved overall survival ($p = 0.004$) and a significant increased 1-year SRE-free survival rate ($p = 0.001$) (Zaghloul et al. 2010).

To evaluate its effect on solid tumors, the previously mentioned RANKL inhibitor denosumab was compared with denosumab in a double-blind randomized study with 1175 patients with solid tumors (endpoint: first skeletal-related event). Patients with prostate cancer, breast cancer, and multiple myeloma were not included. In the whole cohort, 63 patients with bladder cancer were included (Henry et al. 2011). In patients treated with denosumab, the time to the first skeletal-related event was significant prolonged compared to the group treated with zoledronic acid (Henry et al. 2014). However, no subgroup analysis is available for patients with BC.

Altogether, an antiresorptive therapy with denosumab or zoledronic acid should be recommended to patients with bone metastases caused by bladder cancer. Before initiation of an antiresorptive therapy, it is crucial that physicians and patients know about possible side effects of both treatment options. A prophylactic treatment for hypocalcaemia as well as for jaw osteonecrosis is important.

In patients with chronic renal insufficiency, a zoledronic acid therapy should be carefully used, because these cases require a dose adjustment compared to denosumab (Rosen et al. 2004).

Bone Metastases in Patients with Renal Cell Carcinoma

Epidemiology

At the time of primary diagnosis, 15–20% of the patients with renal cell carcinoma present with distant metastases. Dependent on the stage, up to 40% of the patients with a primarily curative-intended treatment of kidney cancer develop distant metastases over time (Motzer et al. 1999). Beside lung metastases, bone metastases are the most frequent distant metastases in patients with advanced renal cell carcinoma. Morphologically, in 66% of the cases, these are composed of osteoblastic and osteolytic compartments. Unfortunately, this "mixed" composition of the metastases complicates the response imaging by computed tomography and scintigraphic bone scan. Only 33% are pure osteolytic in shape (Zekri et al. 2001).

Interestingly, bone metastases of renal cell carcinomas present with a higher rate of skeletal-related events compared to other solid tumors (Table 6). Furthermore, renal cell carcinoma-related bone infiltration represents an additional risk factor for the overall survival, beside the established risk factors (Patil et al. 2011).

Diagnostic

As a consequence of the fact that most bone metastases side with specific symptoms, a routinely performed bone scan at the time of primary diagnosis is not always necessary. However, in patients with specific symptoms or laboratory signs, a bone scan is mandatory (Powles et al. 2016).

In dependence of the clinical stage and the pathology result after surgery, the following radiological surveillance should be chosen. Bone scan and PET or PET/CT are not standard techniques in the follow-up (Powles et al. 2016).

Table 6 Distribution of skeletal-related events in patients with bone metastatic renal cell carcinoma (Woodward et al. 2011)

Skeletal-related event	Portion of the patients with skeletal-related events
Radiotherapy	78.3%
Hypercalcemia	12.2%
Spinal cord compression	26.8%
Bone surgery	28.3%
Fracture	9.3%

Local Therapy of Bone Metastases

In a small trial of 60 patients with renal cell carcinoma metastatic to the bone, the effect of local surgical treatment of solitary bone metastases on survival was evaluated. In this study, the wide resection of the metastases did not result in a better survival but demonstrated a preventive value regarding skeletal-related events and associated complications (Fuchs et al. 2005).

In another trial, the effect of external beam radiotherapy compared to high-dose stereotactic body radiotherapy on painful spinal metastases was evaluated. Both treatment options resulted in a pain relief, but neither was proven to be superior (Hunter et al. 2012).

Both studies were done retrospectively and nonrandomized comparatively and were small-cohort studies and therefore did not influence specific EAU guidelines. Nevertheless, radiotherapy is able to improve local symptoms and therefore represents an individually applicable treatment option of solitary bone metastases.

Antiresorptive Therapy of Bone Metastases in Patients with Renal Cell Carcinoma

The antiresorptive therapy of bone metastases in patients with advanced renal cell carcinoma is accompanied by two basic problems: the standard therapy of the primary tumor has the (partial) nephrectomy with renal failure as a potential side effect. In patients with renal failure, the doses of zoledronic acid have to be adjusted, and renal function has to be controlled frequently.

Another problem is that jaw osteonecrosis, as a potential adverse effect of antiresorptive therapy, may be aggravated by synchronous application of

a tyrosine kinase inhibitor, which is one of the standard therapies for advanced renal cell carcinoma (Brunello et al. 2009). It is therefore important to alert the patients to perform distinct dental hygiene with frequent controls by a dentist.

In a phase III trial of patients with bone metastatic solid tumors, the treatment with zoledronic acid was compared to placebo treatment. In the whole cohort, 46 patients with renal cell carcinoma were included. The appearance of skeletal-related events was significantly reduced under zoledronic acid therapy. Also, the time of the first skeletal-related event was prolonged significantly in the zoledronic acid arm (Lipton et al. 2003, 2004).

In another small trial of 45 patients with bone metastatic renal cell carcinoma, patients were randomized in two groups: one treated with zoledronic acid and one with placebo. Primary endpoint of the trial was overall survival. Patients treated with zoledronic acid showed a significant improved overall survival ($p = 0.0034$) as well as a significant decrease of skeletal-related events ($p = 0.0453$). Also the risk of a spinal compression was significant decreased in the group treated with zoledronic acid ($p = 0.0479$) (Yasuda et al. 2013).

In yet another trial, which compared the treatment with denosumab vs. zoledronic acid in patients with advanced solid tumors and bone metastases, both therapy regimens lead to a reduced rate of skeletal-related events, but the therapy with denosumab was more effective concerning skeletal-related events and preventing pain (Henry et al. 2011, 2014) (Figs. 1 and 2).

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Part II

Prostate Cancer

Screening of Prostate Cancer

5

Martijn B. Busstra and Monique J. Roobol

Contents

Abstract

In this chapter we aim to give insight in the burden of prostate cancer and the effects of early detection and treatments using ample available data from cancer registries and (randomized) clinical trials. Prostate cancer is the leading cancer type in men, and it occurs mainly at age 60–80 remaining asymptomatic during lifetime in many cases. The impact of a disease determines the need and extent of screening. Large-scale population-based prostate cancer screening trials mainly aimed to demonstrate a reduction in disease-specific mortality. After two decades it became clear that disease-specific mortality could be reduced, but at considerable harms including over diagnosis and related overtreatment. Interpretation of trial data is however hampered by, e.g., prostate-specific antigen (PSA) contamination of the control group and the continuous development of new diagnostic tools and treatment options. Nowadays, prostate cancer morbidity and quality of life are at least equally important as survival. Diagnostic strategies in prostate cancer screening protocols are now directed at trying to detect higher-risk prostate cancers in a really early phase and trying to avoid detection of low-volume, low-grade cancers. The ideal test does not (yet) exist meaning that clinically insignificant tumors will still be diagnosed and significant tumors can be missed. Until more advanced markers and diagnostic tools, less invasive

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treatments, and better active surveillance strategies combined into an individually tailored algorithm demonstrate a substantially better cost-effective impact, the decision whether or not to screen remains a shared decision between men and their physicians.

The Epidemiology of Prostate Cancer

Globally prostate cancer is the fourth most common cancer with 1.1 million men in 2012 being diagnosed. In developed countries 69.5 per 100,000 men per year were diagnosed with prostate cancer and in less developed countries 14.5 per 100,000 men (Ferlay et al. 2015). In developed countries, prostate-specific antigen (PSA)-based early detection strategies are offered more frequently and are even more frequently applied in people with higher socioeconomic status (Weber et al. 2013; Tabuchi et al. 2015; Guessous et al. 2016). Mortality rates are less variable as compared to incidence rates but are still higher in less developed countries. Mortality rates are generally high in populations of African descent and very low in Asia (Ferlay et al. 2015). As prostate cancer incidence is increasing with age, prostate cancer can be expected to be diagnosed most often in populations with high life expectancy and widely applied PSA-based screening.

Before the early 1980s, prostate cancer was only detected at an early stage by abnormal findings on rectal examination or by transurethral resection for obstructive hyperplasia. In such cases only 43% was locally confined and 25% already was distally metastasized (Johansson et al. 1989). Approximately two out of three men died of their disease (Hsing et al. 2000). In the early 1990s PSA testing became widely available, and prostate cancer could be detected in a much earlier phase. As is often the case with a screen-detected cancer, a person without having any complaints suddenly becomes a cancer patient. In the case of low-grade, low-volume prostate cancer, it is very likely that the tumor will remain asymptomatic even if it is not treated. These tumors are often referred to as clinically insignificant tumors. Criteria defining clinical significance are a primary Gleason score of less than 4 and a tumor core length of less than 6 mm as assessed in systematic TRUS or MRI-guided prostate core biopsies (Stark et al. 2009; Ahmed et al. 2011; Wolters et al. 2011). The earlier a clinically insignificant prostate cancer is detected, the longer the duration of the disease: this is called lead time (Black and Ling 1990; Bokhorst et al. 2015). PSA testing can account for at least 5 years of lead time. In a prospective aging study using a PSA cutoff of 4 ng/mL, it was found that 78% of prostate cancer patients with localized disease could have been diagnosed a median of 4.9 years earlier than their clinical diagnosis and patients with metastatic disease had elevated serum PSA levels as many as 11.2 years earlier than their clinical diagnosis (Carter et al. 1992). But even before the early days of PSA testing, it was clear that high-grade prostate cancers had an up to tenfold higher mortality rate than low-grade prostate cancers (Chodak et al. 1994). Although these tumors account for a minority of early-detected cancers, they are expected to benefit most from early detection and early treatment. Even prostate cancers diagnosed after the age of 75 tend to be later stage tumors with >50% prostate cancer-related death rates (Scosyrev et al. 2012).

Life expectancy plays a major role in choices to be made addressing diagnostics and treatments. Life expectancy has improved significantly over the last three decades. Though screening protocols tend to advice against any PSA testing when life expectancy is less than 10 years, the estimation of one's life expectancy has to take into account many factors like comorbidity, age, socioeconomic status, race, family history, dietary habits, BMI, and even geographics (De Angelis 2014). And even a favorable life expectancy can make decisions difficult: the younger of age, the lower the risk of prostate cancer, whereas the more favorable life expectancy, the higher the chance that even a very low-risk prostate cancer might become clinically relevant. The prostate cancer guideline of the NCCN (National Comprehensive Cancer Network) refers to several tools but emphasizes that for individuals it is challenging to make a good life expectancy estimate (Mohler 2017).

The Impact of Prostate Cancer

Life Expectancy

Screening for a disease in an early asymptomatic phase is only relevant if early detection leads to a decrease in morbidity and/or mortality in a significant number of cases: the benefit of screening. This benefit should be in balance with the harms and the costs of the tests and the strategies after diagnosis. A negative test should be reassuring enough: it cannot be accepted to miss too many potentially aggressive tumors. A positive test should in fact only detect a clinically significant tumor. Hence, the number of patients needed to test to prevent one prostate cancer death or to prevent one patient with symptomatic metastatic disease should be in balance. So far the theoretical world.

Parameters reflecting the burden of prostate cancer have changed considerably in the last 30 years. The incidence of prostate cancer has increased, diagnostic tests have improved, and treatments have been refined and became more tailored to the individual. In addition, criteria allowing for active surveillance have been standardized and applicable for a considerable part of newly diagnosed patients.

But what if local prostate cancer is not treated? It is clear that only a minority of the patients will become symptomatic and even a smaller fraction of patients will die within 10 years. But many patients will aim at a favorable perspective with a much longer life expectancy. Recently a Swedish study describing the very long-term follow-up data of patients with local disease followed expectantly demonstrated that even in low-risk tumors prostate cancer-specific survival declined between 15 and 25 years of follow-up from 81% to 31% (Popiolek et al. 2013). Again, life expectancy plays a crucial role.

In most cases curative intent must be seen as a long-term strategy and is only expected to influence overall survival in healthy men with a life expectancy of >10 years. New diagnostic tools are therefore aiming at the early detection of intermediate- and high-risk prostate cancers and trying not to detect low-volume low-grade cancers.

Morbidity

Prostate cancer is characterized in most cases by a long asymptomatic phase. The long-term follow-up data of men aged 65 years or older who were SEER residents and diagnosed with stage T1–T2 prostate cancer during 1992–2009.

($N = 31{,}137$) clearly demonstrate that comorbidity and age account for a vast number of competing causes of mortality (Fig. 1) (Lu-Yao et al. 2015).

But even between the first onset of prostate cancer symptoms and cancer-specific mortality, there are often many years to come in which the patient might suffer from disease-related symptoms like skeletal-related events, anemia, hydronephrosis, and other urinary tract symptoms. Later in life most symptoms will be caused by androgen deprivation therapy and other locoregional or systemic palliative treatments. Patients with local disease can be offered treatments with curative intent. The majority of prostate cancer cases are being treated by radical prostatectomy and different modalities of radiation therapy. Minimal invasive treatments like HIFU, cryotherapy, proton therapy, photodynamic therapy, and organ-sparing focal therapies are still often considered as experimental, lacking long-term oncological results or the application is limited by availability and logistics (Porres et al. 2012; van den Bos et al. 2014). Though cardiovascular risks of anesthesia have improved, a radical prostatectomy is still considered to be major surgery with limited mortality but partly predictable morbidity (Abdollah et al. 2012; Ficarra et al. 2012a, b; Bjorklund et al. 2016). Nerve-sparing, adapted apical dissection and suturing techniques have improved but are not always possible, and preoperative information can differ from intraoperative findings and postoperative results. The better we become in predicting oncological outcomes after treatment and thus treatment necessity, the better patients can accept the functional adverse effects of treatments (Korfage et al. 2006). The better we become in predicting outcome, the better patients can deal with treatment decision and functional and oncological outcome.

While a selective diagnosis of those prostate cancers that are destined to cause harm during a

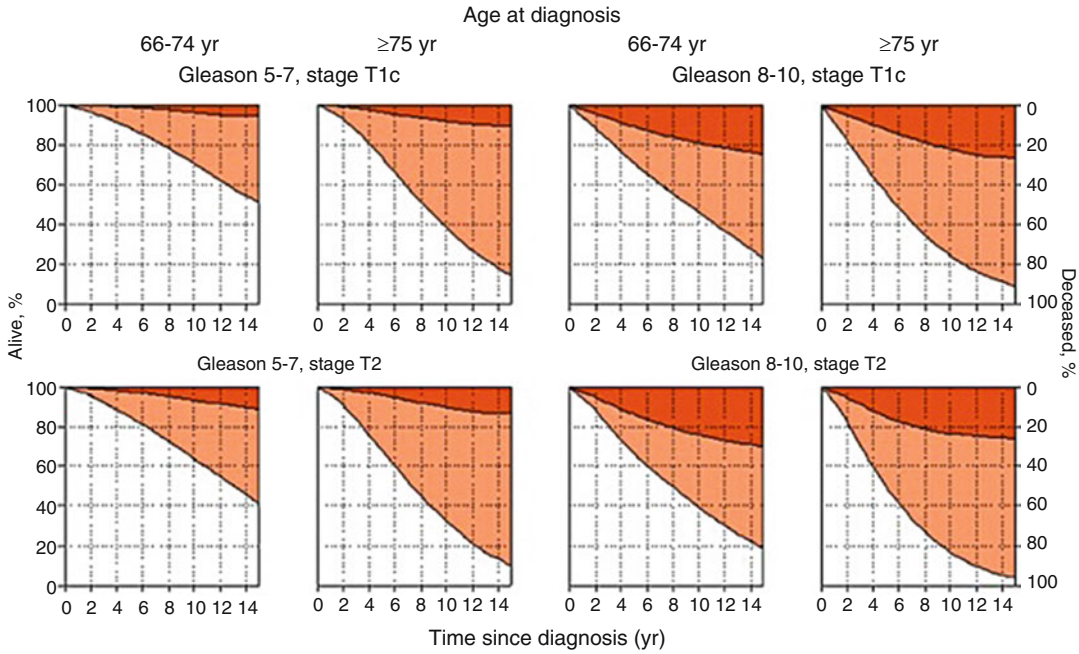

Fig. 1 Competing risks of death by age at diagnosis, cancer stage, and grade. Dark shading indicates prostate cancer-specific mortality and light shading mortality due to competing causes; non-shaded areas represent the probability of being alive. Results for well-differentiated disease are not shown because estimates were unstable due to limited sample sizes (Re-used with permission)

man's lifetime is the way to go, this is currently not possible. This means that also prostate cancers are being detected that would never cause harm if not detected. To avoid more harm in the form of overtreatment, active surveillance is being applied. A typical active surveillance strategy implies visiting a urologist for three-monthly PSA testing, six-monthly rectal examination, and repeatedly prostate biopsies (e.g., yearly or with two-year intervals or longer). In some cases an MRI is being done potentially providing additional insight in disease progression. Independent on what is being done, each visit will cause some anxiety, although being a cancer patient these visits can also be reassuring. Even though diagnostic tools have improved, selecting the ideal candidate for active surveillance is still a challenge. In practice, 24–40% of the patients being followed by an active surveillance strategy will be treated with curative intent within 5 years after being diagnosed (Tosoian et al. 2016). The reasons can be disease reclassification and progression but also patient anxiety despite a favorable course of the disease. Some men suffer most from the suffering they fear, but might never appear. However, in an active surveillance cohort of 129 men, overall only 6 of 129 men (5%) discontinued active surveillance because of anxiety and distress (Venderbos et al. 2015).

Men with a life expectancy of >10 years and an intermediate- or high-risk prostate cancer, according to D'Amico (1998), often require a more invasive strategy in an effort to cure or postpone cancer-related morbidity. And even when treatment with curative intent is being offered, available prediction tools can be very instructive in getting a good perception of the burden and prospects of the disease. Good examples are the prostate cancer nomogram of the Memorial Sloan Kettering Center website (Center 2017) and Briganti tables (Boehm et al. 2016). Although the technique of radical prostatectomy has improved and radiation therapies have been refined, these treatments still have side effects that

have a major impact on quality of life (QoL) (Whiting et al. 2016; Venderbos 2017). Monitoring QoL remains pivotal in men with prostate cancer in order to facilitate treatment decision making (Villa et al. 2017).

Being cured from prostate cancer makes dealing with the side effects of treatments more acceptable (Korfage et al. 2007). In the case of recurrence or metastasized disease-related morbidity and treatment-related side effects may be harder to deal with. In a time where active surveillance plays an increasing role in local, low-risk disease and a time where delay of systemic treatments in asymptomatic slowly progressing disease is commonly applied, there is growing evidence that even in metastasized prostate cancer, treatment of the primary tumor can be beneficial (Culp et al. 2014), and it is also known that in metastasized prostate cancer, early ADT may offer a slightly better life expectancy. Available systemic treatments have increased and have been accepted for reimbursement. In the past 5 years, a whole range of systemic treatments (Crawford et al. 2015) has demonstrated to add significant time of disease-specific survival to metastasized castration-resistant prostate cancer patients, and results from application of docetaxel in early hormone-naïve metastasized setting have changed daily practice dramatically (Sweeney et al. 2015). Locoregional salvage therapies also promise to be able to postpone systemic treatments (Ost et al. 2016). But still, metastasized prostate cancer is generally considered incurable, and many treatments can add years of survival but potentially with a decrease in quality of life as a tradeoff. Fortunately the knowledge of how to constrain toxicity of the current palliative treatments has increased, and the benefits of treatments like pain relief, prevention of skeletal events, or alleviation of urinary obstruction are clear.

Prostate Cancer Screening

Screening trials have been initiated in a time where TRUS-guided random, often sextant biopsies were the standard, and PSA testing was not applied as widespread as it is now. The two largest trials addressing population-based screening are the American Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial (Andriole et al. 2009) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial (Schroder et al. 2014). During the course of these trials, medical checkups became common practice, and more and more men and physicians became aware of the diagnostic possibilities often without fully realizing the existence of potential downsides. PSA testing and subsequent prostate biopsy and early diagnosis in men randomized to the control arm (contamination) jeopardize the power of randomized trials in showing an effect of PSA-based screening (Shoag et al. 2016a). This is clearly shown in the PLCO trial where it recently became obvious that their initial conclusion of no effect of PSA-based screening on disease-specific mortality cannot be drawn from the data available, due to a very high level of contamination in their control arm Shoag et al. (2016a, b).

It has taken the ERSPC screening trial, in which the effect of contamination was much less as compared to the PLCO, two decades to be able to get insight in the overall impact on metastatic disease and disease-specific mortality. This is as said due to the natural course of the disease, the majority of prostate cancer cases are slow growing cancers which eventually may cause harm depending on life expectancy. Despite the fact that disease-specific mortality and perhaps even more important suffering from metastatic disease is reduced by PSA-based screening, the ideal balance between the reduction of morbidity and death from the disease and the harms of screening leading to overdiagnosis and overtreatment with side effects and deterioration of quality of life has not been established. With the currently available follow-up data in the ERSPC trial, it is shown that in order to prevent one prostate cancer death, 781 men have to be screened and an additional 27 prostate cancers need to be detected as compared to a situation without screening (Schroder et al. 2014). Too many men still undergo unnecessary biopsies (with potential risks like up to 5% of septicemia) and other invasive or costly diagnostic procedures.

The increasing use of the PSA tests in the nineties and the intermediate results of the randomized trials

already showing a considerable increase in the detection of low-risk prostate cancer cases were reasons to draft guidelines on the use of PSA testing in daily clinical practice. In 2002 the follow-up time in both screening trials was still considered to be too short, and the US Preventive Services Task Force (USPSTF) could not conclude whether or not PSA-based screening on prostate cancer should be broadly implemented. In 2008 the USPSTF assigned a grade of D (recommending against screening) for men aged ≥75 years and in 2012 for men of all ages (Force 2002; Force 2008; Moyer and Force 2012). This recommendation is contrary to guidelines from urological associations worldwide that promote shared decision making. Despite the negative advice of USPSTF, data on PSA use for screening purposes from the years after 2012 show that many physicians still regularly perform PSA testing for screening purposes and many men still ask their doctor for a PSA test. Rates of PSA screening tests have declined by 3–10% in all age groups, but what could be worrying is that there are slight changes in grade and stage toward more aggressive and extensive disease which are noticeable. It is however too early to draw any conclusions on potential benefit or harm (Fleshner et al. 2017).

What is however clear is that a purely PSA-based screening approach is not the way to go. Diagnostics have improved dramatically since the last 20 years. To find an answer on the merits of population-based screening if new serum markers, urinary markers, mpMRI imaging, current ultrasound devices, and perhaps even elastometry devices or PET imaging techniques would be applied, large trials would have to be repeated in a time where it will be impossible to randomize well-informed people to a control arm. We can however still apply the data from previous trials in simulation models in order to improve available nomograms and decision aids (Bertsimas et al. 2016).

An example of further exploration on improving screening strategies is the German PROBASE study (Prospective, randomized, risk-adapted Prostate Cancer Early Detection Study Based on a "Baseline" PSA Value in Young Men) in which men (age 45 or 50) with a PSA < 1.5 ng/mL will only need to be screened again after 5 years. Only an elevated baseline PSA will lead to more frequent follow-up screening visits (Arsov et al. 2013).

Another example of risk-based prostate cancer screening is the application of the so-called STHLM3 model (a combination of clinical data, serum biomarkers, and SNPs) in the Stockholm 3 trial which leads to a reduction of the number of biopsies by 32% (95% CI 24–39) while avoiding 44% (35–54) of benign biopsies without compromising the ability to diagnose prostate cancer with a Gleason score of at least 7 (Gronberg et al. 2015). Many of these ongoing trials incorporate a wide diversity of serum markers and imaging modalities, and biobanking facilities will facilitate accelerated testing of future biomarkers in these valuable screening cohorts.

In the UK the so-called CAP study results are being awaited. Initiated in 2002 the Comparison Arm for ProtecT (CAP) cluster randomized controlled trial (RCT) evaluates prostate cancer screening effectiveness by comparing primary care centers allocated to only one round of prostate-specific antigen (PSA) testing (intervention) or standard clinical care. This will give insight in the benefits and harms of one single screening versus repeat screenings (Lane et al. 2010).

Lithuania until now is the only country that has been offering a population-based prostate cancer screening program outside a trial. Since 2006 the Early Prostate Cancer Detection Programme (EPCDP) targets men aged 50–75 years and younger men (>45 years) with a family history of prostate cancer. Their most recent analysis showed an unprecedented increase in prostate cancer incidence: more than sevenfold in two decades with mortality rates remaining relatively stable. Overdiagnosis and overtreatment are a risk, and participating men are to be just as well informed about pros and cons of PSA-based screening as any other man (Gondos et al. 2015).

Diagnostic Tools for Early Detection: It's all About Risk Stratification

As mentioned before, since the late 1980s diagnostic tools for detection of prostate cancer have evolved thoroughly. Since the application of

prediction tools is everyday practice nowadays, it is important that these tools are continuously improved with up-to-date and externally validated information.

What we have already learned by analyzing available data has been incorporated in guidelines. It is clear that using PSA as a single parameter to calculate the chance of detecting prostate cancer is insufficient. Using PSA density by adding prostate volume accounts for a significant improvement of detection rates and avoiding unnecessary biopsies. This is shown in the analyses in Fig. 2. Based on the Rotterdam data from ERSPC initial screening round, the discrimination improves considerably when next to the PSA level additional relevant pre-biopsy information (like the outcome of DRE and volume assessment) is taken into account. Combining relevant information including prostate volume is the driving force behind the well-known and repeatedly externally validated prostate cancer risk calculator (www.prostatecancer-riskcalulator.com or in app store RPCRC).

Adding findings on rectal examination, results of and the amount of previous prostate biopsies, and previous PSA values in time and taking into account factors like age, positive family history, and Afro-American descent underline the necessity of a multivariable approach and preferably presented in a format that is readily available for clinical application.

Data on pre-biopsy mpMRI support the application of the scan after a first negative set of prostate biopsies but persisting suspicion of prostate cancer as depicted in a recent AUA (American Urological Association) and SAR (Society of Abdominal Radiology) consensus statement (Rosenkrantz et al. 2016). The primary use of mpMRI (Ahmed et al. 2017) is in theory equally attractive but needs further study,

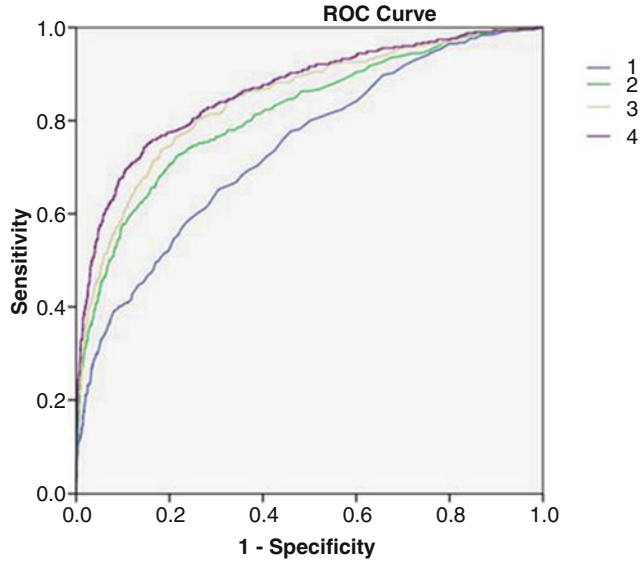

Fig. 2 The area under the curve (AUR) in a ROC graphic is used to demonstrate the accuracy of a diagnostic test in a certain population. This figure shows the improvement of a PSA test (in a screening cohort of the Rotterdam ERSPC study in 3616 men biopsied and 885 tumors being found) by adding information about digital rectal examination (DRE) findings and transrectal ultrasound (TRUS) findings. Here the performance of the tests to detect Gleason >6 cancers is depicted. Analyses provided by Roobol

Model #	Model description	AUC	95% CI
1	PSA	0.74	0.71-0.77
2	PSA+DRE	0.82	0.79-0.84
3	PSA+DRE+DRE assessed volume	0.85	0.82-0.87
4	PSA+DRE+TRUS+TRUS assessed volume	0.86	0.84-0.88

Table 1 Relevant new biomarkers and an estimation of performance related to detection of Gleason ≥7 prostate cancer (Murray et al. 2016; Carlsson and Roobol 2017; Hendriks et al. 2017). From each marker an indication is given of the number of unnecessary biopsies that could be avoided ("saved") at the cost of the number of Gleason ≥7 cancers being missed ("missed"). Unfortunately, head-to head comparison of the separate markers is generally not available

	Diagnosis of GS ≥7 PCa missed (%)	Prostate biopsies avoided (%)
Free PSA	23	66
PCA3	3–13	46
PHI	5	36–41
4 K panel	1.3–4.7	30–58
mCPCs	6	54
STHLM3 model	0	32
MiPS	1	35
SelectMDX	2	42
mpMRI-targeted prostate biopsy	20	27
ERSPC risk calculator 12.5% cutoff	0	33

and cost-effectiveness analyses depend on sufficient evidence.

The PROMIS study has demonstrated the potential benefits of mpMRI in a primary diagnostic setting by comparing with template prostate mapping biopsies (Ahmed et al. 2017).

Urinary markers like PCA3 and SelectMDX also can have added value in the case of rising suspicion of prostate cancer, but the added value is modest and misses the advantage of imaging which enables localizing and taking targeted biopsies from areas of suspicion.

The list of other available biomarkers is extensive and grows almost daily. Biomarkers can be roughly subdivided in urinary and serum markers like PSA subforms and genomics or imaging modalities. There are several markers and diagnostics that are promising (Table 1) (Gaudreau et al. 2016; Loeb et al. 2016; Hendriks et al. 2017).

As an example of technical progression, the measurement of circulating tumor cells (mCPCs) is described as a very promising tool but up to now has only been tested in a limited number of men in Chile. The performance of diagnostic tests can differ considerably in different populations, and hence comparing biomarkers and other diagnostic tools should be done with caution.

In addition, an improved pathological grading system like the presence of cribriform growth patterns helps to get a better understanding of disease burden and as such aids in developing better prediction tools (Kweldam et al. 2016).

Performance of mpMRI and other individual markers has been extensively studied, but as said, head-to-head comparison of different markers on large screening cohorts has not sufficiently been done, and so far these innovations have not lead to significant changes in daily clinical practice. Although PHI, PCA3, and certainly mpMRI with targeted biopsies are very promising, a good analysis of cost-effectiveness and when and how often to apply these markers has to be performed before widespread application is justified.

The ultimate goal is a balance between not missing too many high-risk prostate cancers and avoiding unnecessary biopsies. Although imaging techniques like mpMRI improved the detection of high-grade prostate cancer, high-volume Gleason 6 prostate cancer can remain undetected. In patients with a long life expectancy, these tumors might still become clinically significant. New imaging modalities like PET imaging with PSMA or bombesin analogues may have added value in detecting the lower-grade cancers, but this is to be further explored, and until this day we need pathological confirmation by prostate biopsies. In summary, the number of tests and imaging techniques is constantly increasing and shows an increase in the potential to detect high-

grade prostate cancer. However, we must never forget cost-effectiveness and generalizability.

When to Start and When to Stop Screening

By enriching the cohort of men being at highest risk of having high-grade disease will improve the effectiveness of a screening strategy. Risk factors like age, family history, race/ethnicity, and baseline PSA level in midlife could serve as discriminators to determine the start of screening and rescreening intervals. As prostate cancer is more prevalent at older age, the age at which to start the first prostate cancer screening test should be relatively high. But the higher the age, the higher the chance of missing the opportunity of cure in some cases. The PROBASE study (Arsov et al. 2013) aims to show that an initial screening round in men at age 45–50 could result in deferral of a second screening round by 5 years if initial PSA is <1.5 ug/L. In practice however, recommendations concerning when to screen and when not to may be put aside (i.e., PSA testing within the screening interval in the randomized trials or the USPSTF recommendations) by already raised awareness of doctors and first-screen participants or by practical logistics like yearly medical checkup visits for other common health issues.

And the question when to stop screening is also a difficult one. It is clear that high-grade prostate cancers have an up to tenfold higher mortality rate than low-grade prostate cancers (Chodak et al. 1994). Although these tumors account for a minority of early-detected cancers, they are expected to benefit most from early detection and early treatment. Even prostate cancers diagnosed after the age of 75 tend to be later stage tumors with $>50\%$ prostate cancer-related death rates (Scosyrev et al. 2012). Healthy men with a prosperous life expectancy might still benefit from screening at a higher age. This implies that the overall impact on quality of life and cost-effectiveness has to be taken into account (Carlsson et al. 2016). In the end we need to be able to support individual choices incorporating a reliable life expectancy estimate and risk of life threatening prostate cancer in risk calculators and web-based decision aids.

Conclusions

Randomized controlled trials addressing the merits of population-based prostate cancer screening have shown us that the methods of screening that have been applied need improvement. Much is expected from diagnostic tools being able to detect intermediate- and high-risk prostate cancer in an early still curable way and not detecting prostate cancers that would never in a lifetime of a healthy man would cause symptoms or death. Until the discovery of a prostate cancer treatment with negligible effects on quality of life, screening strategies have to be improved in order to be applied on a population level. These RCTs have given us a huge amount of data that can help us in calculating the extent of potential diagnostic improvement. The available data showed that individual risk stratification is a definite need. Only in this way we can control harms and benefits. Individual prostate cancer screening is here to stay, recommendations on totally avoiding PSA testing for early detection have proven to be ineffective or even counter-effective, and hence it is of upmost importance to apply testing to only those who have a high likelihood of having benefit. The ongoing research on new biomarkers and their combination with clinical data in prediction models is currently the way to go. Obviously, patient wish and expectations should not be forgotten in the decision process, making the decision to screen or not to screen a well-informed individual shared decision. Every individual patient will have to make a personal choice concerning the balance of costs and benefits. And in fact, the first step of this journey starts at the moment he is not yet a prostate cancer patient, the moment he has to decide whether or not he will have his prostate cancer risk evaluated. And to this day the initiative of prostate cancer screening is in general not population based, not by invitation by a government institution, but it is mainly a personal initiative, a dilemma for men and their physicians.

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6 Risk Assessment Based on Molecular and Genetic Markers in Prostate Cancer

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Abstract

The current treatment paradigm of prostate cancer has increasingly emphasized the importance of reliable biomarkers that help stratify patients and aid in decision-making. The rapid development of numerous novel biomarkers in the past decade has made this process much more challenging. In this chapter, we provide a comprehensive review of the widely used biomarkers that are supported by clinical evidence. Specifically, the focus will be on diagnostic (PHI®, 4K score, IsoPSA®, SelectMDx®, ConfirmMDx®, PCA3, TMPRSS2:ERG gene fusion) and prognostic (OncotypeDX GPS®, Prolaris®, ProMark®, Decipher®) biomarkers. In order to better understand the value of these biomarkers in clinical decision-making, there will be an emphasis on clinical context as the literature is reviewed.

Keywords

Biomarker · Prostate cancer · Molecular marker · Genetic marker · Prognostic

Introduction

Prostate cancer (PCa) has now surpassed lung cancer as the most common solid malignancy in men in the United States, with 180,890 new cases in 2016 alone (Siegel et al. 2016). While prostate-specific antigen (PSA) value, imaging diagnostics, and histopathological scores (e.g., Gleason score) enable traditionally enabled risk stratification to a certain degree, it is now clear that there remains significant variability within these patient populations. As such, it remains difficult to predict an individual patient's prognosis at the outset. With this uncertainty, some patients may be overtreated with invasive interventions, while others may be denied potentially beneficial treatment.

As the management of prostate cancer changes on multiple fronts, there has been an increasing need for reliable biomarkers that help physicians and patients in the decision-making process. As the number of potentially indolent low-risk prostate carcinomas increases, there remains uncertainty regarding the management of the patients bordering intermediate-risk disease. On the other end of the spectrum, in advanced prostate cancer, there have been an increasing number of adjuvant therapies with promising clinical outcomes in select patient populations. Current international guidelines, while indicating that various evidence-based treatment options exist for these patients, emphasize that validated biomarkers to guide the pre-treatment decision process are urgently needed for this growing patient population, though they fall short of recommending any specific biomarker in the absence of strong clinical data (Thompson et al. 2007; Mohler et al. 2016; Mottet et al. 2017).

In the following chapter, we focus on diagnostic, prognostic, and predictive biomarkers that are in widespread clinical use and are supported by profound evidence. While a multitude of novel biomarkers have been introduced in the past few years, in this chapter, we focus on clinical situations in which novel biomarkers may guide decision-making. As the treatment of prostate cancer is essentially on a continuum, many of these biomarkers may overlap in their clinical use and are by no means mutually exclusive.

Diagnostic Biomarkers

Traditionally, digital rectal examination (DRE) and PSA alone were utilized to risk stratify at-risk patients. While they correctly stratify many patients, treating physicians remain uncertain whether to perform an invasive prostate biopsy in a significant proportion of patients. In this clinical scenario, diagnostic biomarkers may help guide the physician regarding which patients warrant an initial biopsy and which patients warrant a re-biopsy after an initially negative biopsy but continued suspicion of PCa. Table 1 provides a summary of the studies discussed in this section.

Prostate Health Index PHI® (Beckman Coulter, Brea, USA)

While there is no question that the introduction of PSA has revolutionized the diagnosis of prostate cancer, the fact that it is not specific for prostate cancer has been an important limitation to its utility. As further research has addressed the issue, it is more evident that there is no widely accepted standard for its measurement or any standard cutoffs for screening purposes. Thompson et al. (2004) showed that a significant proportion of men harbor PCa despite having a PSA level <4.0 ng/ml, and it has been reported that the specificity of PSA alone is only 12.8% when using that cutoff, leading to a high false-positive rate and unnecessary subsequent biopsies (Filella et al. 2014).

As PSA alone appears to be inadequate, attempts have been made to increase its utility. In addition to total PSA, there are two additional measurable subforms: percentage of free PSA (% fPSA) and [-2]proPSA (p2PSA). The prostate health index (PHI) (Beckman Coulter, Brea, USA) combines these three PSA subforms into a single mathematical score and has been evaluated in a multicenter setting (Le et al. 2010). Stephan et al. (2013) analyzed a total of 1362 patients with a total PSA value of 1.6–8.0 ng/ml who underwent systematic prostate biopsy with 10 or more cores. PHI [area under the curve (AUC) = 0.74] outperformed each subform in isolation: % p2PSA (AUC = 0.72), p2PSA (AUC = 0.63), % fPSA (AUC = 0.61), and tPSA (AUC = 0.56). In addition, significantly higher median PHI scores were found in patients that harbored Gleason ≥7 PCa (PHI = 60 vs. PHI = 53, $p = 0.0018$). More recently, Tosoian et al. (2017) analyzed 118 patients with PSA levels >2.0 ng/ml and negative digital rectal examination (DRE) who underwent PHI testing and subsequent prostate biopsy. In this study, they augmented PHI by account for prostate volume, thereby calculating PHI density. Median PHI density was 0.70 for patients with significant PCa according to biopsy results [interquartile range (IQR) 0.43–1.21] compared to 0.53 (IQR 0.36–0.75) for patients with insignificant PCa or negative biopsies ($p < 0.001$). The authors defined a PHI density cutoff threshold of 0.43, which was associated with a sensitivity of 97.9% and a specificity of 38.0% for detection of clinically significant PCa, and sensitivity for Gleason ≥7 PCa was 100.0%. The diagnostic accuracy for detection was higher for PHI density (AUC = 0.84) compared to tPSA (AUC = 0.52), %fPSA (AUC = 0.75), and PHI alone (AUC = 0.76). Similar to the interest in PSA density, PHI density might be a promising tool in PCa diagnosis, ultimately leading to a reduced number of unnecessary biopsies.

As opposed to augmenting PHI with prostate volume data, another area of interest has been combining PHI with currently available imaging diagnostic options. Gnanapragasam et al. (2016) investigated 279 patients undergoing multiparametric MRI (mpMRI)-guided transperineal re-biopsy. They demonstrated that PHI was able to add predictive value to mpMRI regarding diagnosis of all cancer (AUC = 0.71) and clinically significant cancers (AUC = 0.75) compared to mpMRI and PSA alone (AUC = 0.64 and AUC = 0.69, respectively). The authors found that a PHI threshold of 35, when used in combination with mpMRI, was associated with a

Table 1 Summary of the studies investigating diagnostic biomarkers

Study	Biomarker (# patients enrolled)	Analyzed endpoints	Brief summary
Stephan et al. (2013)	PHI (1362)	Detection of any PCa	PHI (AUC = 0.74) with better diagnostic performance compared to %p2PSA (AUC = 0.72), p2PSA (AUC = 0.63), %fPSA (AUC = 0.61), and tPSA (AUC = 0.56)
Tosoian et al. (2017)	PHI (118)	Detection of clinically significant PCa	Sensitivity 97.9%, specificity 38.0% for PHI density for clinically significant PCa/sensitivity 100% for PHI density for Gleason≥7 PCa
Gnanapragasam et al. (2016)	PHI (279)	Detection of any PCa/clinically significant PCa (addition to mpMRI)	Addition of PHI to mpMRI leads to improved detection ability of any PCa and clinically significant PCa (AUC 0.71 and 0.75, NPV 0.97)
Vickers et al. (2010)	4K score (2914)	Detection of any and high-grade PCa	Addition of %fPSA, intact tPSA, and hK2 improved AUC (0.76 vs. 0.64) compared to a hypothetical model containing tPSA and age alone ($p < 0.001$)
Stattin et al. (2015)	4K score (1423)	Risk of metastatic PCa for different tPSA levels and a statistical model based on 4 K score	Among men with tPSA >2 ng/ml, 4K score significantly improves prediction of metastatic PCa compared with tPSA alone ($p < 0.01$)
Nordstrom et al. (2015)	PHI/4K score (513)	Detection of any and high-grade PCa	4K score: AUC 69.0 (any PCa) and 71.8 (high-grade PCa)/PHI: AUC 70.4 and 71.1
van Neste et al. (2016)	SelectMDX (905)	Detection of clinically significant PCa	Multimodal approach (mRNA signature, tPSA density, previous negative biopsies, tPSA, age, family history) with overall AUC of 0.90 (95% CI 0.85–0.95)
Stewart et al. (2013)	ConfirmMDx (483)	Detection of any PCa	Biomarker panel with NPV of 90% (sensitivity 68%, specificity 64%) and independent predictor for any PCa [OR 3.17, 95% CI 1.81–5.53; $p < 0.001$]
Partin et al. (2014)	ConfirmMDx (350)	Detection of any PCa	NPV of 88% (95% CI 85–91) and independent predictor for any PCa (OR 2.69, 95% CI 1.60–4.51)
Fradet et al. (2004)	PCA3 (443)	Detection of any PCa	Overall sensitivity 68%, overall specificity 89%/NPV: 84% [vs. 80% (tPSA cutoff 4.0 ng/ml)], PPV 75% (vs. 38%), overall accuracy 81% (vs. 47%)
Haese et al. (2008)	PCA3 (463)	Detection of any PCa	Increased risk of positive re-biopsy findings for PCA3 levels of ≥35 (39%) compared to patients with PCA3 levels <35 (22%, $p < 0.0001$)/PCA3 score independent predictor of detection of PCa in re-biopsy ($p < 0.007$)

(*continued*)

Table 1 (continued)

Study	Biomarker (# patients enrolled)	Analyzed endpoints	Brief summary
de la Taille et al. (2011)	PCA3 (516)	Detection of any PCa	Increased PCA3 levels correlate with increased probability of positive biopsy findings [mean PCA3 levels: 69.1 vs. 31.0; $p < 0.0001$]/PCA3 score independent of age, tPSA, and prostate volume
Wei et al. (2014)	PCA3 (859)	Detection of any PCa (PPV for initial biopsy, NPV for repeat biopsy)	Initial biopsy: PPV 80% (95% CI 72–86%) for PCA3 levels of >60/ repeat biopsy: NPV 88% (81–93) for PCA3 levels of <35
Ploussard et al. (2011)	PCA3 (106)	Prediction of clinically insignificant PCa	PCA3 levels correlate with tumor volume ($p < 0.001$, $r = 0.409$) and PCA3 score ≥25 independent predictive factor for tumor volume ≥0.5 cm^3 (OR 5.4; $p = 0.010$) and significant PCa (OR 12.7; $p = 0.003$)
Demichelis et al. (2007)	TMPRSS2:ERG (252)	CSS	Significant association between TMPRSS2:ERG status and CSS (95% CI 1.3–5.8; $p < 0.01$)
Pettersson et al. (2012)	TMPRSS2:ERG (1180)	BCR and CSS	TMPRSS2:ERG associated with stage at diagnosis [RR (≥pT3 vs. pT2) 1.23; 95% CI 1.16–1.30] but not correlated with BCR (RR 1.00; 95% CI 0.86–1.17) and lethal PCa (RR 0.99; 95% CI 0.47–2.09)
Leyten et al. (2014)	TMPRSS2:ERG/ PCA3 (497)	Detection of any PCa compared to tPSA and ERSPC risk calculator	PCA3 and TMPRSS2-ERG add significant PV to ERSPC risk calculator ($p < 0.001$, $p = 0.002$, AUC of combination 0.842)/ addition of TMPRSS2:ERG increases sensitivity of PCA3 from 68% to 76%
Klein et al. (2017)	IsoPSA (261)	Detection of any PCa and high-risk PCa compared to tPSA	Outperformed PSA in the detection of any cancer (AUC 0.79 [IsoPSA] vs.0.61 [tPSA]) and high-grade cancer (0.81 vs. 0.69). KR cutoff 35–90% sensitivity/48% specificity to identify any cancer. High-risk PCa: KR cutoff 17% ➔ 96% NPV, while KR cutoff 70% ➔ 76% PPV

AUC area under the curve, *BCR* biochemical recurrence, *CI* confidence interval, *CSS* cancer-specific survival, *DRE* digital rectal examination, *mpMRI* multiparametric MRI, *NPV* negative predictive value, *OR* odds ratio, *PCa* prostate cancer, *PHI* prostate health index, *tPSA* total prostate-specific antigen, *%fPSA* percentage of free PSA, *PPV* positive predictive value, *PV* predictive value, *RR* risk ratio

negative predictive value (NPV) of 0.97 for excluding clinically significant PCa. Importantly, only 1 of 21 significant cancers was missed, and 42% of patients could have been spared a re-biopsy.

Ultimately, PHI, either in combination with prostate volume or available imaging diagnostic options, represents a potentially important tool to help risk stratify patients for prostate biopsy.

4K Score

In contrast to PHI, the 4K score combines age and DRE with four different kallikrein markers (tPSA, %fPSA, intact PSA, hK2). Initially described by Vickers et al. (2010), its aim was to specifically detect potentially lethal PCa, thereby reducing the numbers of unnecessary biopsies and reducing the diagnosis of clinically insignificant or indolent prostate cancer. In a group of 2914 men that underwent prostate biopsy due to elevated PSA levels of 3 ng/ml or more, PCa was detected in 28% of men. Addition of the kallikrein marker panel to PSA level and age alone resulted in a significantly improved diagnostic accuracy with (AUC = 0.78 vs. 0.70, $p < 0.001$) or without (AUC = 0.76 vs. 0.64, $p < 0.001$) inclusion of DRE findings. Based on this, in a population of 1000 men with elevated PSA levels, the 4K score would reduce the number of biopsies by 513. However, 12 out of every 100 high-grade cancers would have been missed. Subsequent validation was completed in a population-based case-control study of 40,379 patients by Stattin et al. (2015). They measured the 4K markers in cryopreserved blood and analyzed the diagnostic value of the marker panel regarding the risk of distant metastasis during long-term follow-up. In a statistical model focusing on patients with a PSA level of >3.0 ng/ml, the patients were separated by 4K score: >7.5% (62% of all patients) and ≤7.5% (38%). Using this stratification, the risk of distant metastases was found to be 2.4%, 5.6%, 9.9%, and 16.4% after 5, 10, 15, and 20 years for the high-risk >7.5% group and 0%, 0.2%, 1.0% and 1.8% for the low-risk ≤7.5% group.

PHI® and 4K Score Combined

Nordstrom et al. (2015) took this one step further by combining these two tests. The predictive value of the combination was assessed in 513 men who underwent initial prostate biopsy due to elevated PSA levels that ranged between 3 and 15 ng/ml. The AUCs for both tests were similar for prediction of any PCa [69.0 (4K score) vs. 70.4 (PHI)] as well as high-grade PCa (71.8 vs. 71.1), and both tests outperformed PSA levels alone ($p < 0.0001$, respectively). After defining cutoff values for both scores [10% (4K score), 39 (PHI score)], they found that 29% of biopsies could be spared based on the combination model, but 10% of high-grade PCa would be missed by strictly following these cutoff levels. The authors concluded that both marker panels represent simple blood tests that are able to reduce the number of unnecessary prostate biopsies compared to screening with PSA only and therefore represent promising options to reduce harm.

IsoPSA® (Cleveland Diagnostics, Cleveland, USA)

In contrast to the 4K score and prostate health index, which focus on the concentration of various isoforms of PSA, a novel technology developed by Cleveland Diagnostics focuses on the structure of PSA. Using an aqueous two-phase solution, it partitions the isoforms of PSA; however, as it assesses broadly for structural changes in PSA, it is not limited by the heterogeneous expression of isoforms across patient populations.

Klein et al. (2017) described the initial experience of IsoPSA in a multi-institutional prospective study of 261 men scheduled for prostate biopsy at 5 centers. After obtaining samples within 30 days of biopsy, men underwent initial 12-core transrectal ultrasound (TRUS) or MRI-TRUS fusion biopsy. The IsoPSA assay readout, or test parameter *K*, was used directly to classify patients but also converted by logistic regression to an individual risk probability, KR. There was no significant correlation between IsoPSA *K* and serum PSA levels. IsoPSA outperformed PSA in the detection of any cancer (AUC 0.79 [IsoPSA] vs.0.61 [tPSA]) and high-grade cancer (0.81 vs. 0.69). The authors identified a KR cutoff of 35% that provided high sensitivity (90%) and specificity (48%) for the identification for any cancer, as compared to a tPSA cutoff of 4 ng/mL, which for a similar sensitivity (87%) has significantly inferior specificity (15%). Similarly, in the assessment of high-risk cancer vs. low-risk/benign disease, the authors

noted a KR cutoff of 17% yielded a NPV of 96%, while KR cutoff of 70% yielded a PPV of 76%.

While novel in concept, this biomarker is still early in its clinical evaluation. Further validation studies are required before any recommendations can be made regarding its utility.

SelectMDx® (MDx Health, Irvine, USA)

The SelectMDx test uses reverse transcription PCR to measure messenger RNA (mRNA) levels of a 2-gene panel (DLX1 and HOXC6) in a urine sample obtained immediately following a DRE while using KLK3 expression as an internal reference (Leyten et al. 2015). Combined with traditional risk factors, such as tPSA, age, history of prostate biopsy, and family history, the test also serves as a diagnostic assay.

Clinical validation on post-DRE urine samples from 905 patients from two independent prospective clinical trials was performed by Van Neste et al. (2016). They evaluated the diagnostic value and clinical utility of the 2-gene panel against prostate biopsy specimens. An overall AUC of 0.90 [95% confidence interval (CI) 0.85–0.95] was observed when using the gene panel in combination with the aforementioned traditional risk factors in the validation cohort. AUC was 0.86 (95% CI 0.80–0.92) with the addition of DRE, however. Subsequently, a decision curve analysis was performed to evaluate the clinical utility of the model, comparing it to other decision-making models (e.g., Prostate Cancer Prevention Trial risk calculator with or without PCA3 test). A 42% total reduction of biopsies and a 53% decrease in unnecessary biopsies could be observed for the model. It was also associated with a negative predictive value of 98% for clinically significant Gleason $\geq$7 PCa.

ConfirmMDx® (MDx Health, Irvine, USA)

Among epigenetic alterations, which are frequently observed in all tumor stages, DNA (hyper)methylations are considered to be very suitable for biomarker assessment. As they occur very frequently and can induce a very stable knockdown of their respective gene, they can lead to significant changes in cell biology. *GSTP1* (glutathione-S-transferase P1), in particular, has been highlighted as a promising tissue marker. The sensitivity of *GSTP1* methylation in detecting PCa was 81.8% (specificity 94.9%, NPV 94.9%, accuracy 92.0%) in a standardized cohort, as demonstrated by Van Neste et al. (2012) in a recent meta-analysis. By including the methylation status of the tumor suppressor gene *APC* (adenomatous polyposis coli) in the biomarker panel, they demonstrated that they could increase the sensitivity to 92.8%, while the specificity was 95.3% and NPV was 97.9%. Trock et al. (2012) found similar results when comparing the methylation status of *GSTP1* and *APC* in 86 patients in the primary biopsy specimen after a negative prostate biopsy to the findings in the re-biopsy specimen. Sensitivity and NPV was 95% and 96% for *APC* hypermethylation and 43% and 80% for *GSTP1* hypermethylation, respectively.

Analyzing the methylation status of *GSTP1*, *APC*, and *RASSF1* (Ras association domain-containing protein 1), the ConfirmMDx is a commercially available biomarker test that expands on the idea that epigenetic changes influence gene expression without changing the genome. By assuming that a field effect (halo effect) is associated with the presence of cancer at the DNA level, this biomarker assesses for an epigenetic halo around PCa lesions that may be present despite having a normal morphologic appearance under microscopic evaluation by the pathologist. As such, it utilized residual tissue from previous negative biopsies as its source material to rule out prostate cancer. Stewart et al. (2013) evaluated 483 patients who had a negative initial biopsy and subsequent re-biopsy within 30 months to evaluate the diagnostic performance of the ConfirmMDx marker panel. As the goal of the test was to effectively rule out prostate cancer, the primary endpoint was the NPV, which they found to be 90% (sensitivity 68%, specificity 64%). The biomarker panel was an independent predictor for "any PCa in prostate biopsy" [odds ratio (OR) 3.17, 95% CI 1.81–5.53; $p < 0.001$]. In

a clinical validation study of 350 patients in 5 centers completed by Partin et al. (2014), the NPV was 88%. The main limitation and critique of both studies is that the goal was to rule out any cancer, not specifically clinically significant prostate cancer. As such, its diagnostic role is limited in the current era, which emphasizes clinically significant PCa diagnosis. Current guidelines conclude that additional information may be gained by its use in the re-biopsy setting; however, based on the limited current evidence, no recommendation has been made so far.

Prostate Cancer Antigen 3 (Progensa, Bedford, USA)

Another test that assesses mRNA in a post-DRE urine specimen, as well as in a first-void specimen, is the Progensa prostate cancer antigen 3 (PCA3) biomarker test, which measures PCA3 mRNA. In contrast to the PPV for tPSA alone (38%), the initial study by Fradet et al. (2004) found that the PCA3 test had a sensitivity of 74% [specificity 91%, positive predictive value (PPV) 75%] for predicting positive biopsy results in patients with a PSA level of less than 4 ng/ml. However, establishing a PCA3 cutoff as a subsequent step has been less straightforward. Haese et al. (2008), in a prospective study including 463 men with a prior negative prostate biopsy, used a cutoff of 35. In this study, they found an increased risk of positive re-biopsy findings for PCA3 levels of $\geq$35 (39%) compared to patients with PCA3 levels <35 (22%, $p < 0.0001$), and in univariate and multivariable analysis, the PCA3 score was confirmed as an independent predictor of detection of any PCa at the time of re-biopsy ($p < 0.007$) and had a greater diagnostic accuracy than %fPSA (cutoff 25%). In another European multicenter study including 516 men with suspicious PSA levels, the cutoff of 35 was again utilized. In doing so, the authors found the highest diagnostic accuracy for a cutoff level of 35 (sensitivity 64%, specificity 76%). The AUC was similar for patients with tPSA levels <4 ng/ml (AUC = 0.754) compared to those with PSA levels of 4 ng/ml or more (AUC = 0.760), and increased mean PCA3 levels were observed for patients with positive biopsy findings (69.6 vs. 31.0, $p < 0.0001$). Ultimately, like PSA, PCA3 is a continuous variable, as demonstrated by the fact that on a univariable logistic regression model, continuous PCA3 scores demonstrated the highest accuracy in predicting any kind of PCa (OR 1.02, 95% CI 1.01–1.02, $p < 0.001$, predictive accuracy 0.749) and outperformed tPSA, PSA density (PSAD), and %fPSA (de la Taille et al. 2011). Furthermore, as the PPV was 80% for PCA3 levels >60 before primary biopsy and the NPV was 88% for PCA3 levels <20 before re-biopsy after a negative primary biopsy, Wei et al. (2014) concluded that PCA3 levels >60 increase the probability of PCa detection in the initial biopsy significantly.

The PCA3 test has also transitioned to being evaluated as a prognostic marker guiding active surveillance decisions in low-risk PCa patients. In 106 patients with low-risk PCa before radical prostatectomy (RP), Ploussard et al. (2011) found a correlation between PCA3 score, tumor volume, and an increased rate of clinically significant PCa using a PCA3 cutoff level of 25. While the results of these prior studies highlight the fact that no globally accepted cutoff value for PCA3 scores can be established, it should be noted that the cutoff levels should be evaluated based on the indication of the biomarker test. Since being FDA approved for repeat biopsies after an initial negative biopsy in 2012, the current guidelines recommend the use of the PCA3 test before re-biopsy after a negative primary biopsy, but not as an active surveillance monitoring tool.

Transmembrane Protease Serine 2:ERG (TMPRSS2:ERG Gene Fusion)

Gene fusions are not uncommon in the cancer setting, and the fusion of the enzyme transmembrane protease, serine 2 (TMPRSS2), and the *ERG* gene can be detected in up to 50% of PCa. Duplication of the TMPRSS2:ERG gene fusion led to a significantly decreased 8-year overall survival (25% vs. 90%, $p < 0.001$) in a watchful waiting cohort of 445 patients (Attard et al. 2008) In a separate study, Demichelis et al. (2007) found a statistically significant correlation between

TMPRSS2:ERG gene fusion and cancer-specific death rates (95% CI 1.3–5,0.8; $p < 0.01$), confirming the previous results. However, the prognostic value of TMPRSS2:ERG gene fusion seems to be lower after RP. A meta-analysis of 5074 patients by Pettersson et al. (2012) assessed for biochemical recurrence after RP as well as lethal disease in 2049 patients. They did not find a significant correlation between TMPRSS2:ERG gene fusion status and biochemical recurrence (95% CI, 0.86–1.17, relative risk 1.00) or lethal disease (95% CI, 0.47–2.09, relative risk 0.99).

On the other hand, prior to RP, Leyten et al. (2014) demonstrated that addition of TMPRSS2:ERG gene fusion status was able to improve the sensitivity of the PCA3 test from 68% to 76%. However, as these promising results could not be confirmed in validation studies, the prognostic and diagnostic value of the TMPRSS2:ERG gene fusion status remains controversial.

Prognostic Biomarkers

In contrast to the diagnostic biomarkers reviewed previously, the following biomarkers focus on predicting cancer-specific outcomes. As indicated in the guidelines, traditional cancer-specific outcomes, such as cancer-specific survival and overall survival, while clinically important, require long-term follow-up to adequately assesse differences. Surrogates for these traditional outcomes, including biochemical recurrence (BCR)-free survival, metastases-free survival, and the presence of adverse features at the time of radical prostatectomy, among others, have become an important tool to clinically assess these novel biomarkers.

The tests below may help guide decision-making by predicting cancer-specific outcomes, thereby better informing the patient and physician. Table 2 provides a summary of the studies discussed in this section.

OncotypeDX Genomic Prostate Score® (Genomic Health, Redwood City, USA)

Predicated on the thought that a combination of multiple biological pathways may improve predictive accuracy over a test assessing a single pathway, the OncotypeDX Genomic Prostate Score (GPS) is based on a multigene assay consisting of 17 genes (12 genes related to androgen metabolism, cellular organization, proliferation, and stromal response and 5 reference genes). Designed to specifically allow risk assessment for selecting candidates for active surveillance, it predicts adverse pathologic features at the time of radical prostatectomy (RP), generating valid results particularly for patients with small volume tumors in biopsy specimens (Klein et al. 2014) Analytical validation of the assay was performed by Knezevic et al. (2013), and they demonstrated that reproducibility and precision were excellent with only minimal variation (standard deviation 2.11 and 1.86 on a 100-point scale).

Klein et al. (2014) provided the assessment of prognostic accuracy and clinical validation of the GPS using three independent study cohorts. In the discovery cohort consisting of 441 patients who underwent RP between 1984 and 2004, 110 had biochemical recurrence [BCR] and were matched 1:3 with patients who did not develop BCR. The remaining two cohorts were 167 patients after prostate biopsy and subsequent RP within 6 months between 1999 and 2007 or 395 patients who were candidates for active surveillance but who chose RP within 6 months of diagnosis. First, the authors identified the abovementioned 17-gene signature out of 732 initial candidate genes in a multistep procedure. The GPS (ranging from 0 to 100), in which higher scores indicate more aggressive disease, was generated and validated in the prospective study cohort. Even accounting for the validated CAPRA score (OR 2.1, 95% CI 1.4–3.2, $p < 0.005$), the GPS was still able to predict both high-grade (Gleason ≥ 7) and high-stage (pT stage ≥ 3) disease [OR for 20 units 2.3, 95% CI 1.5–3.7, $p < 0.001$ (high-grade); 1.9, 1.3–3.0, $p = 0.003$ (high-stage)]. By assessing multiple pathways, the authors felt that GPS could overcome issues of tumor heterogeneity and multifocality and, in doing so, would reduce the risk of undersampling during prostate biopsy. Focusing more on prognosis, Cullen et al. (2015) assessed recurrence-free survival in a study cohort of 431 patients with biopsy-proven low-risk or intermediate-risk PCa, with a median

Table 2 Summary of the studies investigating prognostic biomarkers

Study	Biomarker (# patients enrolled)	Analyzed endpoints	Brief summary
Klein et al. (2014)	Oncotype DX GPS (1003)	Clinical recurrence rate, cancer-specific mortality, adverse pathology at RP	Identification of a score (GPS) based on a 17-gene panel/GPS predicts high-grade (OR 2.3; 95% CI, 1.5–3.7; $p < 0.001$) and high-stage (OR 1.9; 95% CI, 1.3–3.0; $p = 0.003$) disease in RP specimen
Cullen et al. (2015)	Oncotype DX GPS (431)	Recurrence-free survival, adverse pathology at RP, time to metastatic disease	GPS predicts time to recurrence (HR 2.73, 95% CI 1.84–3.96, $p < 0.001$) and is an independent predictor of BCR (1.69, 1.08–2.66, $p = 0.022$)
Cuzick et al. (2011)	Prolaris (703)	BCR (RP cohort), CSS (WW cohort)	Increase of developed mathematical (CCP) score predicts BCR (HR 1.77, 95% CI 1.40–2.22, $p < 0.0001$) and CSS (HR 2.57, 95% CI 1.93–3.43, $p < 0.0001$)
Freedland et al. (2013)	Prolaris (141)	BCR	Increase of CCP-score independently predicts BCR (HR 2.11, 95% CI 1.05–4.25, $p = 0.034$)
Bishoff et al. (2014)	Prolaris (582)	BCR, metastatic disease (biopsy-based)	CCP-score independent predictor of BCR (HR 1.47, 95% CI, 1.23–1.76, $p < 0.0001$) and metastatic disease (HR 4.19, 95% CI 2.08–8.45, $p < 0.0001$)
Cooperberg et al. (2013)	Prolaris (413)	Biochemical/clinical recurrence	CCP predicts biochemical recurrence (HR 1.7; 95% CI 1.3–2.4) and is able to stratify patients with low clinical risk (HR 2.3; 95% CI 1.4–3.7)
Cuzick et al. (2015)	Prolaris (585)	Cancer-specific mortality	CCP-score predicts cancer-specific mortality (HR 2.08, 95% CI 1.76–2.46, $p < 0.001$)
Shipitsin et al. (2014b)	ProMark (380)	Cancer-specific mortality, adverse pathology at RP	12-biomarker panel is correlated with high-risk PCa (AUC 0.72; OR 20.0, 95% CI 4.3–257.0) and cancer-specific mortality (AUC 0.71; HR 36.0, 95% CI 3.3–2889)
Blume-Jensen et al. (2015)	ProMark (657)	Adverse pathology at RP	8-biomarker panel: PPV for favorable pathology in low-risk patients: 87.2%/ prediction of favorable pathological findings (AUC 0.68; OR 20.9, $p < 0.0001$) and Gleason-6 PCa (AUC 0.65; OR 12.95, $p < 0.0001$)
Den et al. (2014)	Decipher (139)	BCR, metastatic PCa	Newly developed genomic classifier able to predict freedom of metastases (AUC 0.78) and freedom of BCR (AUC 0.75)
Karnes et al. (2018)	Decipher (561)	Cancer-specific mortality within 10 years	Genomic classifier as independent predictor of 10-year PCSM (high-risk vs. low-risk, OR 3.91, 95% CI 2.43–6.29, AUC = 0.77)
Ross et al. (2014)	Decipher (85)	Metastatic PCa	A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy.
Klein et al. (2016)	Decipher (57)	Metastatic PCa	Genomic classifier able to predict 10 years risk of metastatic PCa following RP at time of prostate biopsy (HR 1.75, 95% CI 1.97–2.81, $p = 0.02$)

AS active surveillance, *AUC* area under the curve, *BCR* biochemical recurrence, *CCP* cell cycle progression, *CI* confidence interval, *CSS* cancer-specific survival, *HR* hazard ratio, *OR* odds ratio, *PCa* prostate cancer, *PPV* positive predictive value, *tPSA* total prostate-specific antigen, *dtPSA* PSA double time, *%fPSA* percentage of free PSA, *RP* radical prostatectomy, *RT* radiotherapy, *WW* watchful waiting

follow-up of 5.2 years. During this period, 62 patients (15%) had BCR; GPS was able to significantly predict the time to recurrence (hazard ratio [HR] for 20 units: 2.73, 95% CI 1.84–3.96, $p < 0.001$) and, on multivariable analysis, was an independent predictor of BCR (1.69, 1.08–2.66, $p = 0.022$).

OncotypeDX can be used by physicians if active surveillance is considered, as it helps predict which patients will have higher stage or grade disease at the time of RP and also predicts higher BCR rates. However, current guidelines state that results of prospective multicenter trials need to be awaited before a final recommendation can be made.

Prolaris® (Myriad Genetics Inc., Salt Lake City, USA)

The Prolaris test (Myriad Genetics Inc., Salt Lake City, USA) is constructed on a gene signature and consecutive score that is based on the work of Cuzick et al. (2011) and assesses alterations in cell cycle regulation, which are key players in cancerous transformation. Based on 96 commercially available prostate cancer tissue specimens and an evaluation of 126 genes that have been related to cell cycle regulation, they developed a gene signature consisting of 31 cell cycle genes. Utilizing RT-PCR and normalizing against 15 housekeeping genes, they quantified RNA expression of these respective genes. Their subsequent mathematical score, called the CCP-score, reflects the general expression of cell cycle regulators. Positive values corresponded to overexpression, while negative values corresponded to underexpression; an increase of the CCP-score by one unit represents a doubling of the gene expression. The CCP-score was then tested retrospectively in two cohorts. In the first cohort, 366 men after RP were included, and biochemical recurrence (BCR) was the intended endpoint. The second cohort included 337 men with incidental PCa after transurethral resection of the prostate (TURP) due to benign prostate enlargement, and the primary endpoint was cancer-specific survival. An increase in the CCP-score was able to independently predict BCR in the RP cohort (HR 1.77, 95% CI 1.40–2.22, $p < 0.0001$) and cancer-specific survival in the watchful waiting TURP cohort (HR 2.57, 95% CI 1.93–3.43, $p < 0.0001$). In contrast to surgical primary treatment, in a retrospective cohort of 141 patients after primary radiotherapy of the prostate, an increase of the CCP-score by one unit was able to independently predict BCR (HR 2.11, 95% CI 1.05–4.25, $p = 0.034$) (Freedland et al. 2013). Bishoff et al. (2014) went back to biopsy-based analysis of the CCP-score. The prognostic value in a 3-center cohort of 582 patients that underwent prostate biopsy and subsequent RP was assessed. The CCP-score was a significant predictor of BCR (HR per score unit 1.47, 95% CI, 1.23–1.76, $p < 0.0001$) and was also the strongest predictor of metastatic disease, even after adjusting for clinical variables (HR per score unit 4.19, 95% CI 2.08–8.45, $p < 0.0001$), so the authors concluded that the CCP-score might be an appropriate tool to increase prognostic precision at the time of PCa diagnosis. Cooperberg et al. (2013) evaluated the CCP-score regarding prediction and risk stratification of RP outcomes and found that the CCP-score was able to discriminate between patients with low clinical risk (HR 2.3, 95% CI 1.4–3.7). In a cohort of 585 patients under a watchful waiting regimen with a PCa diagnosis between 2000 and 2003, Cuzick et al. (2015) evaluated the prognostic value of the CCP-score regarding cancer-specific survival, and they found that the CCP-score has a significant impact (HR 2.17, 95% CI 1.83–2.57, OR 89.0, $p < 0.0001$). They therefore concluded that the CCP-score added prognostic value to traditional tools such as the CAPRA score or Kattan nomogram.

As opposed to prognostic value, several studies have instead evaluated the CCP-score's role in decision-making for choice of treatment. In a questionnaire sent out to treating urologists and 294 patients, Shore et al. (2014) analyzed the clinical utility of the score. From the urologist perspective, 55% stated the test generated a mortality risk that was higher or lower than expected. More importantly, one-third indicated that the test results would definitely or potentially change

treatment decisions. Along this same thread, Crawford et al. (2014) found a 37.2% reduction of invasive therapy recommendations after CCP testing, which ultimately leads to a 49.5% and 29.6% reduction in surgical interventions and radiotherapy, respectively.

While expert opinion varies greatly with regard to the utility of the CCP-score, it may still have a future role in improved pre-therapy risk stratification and in treatment decision-making. The goal will be to ultimately reduce unnecessary interventions. As with other biomarkers, current guidelines state that results of prospective multicenter trials need to be awaited before a final recommendation can be made.

ProMark® (Metamark, Cambridge, USA)

In contrast to genomics, the ProMark test is based on a proteomics platform. Shipitsin et al. (2014a, b) have completed much of the work leading to this biomarker. Of an original panel of 160 candidates, 12 total biomarkers were identified using a quantitative multiplex proteomics in situ imaging system. Based on the results of the assay, a risk score with a range from 0 to 1 was developed. Subsequently, this test was tested in a study cohort of 380 patients after RP with a mean follow-up of almost 4 years, and the primary endpoints were development of "lethal disease" and "aggressive disease." The ProMark test was significantly associated with development of aggressive disease (AUC 0.72; OR per unit change in risk score 20.0, 95% CI 4.3–257.0) as well as lethal outcomes (AUC 0.71; HR per unit change 36.0, 95% CI 3.3–2889). Prior to a clinical validation study, the 12-marker test was refined to a more specific 8-marker test. In a clinical validation study, the newer ProMark panel was tested in two cohorts: 381 patients with biopsy and matched RP specimens and a separate blinded validation cohort of 276 men that were analyzed regarding the ability to distinguish "favorable" versus "non-favorable" pathology results. When the ProMark panel cutoff was set to $<= 0.33$, the PPV of favorable pathology in D'Amico low risk patients was 87.2%. On the other hand, the PPV for non-favorable pathology was 76.9% when the cutoff was >0.8. The ProMark panel could distinguish between favorable and non-favorable pathological findings (AUC 0.68; OR 20.9, $p < 0.0001$) or Gleason 6 vs. non-Gleason 6 disease (AUC 0.65; OR 12.95, $p < 0.0001$) in the validation cohort, so the authors concluded that ProMark might be helpful in evaluating patients that are considered for active surveillance (Blume-Jensen et al. 2015). However, as there is no evidence based on studies of untreated patients, these recommendations must be carefully considered. Further data is needed before stronger recommendations can be made.

Decipher® (GenomeDX, Vancouver, Canada)

The Decipher gene signature consists of a 22-gene panel representing multiple biological pathways. Initially described by Nakagawa et al. (2008), it assesses pathways that are involved in aggressive prostate cancer, including cell proliferation, cell structure, immune system modulation, cell cycle progression, and androgen signaling. Specifically developed to predict systemic progression after definitive treatment, it outputs a score between 0 and 1, where levels >0.6 are considered high risk for progression.

In the setting of RP, there is level 1 evidence from three randomized controlled trials that indicate benefit from adjuvant external beam radiation, specifically on progression-free survival and recurrence-free survival in patients (Bolla et al. 2012; Thompson et al. 2009; Wiegel et al. 2014). The emphasis has always been on patients with adverse pathologic features at the time of RP, including extracapsular extension and positive surgical margins. However, utilizing adjuvant therapy, there will be a significant proportion of men being treated with EBRT but not deriving any benefit. In this clinical scenario, molecular biomarkers may improve and potentially guide decision-making on patient selection for adjuvant EBRT.

The initial assessment of the Decipher gene signature was in a 139-patient cohort who

received adjuvant or salvage radiotherapy due to high-risk features, such as pT3-stage disease or positive surgical margins at RP, and were then stratified based on the genomic classifier score into three risk groups (low-risk, <0.4; intermediate-risk, 0.4–0.6; high-risk, >0.6). When compared, the low-risk group had a much lower 8-year BCR rate (21% vs. 81% high-risk, $p < 0.0001$) and 8-year incidence of distant metastases (0% vs. 17% high-risk, $p = 0.032$). It also predicted freedom from metastases (AUC 0.78) as well as freedom from biochemical recurrence (AUC 0.75). Adding the Decipher classifier to the Stephenson model, a validated clinical model, led to an increase of the predictive value (AUC 0.78 for biochemical failure, AUC 0.80 for distant metastases). In patients with a high classifier score, the hazard ratios for developing biochemical recurrence and for distant metastases were 8.1 and 14.3, respectively (Den et al. 2014). In a more recent study, Karnes et al. (2018) assessed 561 men with a median follow-up of 13.0 years and stratified them into a high (>0.6) and low (≤0.6) genomic classifier score groups. Incorporating and controlling for the validated CAPRA-S model, they found that the odds ratio of prostate cancer-specific mortality (PCSM) within 10 years of RP was 3.91 (95% CI: 2.43–6.29) with an AUC of 0.77, which is an increase of 0.04 compared with CAPRA-S alone. Utilizing the genomic classifier and CAPRA-S stratification, they noted cumulative 10-year PCSM incidence ranged from 2.8% in low-risk CAPRA-S/GC ≤0.6 patients to 30% in the high-risk CAPRA-S/GC >0.6 patients. In a recent publication, Klein et al. (2016) were able to show that the genomic classifier is able to predict the risk of metastasis within 10 years following RP even at the time of prostate biopsy (HR 1.75, 95% CI 1.97–2.81, $p = 0.02$).

Badani et al. (2015) evaluated the effect of the genomic classifier on clinical decision-making by asking 51 US board-certified urologists to give adjuvant treatment recommendations for 10 randomly chosen patients out of a pool of 110 patients with adverse pathologic features after RP. When making recommendations based on the clinical variables alone, without the Decipher test result, observation was recommended for 57% of patients, adjuvant radiotherapy for 36%, and other therapies for the remaining 7%. With the addition of the Decipher test results, 31% of the treatment decisions changed (95% CI 27–35%). For instance, 40% of the former radiotherapy recommendations changed to observation if the genomic classifier risk score was added (95% CI 33–47%), whereas only 13% of the patients previously observed were changed to radiotherapy (95% CI 9–17%). The genomic classifier score was the dominant factor in decision-making (OR 8.6, 95% CI 5.3–14.3, $p < 0.001$). In an extension of this evaluation, a larger study by Gore et al. (2017) assessed clinician decision-making before and after Decipher test knowledge in the management of 275 patients considering adjuvant or salvage radiotherapy after RP. The authors found that 18% (95% CI: 12%–25%) of treatment recommendations changed in the group considering adjuvant therapy and 32% (95% CI: 24%–42%) of management recommendations changed in the group considering salvage radiotherapy. In the high-risk subset, the percentage was much higher – 31% and 56% among high-risk patients considering adjuvant and salvage radiotherapy, respectively. Utilization of the Decipher test reduced decisional conflict within the clinician and reduced anxiety in the low-risk patients in both arms. In both these studies, the authors concluded that implementation of the Decipher genomic score led to significant changes in clinical decision-making in the treatment of high-risk PCa patients after definitive surgical therapy.

As with the other biomarkers, the Decipher test is not mentioned in current guidelines yet. Expert opinions are the only decision tool available to date. Based on current expert opinions, the Decipher test may be rationally used as a tool in the clinical decision-making process, if adjuvant radiotherapy is considered in a high-risk PCa patient.

Conclusion

Despite the growing evidence for the rational use of biomarkers and the urgent clinical need for their incorporation, the use of biomarkers should be

cautioned by the fact that most studies were either in small cohorts or retrospective in nature. The lack of prospective studies, as noted in the guidelines, limits their use. Due to the small number of events that can be captured in these outcome studies, large cohort studies are required to truly assess the efficacy of these novel biomarkers. Additionally, the currently available biomarker studies, especially those regarding the pre-treatment decision-making, are mostly independent of the rapid advancements in the area of imaging diagnostics, including the introduction of multiparametric MRI techniques and PSMA PET/CT. Lastly, the biomarkers based on tissue specimens are limited by the potential multifocality and the intratumoral heterogeneity of PCa, which may lead to the risk of undersampling. Based on tissue from a focus of tumor, the novel tissue-based biomarkers may not accurately assess a single patient's clinical risk or potential for progression.

While these limitations are well-known, PCa biomarkers continue to be of great clinical interest. By providing diagnostic, prognostic, and predictive information, they may help guide patients and clinicians in multiple clinical scenarios in the management of PCa. For instance, biomarkers that aid in the decision-making process and selection criteria regarding potential active surveillance in patients with low-risk PCa represent a large unmet need. By providing additional information regarding patient risk of progression, the biomarkers described previously can change the intended therapy or help reassure patients on a previously made treatment strategy decision. With the multitude of biomarkers available, unfortunately there has yet to be a prospective randomized trial, making the optimal of the currently available biomarker tests difficult to determine. Conflicting expert opinions and noncommittal international guidelines allude to this lack of definitive evidence.

Thus, the challenge moving forward is to improve patient selection to increase the utility of these biomarkers. Additionally, cost-benefit analyses also have to be considered, particularly in the context of diagnostics, due to the large number of patients that may be impacted.

It is important to note that biomarkers will never be used in isolation. Hence, studies and guidelines must incorporate molecular biomarkers, clinical and histopathological features, and imaging diagnostics in a complementary manner, rather than a competitive fashion, in order to provide the best possible patient selection.

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Local and Systemic Staging by Modern Imaging Modalities in Prostate Cancer

7

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Contents

Abstract

The management of prostate cancer is very much depending on the disease stage before treatment. Localized or organ-confined prostate cancer will be treated differently than locally advanced prostate cancer, or prostate cancer with loco-regional extension to the pelvic lymph nodes, or metastatic prostate cancer with extension to the bone or distant lymph nodes or even viscera. The need for staging in a patient might be necessary in several clinical scenarios, such as the initial staging after new diagnosis of prostate cancer, but also at the moment of recurrence of the disease in form of biochemical recurrence or clinical recurrence, as well as at the moment of advanced

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or metastatic disease before or during systemic treatment.

The local staging of prostate cancer with conventional imaging is limited. The results are linked to the problem to detect minimal or microscopic extraprostatic extension or lymph node invasion with a macroscopic imaging modality.

For the staging of lymph node metastasis, molecular imaging such as choline-based imaging holds suboptimal performance, while preliminary results present in literature support a possible role of PSMA PET imaging for regional staging of prostate cancer.

When it comes to staging for distant metastasis, modern imaging such as whole-body MRI and molecular imaging using choline or PSMA as tracer or ligand do outperform conventional imaging based on bone scintigraphy and cross-sectional imaging. Of note, mpMRI is of special interest to detect local recurrence after radiotherapy for prostate cancer, when patients show biochemical recurrence.

Introduction

The management of prostate cancer is very much dependent on the disease stage before treatment. Localized or organ-confined prostate cancer will be treated differently than locally advanced prostate cancer, or prostate cancer with locoregional extension to the pelvic lymph nodes, or metastatic prostate cancer with extension to the bone or distant lymph nodes or even viscera (Mottet et al. n.d.). The need for staging in a patient might be necessary in several clinical scenarios, such as the initial staging after new diagnosis of prostate cancer, but also at the moment of recurrence of the disease in the form of biochemical recurrence or clinical recurrence, as well as at the moment of advanced or metastatic disease before or during systemic treatment. In view of this, it is clear that prostate cancer staging is playing a key role in the management of the disease as well as in the clinical decision-making. Several years ago, the staging of prostate cancer consisted of the following: the digital rectal exam, searching for tumor bulb on the posterior aspect of the prostate which was suggestive of extraprostatic extension or seminal vesicle invasion; transrectal ultrasound (TRUS), looking for deformation of the prostate contours and signs of extraprostatic extension; bone scintigraphy with 99m-technetium-labeled diphosphonates looking for bone lesions with increased mineral turnover, suggesting bone metastasis; and cross-sectional imaging with computed tomography (CT) looking for enlarged lymph nodes and changes in bony structures in the form of osteoblastic or, in rare cases, osteolytic lesions as well as lesions in the viscera such as the lung or liver. Today several new imaging modalities are available for prostate cancer staging such as magnetic resonance imaging (MRI) in the form of whole-body MRI and pelvic or prostate multiparametric MRI (mpMRI) and positron emission tomography (PET) using several tracers such as ^{11}C-choline, ^{18}F-choline, and gallium-labeled prostate-specific membrane antigen (PSMA). All of these modalities aim to improve the diagnostic performance of prostate cancer staging rendering the exam more reliable and precise and allowing to better characterize the patient's situation and to better individualize the appropriate treatment. The following chapter will address each of the imaging modalities in the performance of staging in the different clinical scenarios mentioned above.

Initial Staging

The initial staging of prostate cancer after the diagnosis of the disease by biopsy can address several aspects. It can address the question if the disease is organ confined or extends outside of the prostate into the periprostatic fat/tissue or into the seminal vesicles, resulting in locally advanced disease. This information is of importance to tailor local treatment such as surgery with neurovascular bundle sparing, or radiotherapy and its association with androgen deprivation therapy. Initial staging can also address the question if the disease has spread to the regional lymph nodes, resulting in locoregional disease that might still be curable by surgical pelvic lymph node dissection or radiotherapy with an extended field to the

regional lymph nodes. Moreover, the initial staging can address the question if the disease has spread to distant lymph nodes such as the retroperitoneal lymph nodes or to the bone or viscera such as the lung or liver, resulting in initially metastatic disease that would need early systemic treatment by either androgen deprivation therapy or chemotherapy. It is clear that the information coming from initial staging has significant consequences for clinical decision-making and on patient management. The more reliable the staging becomes, the better will be the individual treatment of a patient and with this the short-, intermediate-, and long-term outcome of the patient. This applies for cancer control as well as for functional outcome regarding urinary continence and erectile function.

Local Staging

Classic Modalities

Classically the digital rectal exam represented, and still represents, an important staging exam. Once the tumor burden is recognized at the posterior prostatic surface, the risk of extraprostatic extension increases by two to four times (Ohori et al. 2004; Steuber et al. 2006). This information can be used in multivariable prediction models together with PSA, biopsy Gleason score, and biopsy information about cancer volume to predict the risk of locally advanced disease. TRUS represents also a staging exam that could provide the clinician with information about extraprostatic extension and seminal vesicle invasion. The performance in local staging with TRUS reported in the literature is varying, suggesting a strong operator dependency. The sensitivity, specificity, and accuracy of TRUS in local staging vary between 15–50%, 85–97%, and 80–84% (Brock et al. 2012; Ukimura et al. 1998). A limitation of TRUS is the difficulty to detect microscopic extraprostatic extension, a limitation shared with all other imaging modalities used for local staging of prostate cancer.

CT does not play a role in local staging due to its low soft tissue resolution in the pelvis. CT is unable to differentiate pelvic muscular structures from prostate tissue and does therefore not allow any conclusions about locale extension of prostate cancer.

mpMRI

mpMRI in the pelvis is associated with a high soft tissue contrast allowing to clearly identify the zonal anatomy of the prostate as well as its borders to the periprostatic tissue and the adjacent structure such as the pelvic muscular structures, seminal vesicles, periprostatic fat, and rectal and urethral sphincter. These characteristics render mpMRI a potential tool for local staging. It is of note that the performance of mpMRI in the detection and diagnosis of prostate cancer is addressed elsewhere in this edition.

When it comes to the detection of extraprostatic extension or seminal vesicle invasion, the literature reports a wide range of diagnostic performances, suggesting a strong dependency on center, experience, sequences, and technology as well as patient characteristics and patient selection. The current technical recommendations for a staging MRI are to use a 3 T MRI or a 1.5 T MRI with an endorectal coil in order to reduce the signal-to-noise ratio. In the literature, the reported sensitivity to detect extraprostatic extension ranges from 30% to 78% and the specificity from 78% to 98% (de Rooij et al. 2016). This large variability makes a general interpretation of the data difficult. For this reason the results of a recent meta-analysis are discussed in more detail (de Rooij et al. 2016). It included 75 studies of moderate quality and 9796 patients and showed for the detection of extraprostatic extension a pooled sensitivity of 0.57 (95% CI 0.49–0.65) and a pooled specificity of 0.91 (95% CI 0.88–0.93). The pooled sensitivity for the detection of seminal vesicle invasion was at 0.58 (95% CI 0.47–0.68), and the pooled specificity was at 0.97 (95% CI 0.95–0.98). The pooled sensitivity and specificity for the detection of overall stage T3 were 0.61 (95% CI 0.54–0.67) and 0.88 (95% CI 0.85–0.91), respectively. The meta-analysis also addressed the question if there are differences

depending on technical aspects as well as differences that depend on cancer and patient characteristics. Regarding the technical aspects, studies using mpMRI instead of T2-weighted imaging alone showed higher sensitivity to detect extraprostatic extension. The same improvement was observed in favor of 3 T MRI relative to 1.5 T MRI. The highest sensitivity was observed in the studies using 3 T MRI without an endorectal coil. When it comes to the detection of seminal vesicle invasion, studies that used mpMRI instead of T2-weighted imaging alone showed a higher sensitivity. However, there was no difference in sensitivity between the use of 3 T or 1.5 T scanners. The use of 3 T MRI without an endorectal coil showed a higher sensitivity relative to the use with an endorectal coil, whereas the situation was inversed when using a 1.5 T scanner, favoring the use of an endorectal coil. The highest sensitivity was achieved with 3 T MRI using multiple parameters. Based on this analysis, it can be concluded the most reliable results for local staging of prostate cancer will be achieved using multiparametric 3 T MRI without an endorectal coil, confirming the current recommendations. Regarding the patient characteristics, the highest sensitivity to detect extraprostatic extension or seminal vesicle invasion was achieved in patients being in the high-risk group relative to the intermediate -risk group or the low-risk group. Despite this the sensitivity remained at a low level of around 0.60 (de Rooij et al. 2016).

Based on this meta-analysis, it can be concluded that the detection of locally advanced disease is limited or poor. The results are again linked to the problem to detect minimal or microscopic extraprostatic extension with a macroscopic imaging modality. It is of note that the specificity is high, suggesting that if there are signs of extraprostatic extension or seminal vesicle invasion, it is very likely that the disease indeed is locally advanced.

PET

PET/CT can also be used for intraprostatic detection of prostate but is not used for local staging as the spatial resolution of PET and the soft tissue contrast of CT in the small pelvis are poor. The usefulness of choline PET/CT for the evaluation of the intraprostatic lesion was evaluated over the last decade. Farsad et al. produced the first study performed on a sextant basis in comparison with histology in a cohort of 36 patients (Farsad et al. 2005). ^{11}C-choline PET/CT showed sub-optimal performance reporting a sensitivity of 66%, a specificity of 81%, an accuracy of 71%, a positive predictive value (PPV) of 87%, and a negative predictive value (NPV) of 55%. The lack of accuracy for choline PET/CT in evaluating the intraprostatic lesion was assessed in several studies during the last decade (Martorana et al. 2006; Giovacchini et al. 2008). Recently, Bundschuh et al. correlated the uptake of ^{11}C-choline PET/CT in the prostate gland with histopathology (Bundschuh et al. 2013). The assessed sensitivity resulted to be not optimal since only 46% of lesions evaluated by histology showed an increased choline uptake. In a study proposed by Grosu et al., increased ^{11}C-choline uptake has been found in neoplastic and nonneoplastic tissue (Grosu et al. 2014). Thus, in some cases, the intensity of choline uptake was even higher in nonneoplastic tissue. Van den Bergh et al. evaluated the additional value of ^{11}C-choline PET to mpMRI, showing increased sensitivity and decreased specificity combining both modalities (Van den Bergh et al. 2012). Thus, according to the literature, the main drawback for choline PET/CT in the evaluation of the intraprostatic cancer is represented both by the sub-optimal sensitivity, related with the presence of small lesions, and by the sub-optimal specificity, related with the presence of benign disease that may show increased choline metabolism (e.g., benign prostatic hyperplasia (BPH), prostatitis).

Recently, PSMA-based imaging was proposed to investigate prostate cancer patients prior to radical prostatectomy. Fendler et al. evaluated the accuracy of PET/CT with 68Ga-PSMA to localize cancer in the prostate and surrounding tissue at initial diagnosis in a cohort of 21 patients (Fendler et al. 2016). The following were assessed: a sensitivity of 0.67, a specificity of 0.92, an accuracy of 0.72, a PPV of 0.97, and a

NPV of 0.42. Histopathology-positive segments (100/126; 79%) demonstrated a significantly higher mean SUVmax than histopathology-negative segments. However, despite better values for specificity and PPV, if compared to choline PET/CT, the sensitivity still remains sub-optimal. Thus, the combination of PSMA-based PET with MRI to improve the performance of both methodologies was recently proposed. Zamboglou et al. demonstrated in a small cohort of patients that the combination of both methods performed even better in terms of sensitivity (0.82) and specificity (0.89) (Zamboglou et al. 2017). Eiber et al. confirmed these results and compared the diagnostic performance of simultaneous 68Ga-PSMA PET/MRI for the localization of primary prostate cancer with mpMRI and PET alone in a cohort of 53 patients (Eiber et al. 2016). Simultaneous PET/MRI statistically outperformed mpMRI and PET imaging alone for a precise localization of prostate cancer, correctly detecting the lesion in the 98% of cases with a sensitivity of 0.76 and a specificity of 0.98 (MRI alone 0.43, 0.98; PET alone 0.58, 0.82). Moreover, according to the data present at the moment in literature, it seems reasonable to assume that PSMA-based imaging is able to distinguish with good accuracy between intraprostatic prostate cancer lesion and BPH (Fendler et al. 2016; Eiber et al. 2016).

Summarizing, mpMRI still remains the standard of reference for detecting localized prostate cancer prior to radical treatment. Choline-based imaging holds sub-optimal performance, while preliminary results present in literature support a possible role of hybrid PSMA-based PET/MRI for the localization of primary prostate cancer.

Lymph Node Staging

Classical Staging

Cross-sectional imaging such as CT or MRI can be used for regional and distant staging looking for lymph node metastasis and/or bone metastasis or visceral metastasis. To detect lymph node metastasis, the use of CT or MRI allows only to address morphological criteria. The rounder a lymph node is in cross-sectional imaging, the more suspicious it is to be a lymph node metastasis. The size of the lymph node is also used to differentiate lymph node metastasis from normal lymph nodes. Usually a cutoff of 8–10 mm in the short axis of the lymph node is used for this purpose. Of note the lower the size cutoff for a suspicious lymph node chosen, the more the sensitivity to detect lymph node metastasis, but this improvement will at the same time lead to a decrease in specificity, leading to a higher number of false positive. The higher the size cutoff chosen, the lower the sensitivity and the higher the specificity. Moreover, changes in lymph node size are also informative. If a lymph node increases over time in size, it is likely to be associated with a lymph node metastasis. Unfortunately, the information on growth kinetics is only available if previous cross-sectional imaging was performed and is available, a situation that rarely is fulfilled in patients with a newly diagnosed disease. The performance of cross-sectional imaging with CT or MRI in lymph node staging is rather poor. Generally speaking, the sensitivity for the correct identification of lymph node metastasis ranges between 0.20 and 0.60 and the specificity between 0.78 and 0.92 (Daneshmand et al. 2012; Giannarini et al. 2012). An older meta-analysis using CT for lymph node staging in prostate cancer and analyzing 4264 patients, where 15% had confirmed lymph node metastasis, showed a sensitivity of 0.07 and a specificity of 1.0 (Abuzallouf et al. 2004). More recent studies showed that even in patient with a high risk of lymph node metastasis, the performance is limited. Briganti et al. showed that in patients undergoing an extended pelvic lymph node dissection and using a size cutoff of 10 mm, the overall sensitivity was at 0.13 and the specificity was at 0.96 (Briganti et al. 2012). When limiting the analysis to high-risk prostate cancer patients, CT achieved a sensitivity of 0.18 and a specificity of 0.94 to correctly identify lymph node metastasis. Even in patients with a very high risk of lymph node metastasis according to a nomogram, the performance remained poor with a sensitivity and specificity of 0.24 and 0.95 (Briganti et al. 2012). Another

recent study by Budiharto et al. using whole-body MRI with diffusion-weighted imaging for staging of patients also with a high risk of lymph node invasion according to a nomogram showed that the performance of MRI to identify lymph node metastasis per region was low with a sensitivity of 0.19 and a specificity of 0.98 (Budiharto et al. 2011). In a patient cohort at very high risk of lymph node metastasis (68% of patients were metastatic), the performance was better and sensitivity and specificity are reported to be at 0.77–0.82 and 0.05–0.96, respectively (Lecouvet et al. 2012). In view of this poor performance of cross-sectional imaging for lymph node staging, it is clear that surgical pelvic lymph node dissection remains the gold standard in lymph node staging for prostate cancer. It is of note that the indication for lymph node staging as well as for pelvic lymph node dissection is dependent on the risk of lymph node invasion that can be estimated based on pretreatment variables such as clinical stage, PSA, biopsy Gleason score, and biopsy information of cancer volume (Briganti et al. 2006). Currently the most reliable approach is the use of prediction models that allow to systematically assign a certain risk of lymph node metastasis to an individual patient.

PET

The diagnostic performance of choline-based imaging for assessing the lymph node involvement has been recently discussed in a systematic review by Evangelista et al. (2013). Most of the papers analyzed in this meta-analysis confirmed the preliminary findings showing a lack of sensitivity but high specificity for nodal staging. Pooled sensitivity and specificity were, respectively, 0.49 and 0.95 on a patient-based analysis (Evangelista et al. 2013). On one hand, ^{11}C-choline PET/CT's low sensitivity could be explained by the presence of micrometastasis since it is very unlikely that ^{11}C-choline PET/CT may detect lesions smaller than 5 mm. On the other hand, the main reason for the false-positive findings is due to the presence of inflammation in the lymph nodes that might result in an increased choline uptake. Therefore, choline PET/CT has only limited place for up-front staging in nodal metastases even in high-risk patients.

The role of PSMA PET/CT for initial staging currently remains investigational. The first results presented by Budäus et al. in a cohort of 30 patients revealed a poor sensitivity for PSMA PET/CT in identifying LNM: the sensitivity assessed in the per-patient analysis was 0.33, while the sensitivity assessed in the per-side analysis was 0.27 (Budaus et al. 2016). Conversely, according to the authors' assessment, both optimal specificity and PPV resulted to be 1.0 in the per-patient and in the per-side analysis. Nevertheless, this study presented several limitations including the retrospective design of the study and the low incidence of lymph node metastasis in the enrolled population (53 lymph node metastases in 608 lymph nodes removed = 8.7%) (Budaus et al. 2016). In the study presented by Maurer et al., the diagnostic performance of PSMA PET/CT in assessing the presence of lymph node metastasis before radical prostatectomy was tested in a cohort of 130 patients (Maurer et al. 2016). On a patient-based analysis, the sensitivity, specificity, and accuracy of PSMA PET were 0.66, 0.99, and 0.89, and those of morphological imaging were 0.44, 0.85, and 0.72, respectively. Of the 734 dissected lymph node templates, 117 (15.9%) showed metastases. On a per-side-based analysis, the sensitivity, specificity, and accuracy of PSMA PET were 0.68, 0.99, and 0.95, and those of morphological imaging were 0.27, 0.97, and 0.87, respectively. On ROC analysis PSMA PET performed significantly better than morphological imaging alone on patient- and template-based analyses ($p = 0.002$ and <0.001, respectively) (Maurer et al. 2016). These results were confirmed by van Leeuwen et al., who assessed the accuracy of PSMA/PET/CT for lymph node staging in a cohort of 30 intermediate- and high-risk prostate cancer patients (van Leeuwen et al. 2017). Here 37% of patients presented lymph node metastasis: in total, 180 lymph node fields were analyzed and 26 lymph node metastases were identified in the histological analysis. Patient analysis showed that PSMA PET/CT had a sensitivity of 0.64 and a

specificity of 0.95. In the region-based analysis, the sensitivity was 0.56 and the specificity was 0.98 (van Leeuwen et al. 2017).

Staging for Distant Metastasis or Systemic Disease

The metastatic spread of prostate cancer is either to the regional or distant lymph nodes or to the bone. Metastasis to the visceral organs, such as the lung or liver, is rather rare and found in cases of prostate cancer patients showing Gleason pattern 5 on biopsy or prostatectomy specimen. When it comes to staging for metastatic disease, especially of bone metastasis, the standard exam is bone scintigraphy. It is of note that bone metastasis of prostate cancer is the result of an infiltration of the bone marrow by prostate cancer cells due to the expressions of adhesion molecules similar to those found on hematopoietic stem cells (Rahim et al. 2014). Therefore, bone metastasis of prostate cancer will develop in the bone marrow first and only later lead to changes in the bony structures itself. This is of importance to explain the differences in sensibility to detect bone metastasis between modern imaging modalities and classical imaging modalities such as CT or bone scintigraphy. In order to detect bone metastasis with bone scintigraphy, a bone mineral turnover >10% is necessary to render the lesions visible (Messiou et al. 2009). In order to detect bone metastasis with conventional X-ray or CT, changes in the bone mineralization are necessary and usually become visible at a more advanced stage relative to the stage where bone scintigraphy could detect the lesions. The combination of bone scintigraphy and conventional X-ray or CT is considered the gold standard for bone staging and often represents the reference test in studies evaluating new imaging modalities. Therefore, its sensitivity is considered to be 1.0. However, the specificity is below 1.0 as bone scintigraphy can be false positive, when showing lesions with increased mineral turnover linked to, i.e., bone trauma or benign causes. In a recent meta-analysis, its specificity was estimated to be 0.82 (Lecouvet et al. 2012; Oesterling et al. 1993; Bruwer et al. 1999; Shen et al. 2014).

Modern Imaging Modalities for Bone Staging

There are two modern imaging modalities available for systemic staging of prostate cancer. These are whole-body MRI and PET scanning.

Whole-Body MRI

Whole-body MRI implies an MRI scan of at least the entire axial skeleton but ideally covers the body from the head to the tibia and includes T1- and T2-weighted imaging as well as diffusion-weighted imaging. MRI is sensitive to early changes in bone marrow that precede the osteoblastic response that usually is depicted by classical imaging modalities (Messiou et al. 2009). These changes linked to bone metastasis of prostate cancer result in a signal loss in T1-weighted imaging which contrasts to the surrounding high signal of the bone marrow fat. This infiltration can be depicted before any changes in the bony structures. As mentioned, bone scintigraphy combined with conventional X-ray is considered the reference test. Therefore, the performance of new imaging modalities that might perform better than the standard test can only be evaluated by quantification of the lesions that are detected in addition to the lesions identified with the standard test. Therefore, in this setting it is difficult to apply the usual measures of sensitivity and specificity. When using whole-body MRI for the detection of bone metastasis of prostate cancer in patients with a high likelihood of having metastatic disease, whole-body MRI will detect between 22% and 38% more metastatic bone lesions relative to the lesions that are identified with bone scintigraphy and X-ray/CT. Moreover, 15–22% more patients will be diagnosed with metastatic disease, despite the absence of metastatic disease based on classical imaging modalities (Lecouvet et al. 2012, 2007; Del Vescovo et al. 2014). These data show that whole-body MRI indeed is more sensitive in detection than the classical staging modalities. The main drawback of this technology is the lack of standardization regarding the sequences which limits its reproducibility. Moreover, whole-body

MRI is time and resource consuming as it needs significant MRI gantry time to perform the exam. It is unclear if current healthcare systems and resources allow the systematic use of this as a standard imaging modality in prostate cancer patients.

PET

PET/CT with sodium ^{18}F-fluoride, ^{11}C-choline, or ^{18}F-choline can detect more skeletal lesions than bone scintigraphy. There is increasing evidence that sodium ^{18}F-fluoride and ^{11}C-choline could change patient management, either as a first imaging study or as a secondary study after bone scintigraphy (Gandaglia et al. 2014; Fuccio et al. 2012). Currently, the role of PSMA imaging to assess the presence of bone metastases during stating work-up has not been tested yet. However, according to the data published in patients who experienced BCR, PSMA PET/CT showed an optimal performance to detect the presence of bone lesions. In particular, in the largest patient series published so far, an optimal tumor-to-background ratio for 68Ga-PSMA PET/CT was demonstrated, allowing for a proper visualization of the suspected bone metastases (Afshar-Oromieh et al. 2015; Eiber et al. 2015). Moreover, in a direct comparison between PSMA PET/CT and choline PET/CT, a major detection rate for PSMA over choline regardless of the PSA level was confirmed (Morigi et al. 2015). Within this patient cohort, a total of 16 bone lesions were identified by PSMA while only 9 lesions with choline.

There is no study that provides a head-to-head comparison between whole-body MRI, PET/CT, and bone scintigraphy in the same patient cohort. However, there is a recent meta-analysis including 18 studies and analyzing 1102 patients (Shen et al. 2014). This meta-analysis at least applies the same methodology and quality standards to the studies included into the analysis, allowing some conclusions regarding the differences in performance. For the detection of bone metastasis, this analysis shows a pooled sensitivity for whole-body MRI of 0.95, for PET-T of 0.87, and for bone scintigraphy of 0.79. The results for the pooled specificity were as follows: for whole-body MRI, 0.96; for PET/CT, 0.97; and for bone scintigraphy, 0.82. The results for the pooled area under the curve were as follows: for whole-body MRI, 0.99; for PET/CT, 0.95; and for bone scintigraphy, 0.89 (Shen et al. 2014). Based on this analysis, it seems that whole-body MRI provides the best performance in the detection of bone metastasis, followed by PET/CT and by bone scintigraphy. It is of note that PET/CT has a superior performance in the detection of lymph node metastasis relative to whole-body MRI and might therefore represent the most complete staging modality, allowing reliable detection of bone metastasis as well as the best performance in the detection of lymph node metastasis short of a true surgical pelvic lymph node dissection.

Staging at the Moment of Biochemical and Clinical Recurrence After Treatment with Curative Intent

When PSA becomes detectable or rises after achieving a nadir following treatment with curative intent (such as radical prostatectomy or external beam radiotherapy), relapse might come from local recurrence in the prostatic bed or the prostate, from locoregional lymph nodes, or from distant systemic disease such as bone metastasis or any or all of these scenarios combined. Local or locoregional recurrence could be amenable to salvage, possibly curative treatment, whereas truly systemic disease with bone metastasis will be less likely to be curable and would need systemic treatment instead of local salvage treatment (Suardi et al. 2015). Therefore, at the time point of biochemical recurrence, the important question to answer is the question of whether the patient has local or distant recurrence or both. Older studies suggest that after local treatment, 30–40% of patients with recurrence will have local recurrence and the remaining distant recurrence or local and distant recurrence combined (Pound and Partin, 2000; Coen et al. 2002). Classically, the staging of recurring disease is done by CT and bone scintigraphy, both being associated with a very low diagnostic yield and a poor

diagnostic performance unless the PSA is elevated (i.e., >20 ng/ml) (Beresford et al. 2010). It is of note that if a local salvage treatment for local recurrence after radical prostatectomy or radiotherapy (i.e., salvage radiotherapy or salvage prostatectomy) is considered, it needs to be done early at low PSA levels, i.e., the results for salvage radiotherapy after radical prostatectomy show a long-term disease-free survival rate of roughly 50% when the PSA at the time point of salvage radiotherapy is <0.5 ng/ml. The long-term outcome drops to 30% if the PSA is between 0.5 and 1 ng/ml and to 10% if the PSA is >1 ng/ml (Stephenson et al. 2007). Ideally, the decision in favor or against salvage radiotherapy should be taken at the time point of biochemical recurrence (0.2 ng/ml). The same applies to the results of salvage prostatectomy after radiotherapy, where the most favorable outcome is observed when the PSA before salvage surgery is <4 ng/ml (Chade et al. 2011). It is clear that if salvage treatment is considered, early treatment is key to be effective and PSA is one of the main drivers for prognosis in this situation as it can be considered as a proxy for cancer volume.

mpMRI in the Detection of Local Recurrence

Similar to the situation of the initial diagnosis of prostate cancer, mpMRI becomes more and more used to detect local recurrence after radical prostatectomy or radiotherapy and shows promising results especially after radiotherapy. A recent meta-analysis on the subject by Wu et al. showed a pooled sensitivity and specificity of 0.82 and 0.87, respectively, in the detection of local recurrence after radical prostatectomy with MRI (Wu et al. 2013). The highest contribution to these favorable results came from the dynamic contrast-enhanced sequences, allowing to identify hyper-perfused cancer tissue in the area of post-surgical scar tissue. Of note diffusion-weighted imaging is of limited use as it is prone to major artifacts associated with surgical clips that are frequently encountered after prostatic surgery. The main limitation of the included studies lies in the PSA ranges at the time point of the examination, which ranged between 0.84 and 2.2 ng/ml (Wu et al. 2013). As mentioned above, in order to be clinically relevant and helpful, local recurrence needs to be reliably identified at PSA ranges below 0.5 ng/ml; the above PSA ranges are therefore too high and beyond the clinically relevant PSA range where the decision in favor of salvage radiotherapy is taken. The clinical relevance of MRI in the detection of local recurrence after radical prostatectomy is therefore very limited. The same meta-analysis addressed also the performance of mpMRI in the detection of local recurrence after radiotherapy. It showed a pooled sensitivity and specificity of 0.82 and 0.74, respectively. As in local recurrence after radical prostatectomy, the most informative parameter was dynamic contrast-enhanced MRI, allowing to identify hypervascular cancer tissue inside of the fibrotic prostatic scar tissue after radiotherapy. Moreover, the PSA ranges of the studies were in the clinically relevant ranges from 2.1 to 2.8 ng/ml (Wu et al. 2013). As the biochemical recurrence after radiotherapy is defined as PSA nadir +2 ng/ml, the clinically relevant PSA range is of somewhere above 2 ng/ml. It can be concluded that mpMRI is of clinical relevance in the detection of local recurrence after radiotherapy but not after radical prostatectomy.

PET

Currently, the performance of choline PET at this clinically relevant situation is limited as choline PET exams are positive only in 5–20% when PSA is <1 ng/ml and positive in only 5–8% of cases when PSA is <0.5 ng/ml (Castellucci et al. 2014; Giovacchini et al. 2010a, b; Mitchell et al. 2013; Rybalov et al. 2013). Unfortunately, the optimal timing for salvage treatments to obtain the best chance of cure in case of recurrence would be when the PSA level is low or very low, which reflects a still limited cancer burden (Stephenson et al. 2007). Moreover, when it is positive, there is a non-negligible risk of disease underestimation. Passoni et al. showed that patients with one positive node on choline PET who underwent a

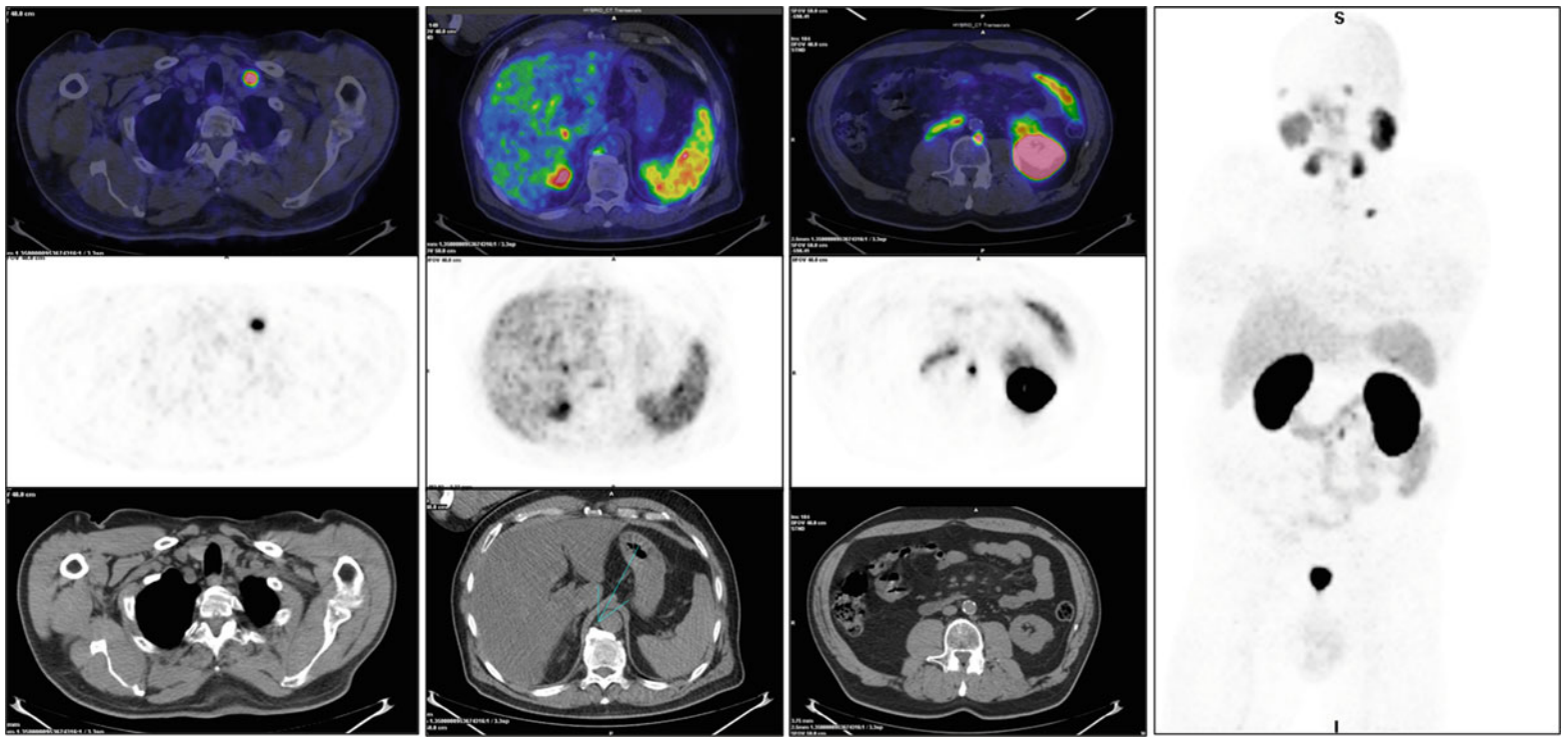

Fig. 1 PSMA PET/CT: A 64-year-old patient after local treatment with radical prostatectomy and adjuvant radiotherapy. PSA relapse with a PSA at 1.27 ng/mL and a PSA doubling time of 4.1 months at the time point of PSMA PET/CT. PSMA PET/CT detected two para-aortic lymph nodes, one small phrenic lymph node, and one supraclavicular left lymph node. The extra-abdominal lymph node was biopsied confirming the presence of a prostate cancer metastasis

meticulously done salvage lymph node dissection showed in 61% of cases positive nodes in other regions that were not detected by choline PET (Passoni et al. 2014). Another study by Decconick et al. showed in the same clinical scenario and design that 79% of all positive nodes were not detected with choline PET (Deconinck 2014). It is clear the PET performs better than conventional imaging with CT and bone scintigraphy in this clinical situation, which could be considered as major improvement, but the above limitations need to be emphasized if choline PET is to be used in the right clinical situation and if choline PET should truly be an added value to clinical pathways.

Several efforts have been made over the last years to develop new probes able to provide better performances when compared with the choline PET/CT, particularly in case of low PSA levels during BCR. The development of radiotracers designed to specifically target the extracellular domains of substrates overexpressed in prostate cancer cells could lead to the development of theranostics tracers, valuable both for diagnostic and therapeutic purposes. The first investigations reported a better accuracy for PSMA PET/CT in detecting suspected prostate cancer metastases when compared with choline PET/CT and very promising performances also at very low PSA levels (Fig. 1) (Eiber et al. 2015; Morigi et al. 2015). In particular, in one of the largest patient series published so far, Eiber et al. reported about the performance of PSMA PET/CT in a population of 248 recurrent prostate cancer with

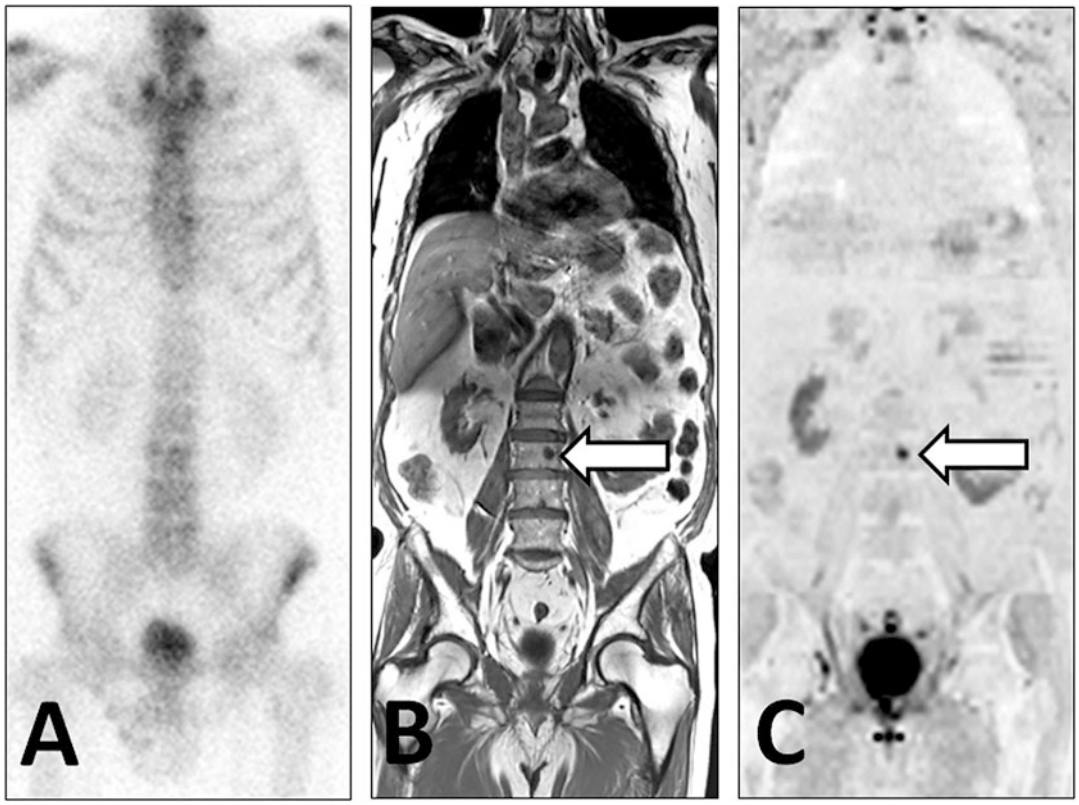

Fig. 2 Whole-body MRI: Illustration of the superiority of whole-body MRI (WB-MRI) in comparison with bone scintigraphy in a man with newly diagnosed prostate cancer at high risk for metastasis. (**a**) The bone scintigraphy shows no abnormality. (**b**) T1- and (**c**) diffusion-weighted MRI sequences show bone metastasis within the L2 vertebral body (arrow), indicating oligometastatic status. (Courtesy of Frédéric Lecouvet, Department of Radiology, Universite catholique de Louvain, Brussels, Belgium)

biochemical recurrence (median PSA 1.99 ng/mL) (Eiber et al. 2015). The authors observed a promising overall positivity rate of 89.5% for PSMA PET/CT. More in detail, the authors observed a considerably high positivity rate with low PSA levels with positivity rate of 93.0% (67 of 72) for a PSA value between 1 and 2 ng/mL, 72.7% (24 of 33) between 0.5 and 1 ng/mL, and 57.9% (11 of 19) for a PSA value between 0.2 and 0.5 ng/m (Eiber et al. 2015). Recently, Ceci et al. investigated the role of PSMA PET/CT in the recurrent setting and evaluated which clinical and pathologic features were associated with PET/CT positivity rate (Ceci et al. 2015). In a cohort of 70 patients (median PSA 1.7 ng/mL), a positivity rate of 74.2% was described. A PSA level of 0.83 ng/mL and a PSA doubling time of 6.5 months were found to be valuable cutoff values for predicting with high probability a positive or negative scan result. Moreover, PSA at the time of the scan and PSA doubling time were associated significantly ($p < 0.05$) with an increased probability of a positive PSMA PET/CT result (Ceci et al. 2015). Recently, the clinical impact of PSMA PET/CT on the management of patients with biochemical recurrence after treatment with curative intent was investigated (Albisinni et al. 2016). In a cohort of 131 consecutive prostate cancer patients (median PSA 2.2 ng/mL) with an overall detection rate of 75% for PET/CT, an impact on subsequent management in 99/131 patients (76%) was demonstrated. The main modifications included continuing surveillance, hormonal manipulations, stereotaxic radiotherapy, salvage radiotherapy, salvage node dissection, or salvage local treatment (Albisinni

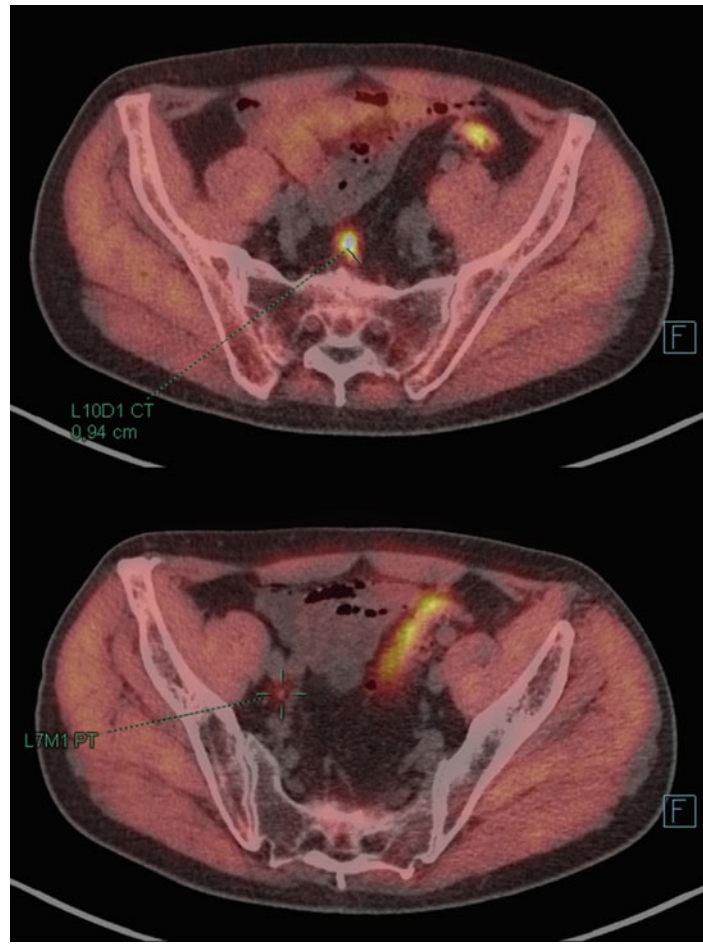

Fig. 3 ^{18}F-choline PET/CT at biochemical recurrence: A 69-year-old patient after local treatment with radical prostatectomy and salvage radiotherapy. PSA relapse with a PSA at 1.81 ng/mL at the time point of ^{18}F-choline PET/CT. The PET shows positive presacral and right-sided pelvic lymph nodes. Pathology after salvage lymph node dissection showed 2 lymph node metastases with capsular extension out of the 21 nodes

et al. 2016). According to the data present in literature, this novel approach proved its promising performance in investigating prostate cancer, confirming the importance of this imaging modality for the precise individualization of the site of recurrence. Pfister et al. compared the usefulness of PSMA PET/CT vs. choline PET/CT as diagnostic tools to guide salvage lymph node dissection (Pfister et al. 2016). They reported better sensitivity and specificity for PSMA (0.87, 0.93) compared to choline (0.71, 0.86) in the detection of lymph node metastasis using histology as a standard of reference (Pfister et al. 2016). These results are consistent with the data presented by Rauscher et al., who evaluated the accuracy of PSMA PET/CT compared with morphological imaging for the assessment of lymph node metastasis in patients with biochemical recurrence, using histopathology as a standard of reference (Rauscher et al. 2016). They observed that PSMA was much more accurate to guide salvage lymph node dissection than conventional morphological imaging with CT and/or MRI (Fig. 2). In detail they observed, for the assessment of lymph node metastasis, a sensitivity of 0.78 and specificity of 0.97 for PSMA vs. a sensitivity of 0.27 and specificity of 0.99 for conventional morphological imaging (Rauscher et al. 2016).

Recently the concept of oligometastatic disease emerged as a subentity of metastatic disease, regrouping patients with a low load and number of metastasis that might also be amenable to treatment with (maybe) curative intent by combining local with systemic and image-targeted ablative treatments (Fig. 3) (Hellman and Weichselbaum 1995). Its emergence comes especially from the clinical situation of relapsing disease after initial local treatment with curative intent, but the concept can be extend to patients with primary diagnosis of prostate cancer and possible low-volume metastatic disease. As PET seems to be more sensitive than conventional imaging, it might play a major role for this new clinical situation in the future (Mottet et al. n.d.; Suardi et al. 2015). Further studies are needed to test if these new approaches will improve the outcome of prostate cancer patients. Several studies evaluating this concept are being recruited.

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Prostate Cancer Biopsy: Strategies

8

Niklas Westhoff and Manuel Ritter

Contents

Abstract

Prostate biopsy is the gold standard for the diagnosis of prostate cancer since many decades. Technical and material advances lead to a 10- to 12-core systematic biopsy as the state of the art to detect prostate cancer in case of an elevated PSA level or suspect digital rectal examination.

Since prostate imaging modalities enable visualization of potentially malignant areas, biopsy paradigm started to change in favor of targeted biopsies for optimization of cancer detection. The implementation of the multiparametric magnetic resonance imaging (mpMRI) is now known to increase detection of clinically significant cancer, improve early risk stratification, and advise patients to an adequate therapy. A variety of different fusion techniques and biopsy platforms have been developed, showing not only diagnostic but also therapeutic relevance with great future potential by integrating biopsy and focal therapy.

However, there is still a debate on the right indication to use systematic, targeted, or saturation biopsies and how to perform them. Biopsy strategies should pursue the following aims: accurate detection of clinically significant cancer, reduction of overdetection of

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insignificant cancer, high negative predictive value, immaculate risk assessment according to the final pathology in prostatectomy specimens, low morbidity, and clinical applicability.

Introduction

The first reports of prostate biopsies derive from the year 1922, when Barringer performed a transperineal needle biopsy. His biopsy cores contained prostate tissue in only 50% (Barringer 1922). Astraldi was the first urologist who used the transperineal entry path to obtain cores from the prostate although the biopsy was only navigated manually by palpation of suspect prostate areas (Astraldi 1937).

Later in 1971, the introduction of transrectal ultrasound for prostate imaging was the first step toward image-guided biopsy techniques (Watanabe et al. 1971). During this period targeting of tumor suspicious hypoechoic lesions became the standard in biopsy strategies for the first time. In further investigations, however, the systematic biopsy outperformed the target technique. The sextant biopsy was developed by Hodge et al. who took one biopsy per base, mid, and apex of each prostate lobe (Hodge et al. 1989). Finally, after expansion of this technique by additional lateral biopsies, a 10- to 12-core biopsy is now the recommended standard for primary biopsies by current guidelines of urological associations (American Urological Association 2013; Deutsche Gesellschaft für Urologie 2016; European Association of Urology 2016).

Innovative imaging modalities revolutionized the landscape of prostate biopsies since approximately 10 years. They intend to enable localization and risk attribution prior to biopsy and can be used for targeted sampling. Nevertheless, there is still an ongoing debate on optimal biopsy strategy. The aim of current biopsy development is a technique that provides highest accuracy in detection of clinically significant cancers with low patient morbidity and simple clinical applicability.

Biopsy Techniques, Relevance, and Limitations

Ultrasound-Guided Systematic Biopsy

Systematic Transrectal Ultrasound Biopsy

The traditional transrectal ultrasound (TRUS)-guided systematic prostate biopsy is a simple procedure that can be offered in hospital or outpatient setting with little effort. In the United States, approximately 1.3 million prostate biopsies have been performed in 2014 (Howlader et al. 2015). This biopsy technique is the most widespread due to its low cost and acceptable comfort for the patient.

There are several conditions that have to be considered before the intervention: informed consent at least 24 h before the biopsy, evaluation of coagulopathies or anticoagulation therapy, and exclusion of a urinary tract infection and resistant rectal bacteria in special cases.

The patient can either be placed in left lateral or in lithotomy position, which depends on the urologists' preference. Usually, there is no need for a general anesthesia. Instillation of an anesthetizing lubricant might be sufficient for pain reduction. In addition, a local infiltration of the neurovascular bundle between the junction of prostate and seminal vesicles by injection of 10–20 ml of a local anesthetic significantly minimizes discomfort. If the patient does not tolerate the procedure in spite of this, an analgosedation or general anesthesia should be provided. Especially if the rectal sphincter remains tensed, these measures are often required.

After an initial digital rectal examination of the prostate to identify indurated regions suspect of cancer, the TRUS probe is inserted into the rectum. Two types of ultrasound probes exist: "Side-fire" probes project laterally. The probe has to be moved by twisting while keeping its axis neutral. In contrast, the "end-fire" probe projects a plane from the end of the probe (Fig. 1). For visualization of the whole prostate from base to apex, the probe must be bent. It is important to facilitate enough freedom of movement by an appropriate patient positioning. Modern biplane transrectal ultrasound probes simultaneously display the

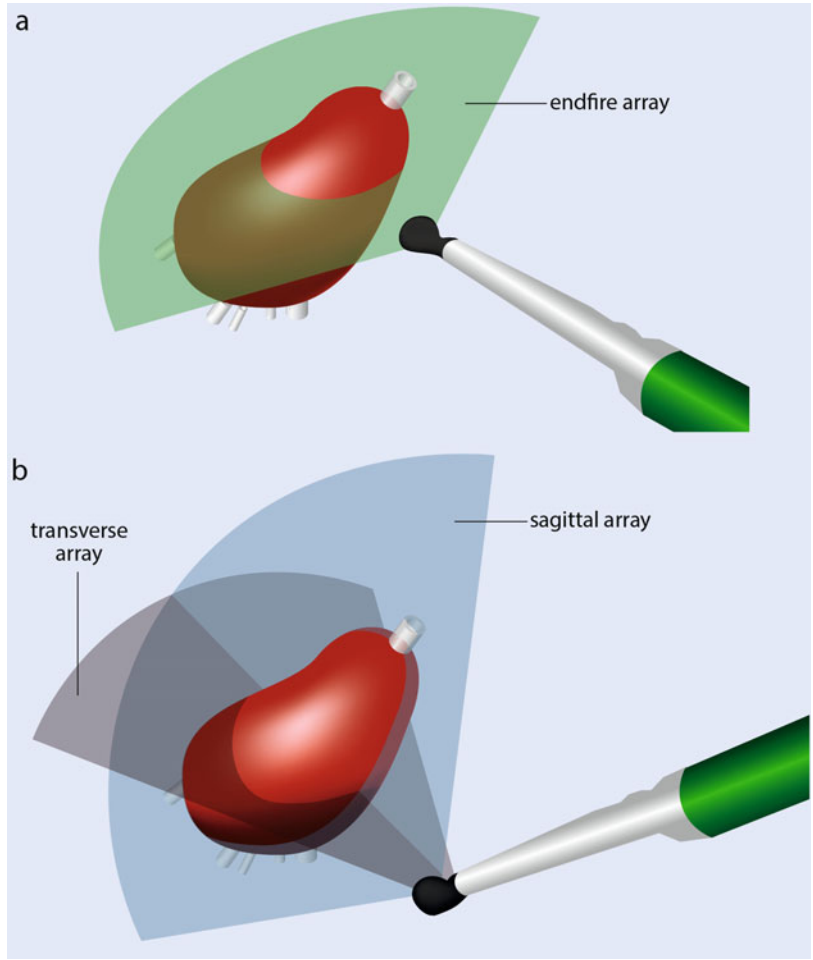

Fig. 1 Ultrasound probes with different projections, (**a**) end-fire probe, (**b**) biplanar probe

sagittal and transversal view which simplifies orientation. Furthermore, by collecting simultaneous data on several planes, three-dimensional visualization of the prostate is possible. Alternatively, 3D volumes can be calculated and visualized from sensors on the probe within an electromagnetic field by modern ultrasound devices. Both methods optimize accurate localization of biopsy samples.

The guidelines recommend usage of a biopsy needle with a diameter of at least 20 gauge. Systematic biopsy sampling should cover both lobes of the prostate from base to apex. In detail, five to six samples from each medial and lateral base, mid, and apex should be obtained. Thereby it is necessary to push forward the needle through the tissue before triggering to reach distant localizations equally. Furthermore, lateral biopsies require precise sampling because the peripheral zone most likely harbors cancer.

Malignancy criteria in transrectal ultrasound are hypoechoic lesions, irregular contours, and interruptions of the capsule (Fig. 2). However, hypoechoic lesions only appear in certain cancers and can be disguised by benign variations like infection, calcification, musculature, or fibrosis. Thus, transrectal ultrasound has a low specificity to detect prostate cancer. Following this, TRUS is not recommended for primary diagnosis, but suspicious lesions should be sampled additionally to the systematic biopsy (Deutsche Gesellschaft für Urologie 2016).

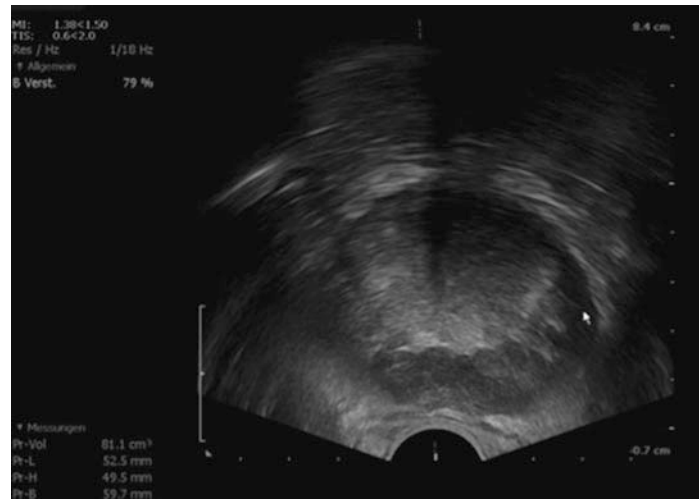

Fig. 2 Transversal TRUS view of a peripheral prostate cancer

Standardized processing of biopsy samples implies that each core should be separately embedded with a defined depiction of its localization. This is fundamental for therapy planning in terms of nerve-sparing during prostatectomy or definition of the treatment area in focal therapy (van der Kwast et al. 2003).

On the one hand, the described systematic procedure offers opportunity to simple and cost-effective diagnosis, even in outpatient setting. It comes along with moderate patient impairment due to its short duration. On the other hand, the random sampling harbors some substantial limitations. Firstly, the random biopsy is subject to error sampling and largely operator dependent. Clinically relevant cancers of a Gleason score higher than 6 (3 + 3) or a tumor volume $> 0.5\ m^3$ can lead to symptomatic disease by local or metastatic progress and a reduced overall survival. They frequently are multifocal or of a small size. Consequently, they often remain undetected by this biopsy strategy. Undersampling error occurs in up to 30–80% of clinically significant cancer (Siddiqui et al. 2013, 2015). Moreover, incorrect risk attribution is demonstrated by an upgrading from systematic biopsy to prostatectomy specimen in up to 50% (Shaw et al. 2014). Secondly, a substantial number of patients have a low-risk cancer with an indolent course of the disease. Random biopsies increase the detection of these cancers followed by overtreatment.

Systematic Transperineal Biopsy

A systematic transperineal biopsy is an alternative technique that was used routinely prior to the 1980s.

In contrast to the transrectal procedure, transperineal biopsies commonly require a general anesthesia for the patient who is placed in lithotomy position. Since the cores are obtained by puncture through the perineum, the procedure has to be performed under sterile conditions. Therefore, a thorough disinfection of the perineum goes ahead. The biopsy is guided by transrectal ultrasound with ultrasound probes compatible to show sagittal and transversal planes. Usually, a template is mounted in front of the perineum that facilitates control of the biopsy gun and exact placement of the needles analogous to brachytherapy procedures **(**Fig. 3**)**. Distances between the puncture gaps within the grids normally measure 5 mm. Moreover, using a template enables labeling of the sample. Alternatively, only one or a few perineal punctures are used to obtain all cores, potentially reducing both morbidity and accuracy.

Different biopsy patterns have been developed during the past decades to ensure optimal covering of all cancer-related prostate regions. Especially for anterior and transitional zone cancers, the transperineal entry path is believed to be superior due to the challenging angles and distances to hit these regions. In general, transperineal systematic biopsy gained importance as a mapping biopsy of the entire prostate in order to enhance

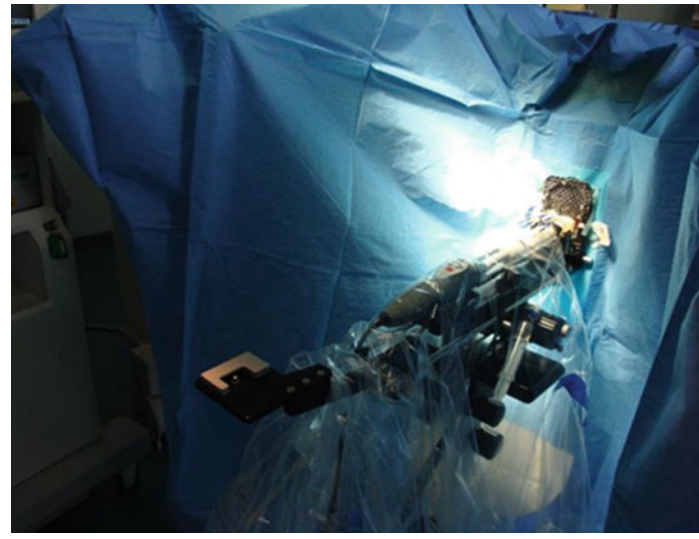

Fig. 3 Setting of a transperineal biopsy with the patient in lithotomy position and a template grid mounted in front of the perineum

cancer detection. Typically more than 12 cores are obtained; hence, transperineal biopsies often are equivalent to a saturation biopsy (see below).

The main limitation of the transperineal technique is the large effort needed to prepare and perform the procedure. Since puncture of the perineum is more painful than transrectal biopsies, local anesthesia is commonly insufficient for analgesia. Consequently, transperineal biopsies are difficult to perform in an outpatient setting. The benefit for targeting anterior or transitional regions is still unclear. Whereas some data constitute advantages for transperineal punctures, others could not find a difference and showed transrectal entry path equivalently in terms of accuracy. In addition, especially in large prostates, the symphysis might inhibit access to the anterior and apical prostate, and the needle has to be pushed forward through a greater amount of prostate tissue to reach basal lesions. Further investigation is necessary to clarify this.

Studies directly comparing transrectal and transperineal biopsies are rare. One study compared the rates of upgrading in radical prostatectomy specimens and found a significant reduction when using the transperineal approach (8% vs. 52%) (Crawford et al. 2013). This could not be confirmed by Scott et al. In their research study, no difference in Gleason score upgrading, final pathological stage, and tumor volume was found between the two approaches (Scott et al. 2015). In addition, another series revealed equivalent overall cancer detection rate but indicate that transperineal biopsies achieve a lower major complication rate while representing a more time-consuming procedure.

Saturation Biopsy

Driven by the different evolving concepts of prostate sampling and the awareness of 10–12 cores being superior to the sextant biopsy, extended systematic biopsies or mapping of the entire gland has been developed. Today the optimal number of cores remains still under debate although extended biopsies were shown to improve cancer detection in some situations.

Saturation biopsies can be performed either from transrectal or transperineal entry path and consist of more than 20 cores. Extended systematic schemes aimed to cover all regions of larger prostates initially and are now used for additional sampling of special regions like the anterior zone, for example. It was already mentioned that transperineal biopsies typically are used for more than a standard 12-core biopsy scheme. Instead, Barzell et al. developed a three-dimensional pathological mapping as standard proposal for transperineal schemes. They divided the prostate into octants, each of them divided into three regions again. Additionally, 1 proximal and 1 distal

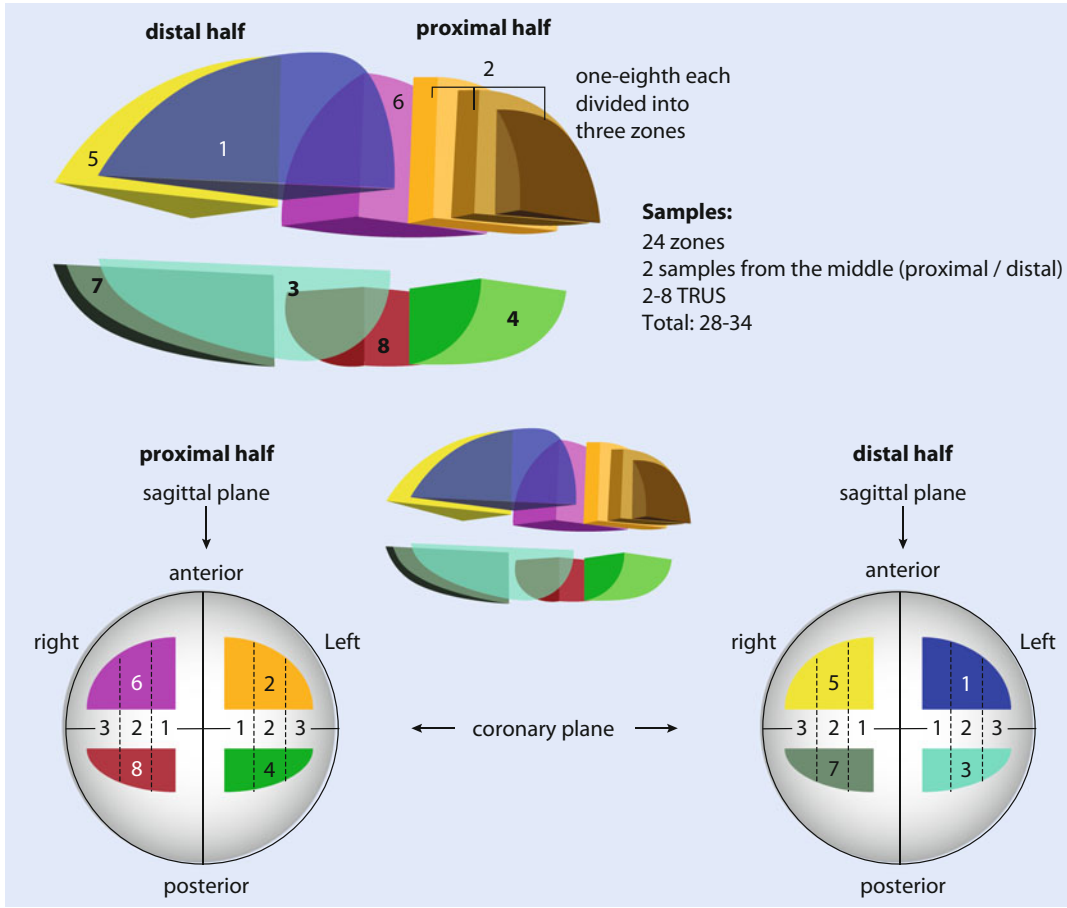

Fig. 4 Schematic transperineal biopsy (Barzell and Melamed 2007)

midline core and 2 to 8 TRUS cores complete the scheme with 28–34 cores added together (Fig. 4) (Barzell and Melamed 2007). Transperineal mapping biopsies are defined as a complete sampling of the gland by puncture of all template gaps. Due to this, there are only distances of 5 mm between the cores, leading not only to an increased detection of clinically significant cancers with higher tumor volumes but also to an increased detection of clinically insignificant cancer.

Several studies have evaluated the use of an extended systematic or saturation biopsy as an initial biopsy strategy. They found no statistically significant difference in contrast to 12-core systematic biopsy. Nevertheless, overall tumor detection rate increased by approximately 10% from 12 to 21 cores in some series (de la Taille et al. 2003). Furthermore, different studies analyzed whether a prior negative 12-core or extended primary biopsy leads to higher cancer detection rates in a repeat extended or saturation biopsy. They found a false-negative rate equivalent between both techniques, concluding that extended or saturation biopsies should remain indicated in repeat biopsy situations.

Targeted Biopsy

Ultrasound-Based Targeting

ANNA/C-TRUS

Computerized (C)-TRUS with artificial neural network analysis (ANNA) is based on the

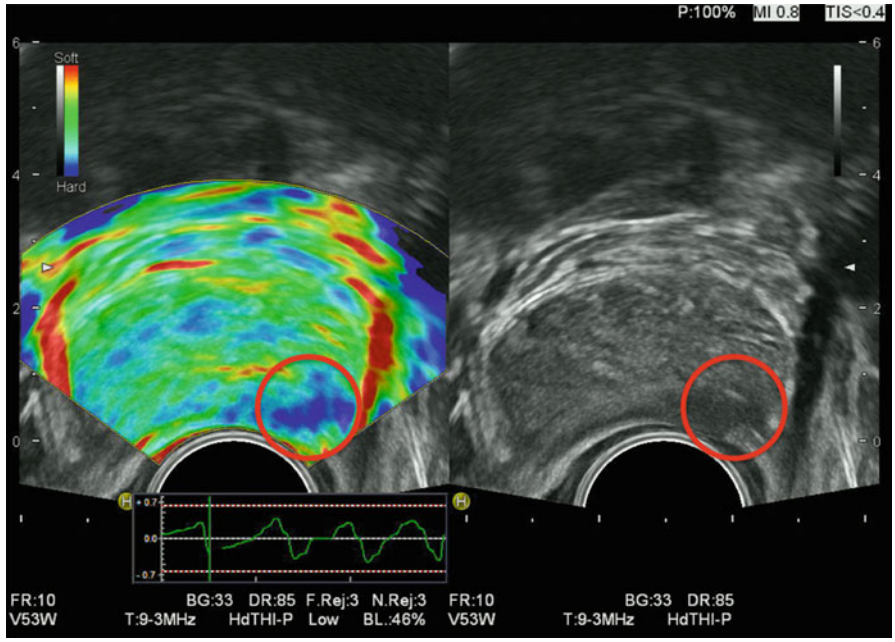

Fig. 5 Elastography shows the suspicious lesion (red circle) in blue due to its differing stiffness. In B-mode it appears as a hypoechoic region

comparison of live ultrasound images with a constantly expanding database. This database consists of thousands of transrectal ultrasound images of the prostate with divergent echogenicity. Moreover, the corresponding results of prostatectomy specimen are stored. After TRUS of the prostate, the surgeon is able to compare the generated images with the database via transmission to a secured server and computer-based analysis. In case of tumor suspicious regions, they will be transmitted back with the regions highlighted in red. During a second ultrasound of the prostate, the delineated regions are now visible for target biopsy. ANNA C-TRUS is a dynamic database that is upgraded by continuous uploads of new TRUS images and pathological results.

The system was introduced in 2001 and enables target biopsy with a low-cost and simple procedure. Different validation studies enrolled approximately 5,000 patients for biopsy using ANNA/C-TRUS. In comparison to the final pathology of radical prostatectomy specimens, target biopsy revealed detection of 12 cancers missed by systematic biopsy in a trial of 132 men and was able to predict the final Gleason score of the index lesion in 85% (Grabski et al. 2011).

Elastography

Increasing cellularity and microvascularity cause stiffening of prostate cancer in most cases. Measurement of elasticity represents the concept of prostate elastography for tumor detection. Using real-time sonography, stiff prostate areas are highlighted color-encoded for target biopsy (Fig. 5).

Two different techniques exist for sound wave generation. The strain elastography registers sound waves that are generated by cyclic compression of the prostate by movement of the TRUS probe. The newer shear wave elastography measures how fast automatically induced shear waves travel through the prostate tissue by exact quantification.

In a recent meta-analysis comparing strain elastography and radical prostatectomy specimens, the pooled sensitivity was 72% and the

specificity was 76% (Zhang et al. 2014). The combination of strain elastography-guided target biopsy and systematic 12-core biopsy leads to an increase of 53% in cancer detection rate (van Hove et al. 2014). However, the free hand prostate cycling movement and interpretation of the color maps are quite subjective and operator dependent. Since there is no absolute measurement of the stiffness, comparison between patients and quantification of the stiffness are not possible. By contrast, fewer studies for shear wave elastography reveal sensitivities and specificities up to 93% (Ahmad et al. 2013).

Studies analyzing multiparametric MRI (mpMRI) and elastography have demonstrated comparable results, with elastography being superior in the apex and mid of the prostate (Pelzer et al. 2013). A future combination of both imaging techniques might increase the diagnostic accuracy and is currently under investigation.

Contrast-Enhanced Ultrasound (CEUS)

CEUS visualizes the enlarged microvascularity of tumor regions. Therefore, a contrast agent is administered intravenously that consists of small microbubbles. These capillary-passable bubbles flow through the blood vessels and can be detected by ultrasound within a few minutes. Identification of an increased contrast enhancement or detection of asymmetric vessels might give a hint of a cancer.

The sensitivity and specificity of CEUS are described as up to 70% and 74%, respectively (Li et al. 2013). Target biopsy alone with CEUS failed to detect a relevant number of clinical significant cancers, whereas combination with systematic 12-core biopsy improved detection rates compared to systematic biopsy alone.

Doppler Ultrasound

In contrast to CEUS, Doppler ultrasound is a more simple way to detect cancer regions due to their enhanced perfusion. Angiogenesis is characteristic for development of significant cancer and leads to an increase in microvascular density as previously mentioned. Color Doppler ultrasound detects ultrasound waves reflected from blood cells that are moving toward or away from the ultrasound probe and visualizes that shift in different colors. It is restricted in the detection of microvessels with the result that only aggressive tumors with higher Gleason grades fed by large vessels might be visualized. Power Doppler ultrasound is more sensitive than Doppler ultrasound as well in vessels as small as 1 mm.

The additional value of Doppler ultrasound varies widely between different studies. The largest one, comparing 620 systematic grayscale ultrasound and Power Doppler ultrasound-guided biopsies with radical prostatectomy specimens, revealed an improved specificity for the combination in contrast to systematic grayscale ultrasound only (47–74%), whereas sensitivity decreased (58–47%) (Eisenberg et al. 2010).

Multiparametric Ultrasound

Similar to the multiparametric MRI, the different ultrasound-based modalities can be used in combination to improve the diagnostic accuracy. The multiparametric ultrasound involves assessment of different physical characteristics of tumor tissue. Since grayscale ultrasound and C-TRUS evaluate the anatomical structure, CEUS and Doppler ultrasound analyze the microvascularity, elastography rates increased stiffness, and usage of all modalities should help to detect cancer more specifically.

There are limited data on its usage so far, but the initial studies show good results in cancer detection comparing the combined modalities to systematic biopsy as a reference. Adding several modalities increases sensitivity and specificity. There is still a need for further studies, comparing different modality combinations with radical prostatectomy specimens as a reference standard. Moreover, there is still lack of a scoring system analogous to the PIRADS system (see below) which enables standardized image interpretation and risk attribution.

MRI-Based Targeting

Multiparametric MRI

Prostate MRI has been introduced in the 1980s in order to visualize the gland. By combining the morphological T2w sequence of a high spatial

solution with functional modalities like diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) ultrasound, multiparametric MRI gained relevance for imaging diagnosis of prostate cancer within the past years. Initially, MR spectroscopy complemented the sequences but was omitted in current recommendations. Multiparametric MRI aims to localize prostate cancer in order to obtain targeted biopsy cores of tumor suspicious regions and to optimally predict cancer aggressiveness and patient risk at diagnosis. Standardized MRI interpretation is substantial for a widespread clinical use and comparison of diagnostic accuracy. The Prostate Imaging Reporting and Data System (PIRADS) was introduced in 2012 by the European Society of Urogenital Radiology (ESUR) to fulfill these criteria. A first and a recently updated second version evaluate the different modalities depending on their significance for each prostate zone. It utilizes a five-grade scoring system according to the likelihood of a prostate lesion to correlate with clinically significant cancer. Whereas a grade 1 lesion is "highly likely" benign, a grade 5 lesion is "highly likely" correlated with clinically significant cancer. The PIRADS score correlates with the cancer detection rate, as shown by many studies, and reaches up to 95% in grade 5 lesions. In recent reviews, MRI-targeted biopsy has been shown to reveal similar overall detection rates when compared to systematic TRUS-guided biopsy but increases the detection of clinically significant cancer (91% vs. 76%), while insignificant cancers decreased from 83% to 44% (Schoots et al. 2015). However, there is still a considerable false-negative rate leading to 10–15% clinically significant cancers that are missed by a targeted biopsy of cancer-suspicious MRI lesions (Baco et al. 2015; Hoeks et al. 2012; Siddiqui et al. 2015). Especially in small lesions, bleeding after biopsy or infections appears hypointense, similar to cancer. Due to this mpMRI in the setting of a re-biopsy is recommended at least 6 weeks after the previous biopsy (Vargas et al. 2016).

Cognitive MRI Fusion

Three methods of targeted MRI-image-fusion biopsies exist. Cognitive fusion biopsy is the simplest way to use the information of the MRI and the ultrasound navigation in combination.

This method is based on the visual estimation of a prior performed multiparametric MRI. The urologist localizes the regions of interest, which have been described previously by a radiologist, within the prostate. Anatomical landmarks like cysts, the urethra, the bladder neck, or calcifications help to memorize the position within the gland. Afterwards these landmarks help to recognize the position in the ultrasound images. This procedure is faster and considerably more favorable than the other methods. It is easy to integrate the cognitively fused targeted biopsies within a systematic sampling protocol. Data show that clinically significant cancer detection rates increased significantly by cognitive image fusion biopsy compared to a TRUS-guided systematic biopsy only, especially in anterior tumors (Lawrentschuk et al. 2010). Besides, this technique is more efficient with a significantly lower cancer per core rate and decreased detection rates of insignificant cancers (Haffner et al. 2011). However, this fusion technique relies on an extremely subjective interpretation of MRI and ultrasound images. Thus, there exists a relevant learning curve for accurate sampling. In addition, if the ultrasound lacks visualization of the anatomical landmarks or the sectional planes between both modalities differ, identification of the MRI lesions remains challenging.

"In-Bore" Biopsy

The "in-bore" biopsy uses direct MRI guidance for targeting. A prior diagnostic mpMRI is performed and interpreted by radiologists. Afterwards, the radiologist obtains single samples of suspect lesions directly within the MRI gantry. Therefore, the patients typically need a local or general anesthesia. Special biopsy guidance or templates and sterile needles are necessary that are compatible with the magnetic field and support the navigation. Depending on the applied system, patients are placed in a modified lithotomy or abdominal position **(**Fig. 6**)**. Under repetitive T2w sequences for localization of the needle, usually only the specific target lesions are sampled. After each core, another sequence is performed to verify correct position.

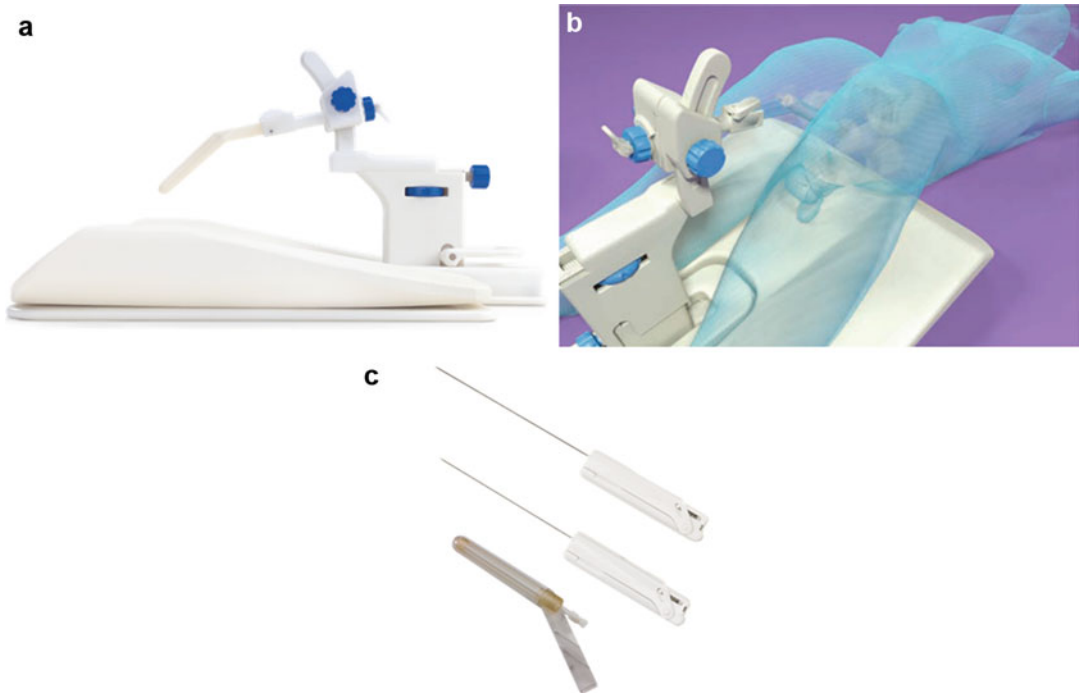

Fig. 6 In-bore biopsy. (**a**) System Dyna Trim (Invivo corp., Philips); (**b**) the patient is placed in abdominal position with an indwelling rectal probe; (**c**) special sterile needles that are MRI compatible

The advantages of this technique are highly precise targeting and the fewer sampled cores that potentially reduce morbidity. Furthermore, the MRI sequences to control accuracy enable an immediate visual feedback.

Nevertheless, "in-bore" biopsy is not widespread in clinical application due to relevant limitations. Obviously, the method requires considerable expenditures in contrast to other biopsy techniques. It is highly cost-intensive and time-consuming and thus straining for the patient. In theory, taking only targeted samples reduces the overdetection of insignificant cancers. However, in fact the lack of systematic biopsy leads to a substantial number of significant cancers.

Series reporting on the detection of clinical significant cancer demonstrate an increase in the diagnosis of intermediate- and high-risk cancers by 17,7%. In patients with prior negative biopsies, cancer detection rates were up to 42% with clinical significant cancers up to (Quentin et al. 2014). Whereas a study described a reduced detection of low-risk cancers by 89.4%, in the same study, 14.7% were upgraded in final Gleason score (Overduin et al. 2013).

MRI/Ultrasound Fusion

A third fusion method is software-based co-registration of MRI and ultrasound that was developed to overcome the limitations of both the cognitive fusion and the MRI/MRI fusion technique.

Various commercially marketed MRI/ultrasound biopsy devices have been developed. They enable an ultrasound-guided biopsy with an automatic overlay of prior acquired MRI images and real-time ultrasound. Most systems require manual delineation of prostate boarders and regions of interest in the MRI images, leading to visualized virtual targets in the live ultrasound after data transfer. The platforms largely differ in the entry path of biopsy (transrectal vs. transperineal), ultrasound image acquisition (3D volumetric, 2D sweep, etc.), technique of image fusion (rigid vs. elastic), tracking mechanism of the ultrasound probe (electromagnetic

Fig. 7 Setting of an Artemis™ biopsy (Eigen, USA) with the typical semirobotic arm for needle guidance

vs. electromechanical), and a freehand or robotic-assisted needle guidance. This leads to some outstanding advantages: fusion errors might be reduced, procedure is less operator dependent, and biopsy accuracy potentially increases. Moreover, most devices offer the ability to store the location of the taken samples which depicts an important implication for patients receiving active surveillance protocols with regular re-biopsies or patients planned for a focal therapy.

Some of the MRI/ultrasound fusion biopsy platforms with the contemporary widest clinical usage are the following:

Artemis™ (Eigen, USA) is a software-based platform that stabilizes the TRUS probe by a semirobotic arm to ensure accurate targeting of suspect lesions (Fig. 7). At first the contours of the prostate and regions of interest are marked in MR images using the proprietary "ProFuse" software. After data transfer to the biopsy platform, a three-dimensional ultrasound model of the prostate is acquired by manual rotation of the TRUS probe. The MRI and ultrasound images are fused by rigid and subsequent elastic fusion. The rigid fusion serves as basis to overlay the correct image layers and prostate position. Elastic fusion aims to correct prostate contours with respect to deformation during biopsy caused by the probe as well as patient position and bladder or rectum filling. An automatic template for the systematic biopsy adjusted to the prostate volume and shape is displayed in addition to the regions of interest. Artemis™ uses electromagnetic tracking with encoders mounted at the mechanical arm. Biopsy cores can be obtained by transrectal or transperineal biopsy and are recorded for re-biopsies or focal planning within the 3D model afterward. Improvement of detection of clinically significant cancers with Artemis™ in comparison to systematic 12-core biopsies ranges between 11% and 25% in large trials including more than 1000 patients. Detection of clinically insignificant cancers can be reduced by up to 38% (Filson et al. 2016).

Urostation® (Koelis, France) uses manually guided transrectal ultrasound and solely elastic image fusion. The tracking is software image registration-based, using a 3D ultrasound probe to create a 3D model. This model is elastically fused with the MRI images for lesion location to visualize the targets within the ultrasound model. It enables a virtual biopsy before taking the core. For each sample, a new short scan has to be performed. Detection rates amount up to 91% depending on suspicion level, and fusion biopsy

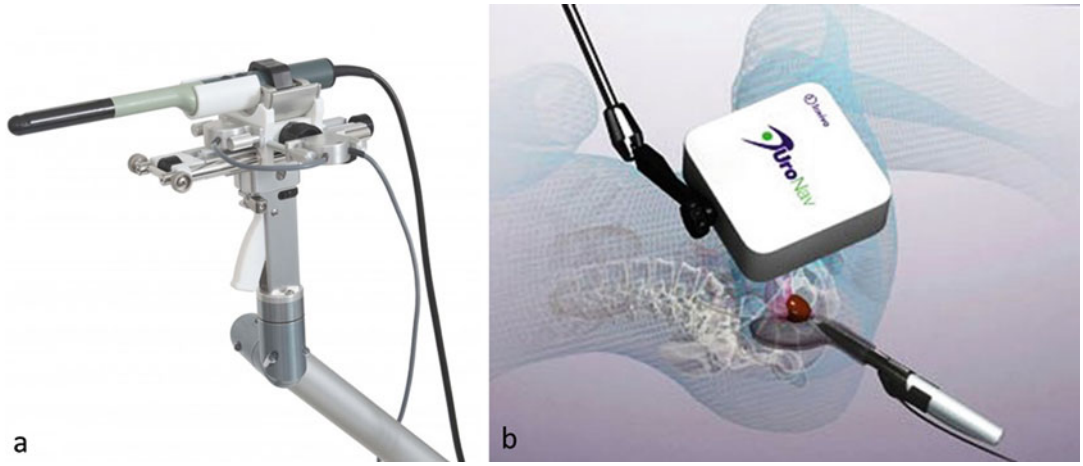

Fig. 8 UroNav (Invivo corp., Philips): The electromagnetic field for needle tracking is created by an external generator superior to the patient

detects more clinically significant cancer than systematic biopsy ($p = 0.03$) (Mozer et al. 2015; Rud et al. 2012).

UroNav (Invivo Corp., Philips, USA) is a device that uses an external electromagnetic field generator to track the transrectal or transperineal prostate biopsy (Fig. 8). Similar to the aforementioned platforms, a 3D model of the prostate is created, here performing a 2D scan. The MRI images are preprocessed using the "DynaCAD for Prostate" platform. UroNav enables transrectal or transperineal biopsy after a rigid image fusion. In their study, Siddiqui et al. demonstrated the results of 1003 patients undergoing fusion biopsy with UroNav and systematic biopsy. Target biopsy found 30% more clinically significant cancers (Gleason Score $\geq 4 + 3$) and reduced detection of insignificant cancers by 17%. Furthermore, systematic biopsy missed 18% of clinically significant cancers that were detected by target biopsy, whereas target biopsy missed only 8% (Siddiqui et al. 2015).

BiopSee® (MedCom, Germany) is a platform for transperineal, transrectal, and transabdominal fusion biopsies. For transperineal biopsies, a mechanical stepper mounted to the operating table is used. By electromechanical tracking of the transrectal ultrasound probe, 3D images are registered. Prostate and target are contoured and images can be fused elastically afterward. Biopsy samples can be obtained either using a template grid in front of the perineum or free handed. Core registration for later analysis is possible. Target biopsies with BiopSee® were shown to detect more clinically significant cancer foci in comparison to systematic biopsies. Moreover, systematic biopsies detected more insignificant cancers (Distler et al. 2016).

Hitachi real-time virtual sonography (HI-RVS; Hitachi, Japan) is based on tracking of the manually guided transrectal or transperineal ultrasound probe within an external electromagnetic field like UroNav. The magnetic field generator is placed near the patient and a sensor is mounted at the probe. The software for image fusion is an integrated component of the ultrasound machine. HI-RVS works with rigid image fusion after previous contouring of suspect targets within the MRI images. Miagawa et al. demonstrated an overall cancer detection rate of 61% in 85 patients with a prior negative systematic biopsy. 87% were detected by target biopsies with HI-RVS and fusion biopsies better predicted tumor aggressiveness (Miyagawa et al. 2010). In another series of 310 patients, target biopsy revealed more Gleason score ≥ 8 cancers than systematic biopsies (28% vs 15%) (Maxeiner et al. 2014).

Several other devices like *BioJet* (D&K Technologies, Germany) or *iSR'obot*^{TM} *Mona Lisa*

(Biobot Surgical, Singapore) complete the wide field of fusion biopsy platforms. In general, irrespective of the single device, most studies demonstrated the capability to increase the detection of those significant cancers that impair patient morbidity. However, since targeted biopsies alone are not able to detect all of those cancers, currently a combination of targeted and systematic biopsy is unavoidable. This is the main reason why in-bore biopsies remain not suitable for a standardized fusion biopsy setting. As long as MRI sensitivity and specificity are limited and in-bore biopsy does not permit systematic sampling of the gland, there is a high risk of missing significant cancers. Moreover, accurate targeting of especially smaller lesions is a challenging procedure that requires a relevant learning curve. Thus, platforms that enable supported needle guidance by (semi-)robotic arms and software-based image fusion techniques appear to reduce limitations of cognitive fusion technique with a shortened learning curve. Some series directly compared visual estimated and software-based image fusion. Whereas Puech et al. found only a difference in overall cancer detection of 47% by cognitive fusion to 53% by rigid software-based fusion, Delongchamps et al. demonstrated that especially elastic image fusion was significantly superior to cognitive fusion (Delongchamps et al. 2013; Puech et al. 2013). Wysock et al. showed that fusion biopsy with Artemis™ improved detection of significant cancers compared to visual estimated fusion, both combined with a systematic 12-core biopsy in the same patient (Wysock et al. 2014).

Comparison studies of biopsy platforms are rare. Thus, the decision for a software-based biopsy platform has to be based on their properties. At first, the major technical hurdle is the registration and fusion of MRI and ultrasound images. Automatic surface registration alleviates the difficulties of different shapes and deformation between both modalities. Rigid image fusion does not change the images themselves which is less appealing to the eyes but does not alter the anatomic integrity. However, since elastic fusion creates an optimized "match" of the borders, the operator is not misled to manually correct for this discrepancy by probe insertion depth. Secondly, freehand or mechanically assisted needle guidance might influence accuracy. Especially insertion of the needle into the guidance at the probe and hand movement during the biopsy itself might lead to a deviation from the planned target. To overcome these inaccuracies, steppers or robotic arms may be used to stabilize the probe. Furthermore, biopsy platforms that enable documentation of biopsy samples and a precise visualization are strongly recommendable because of the feasibility to accurately localize tumors within the gland. This allows precise resampling for the increasing number of patients undergoing active surveillance in order to reduce oversight of changes in tumor size and aggressiveness. Another rising field of interest in prostate cancer treatment is focal therapy of localized tumors, e.g., by high-intensity focused ultrasound (HIFU), cryotherapy, or irreversible electroporation (IRE). Some of the biopsy platforms can be used in combination with focal therapy devices to integrate fusion biopsy in focal therapy planning. Currently this is expected to offer the highest precision for treatment of localized cancer. It remains unclear if a transrectal or transperineal fusion biopsy leads to better results. Nevertheless, platforms that enable both entry paths offer opportunity for each procedure.

Besides the technical differences, clinical applicability and costs have to be considered. Some of the platforms require an additional ultrasound device. Whereas most sizes are rather compact, there is a wide range of costs (35.000–165.000€).

Complications

Prostate biopsy is an invasive diagnostic tool that is generally safe with minor complications but harbors a potential risk of relevant patient morbidity. Several preconditions have to be considered before administration to avoid major adverse events.

Infections are the most relevant complications after transrectal biopsy. Urinary tract infections, bacteremia, and sepsis significantly increased

within the past years and require hospitalization more frequently. This has been affiliated to the growing number of quinolone resistance, which represented the standard recommendation of antibiotic prophylaxis for many years. Potential risk factors attributed to quinolone resistance are international travel in countries with a high risk of resistant bacteria, recent antibiotic therapy, hospitalization, and prior urological infections. Additionally, antibiotic resistances other than quinolones are reported, which affect gentamicin, piperacillin, ampicillin, and trimethoprim/sulfamethoxazole in 22–94% (Feliciano et al. 2008). Transport of the rectal flora into the prostate and surrounding tissue is believed to cause infections. The most causative organism is *Escherichia coli*. But not only resistant species are described as possible reasons for increasing infectious complications. The older patient population and chronic diseases like diabetes mellitus predispose for a higher risk of post-biopsy infection. Furthermore, there is still a debate on the biopsy technique affecting infection rates. Transperineal sampling avoids the passage through rectal mucosa and is therefore potentially more sterile. However, the benefit is still unclear since head-to-head comparisons of infection rates related to the different techniques are rare. A systematic review recently evaluated complications associated with the procedure and found no significant differences between transperineal and transrectal biopsy type. Hospitalization was necessary in 1.1% of transrectal biopsies and 0.9% of transperineal biopsies, whereas sepsis occurred in 0.8% vs. 0.1%, respectively (Bennett et al. 2016). Nevertheless, the included studies were heterogenous in study population, biopsy technique, and antibiotic regimen. In conclusion, there is still a lack of high-quality studies comparing both techniques regarding infectious complications with respect to current antibiotic standards. The influence of repeated biopsies, number of cores, and sampling sites has to be clarified as well.

In addition to initial perineal pain, the most common complication is bleeding. Due to injury of the bladder and urethra, hematuria occurs in approximately 50% of transrectal biopsies. Transient rectal bleeding and hematospermia emerge frequently as well. The patient has to be informed that hematospermia might persist for up to 4–6 weeks. Bleedings are uncomplicated and self-limiting in most cases and severe consequences like vesical tamponade are rare. Information on the patient's case and medical history are obligate, and blood has to be analyzed if a bleeding tendency is known. Except aspirin, anticoagulation therapy should be disrupted prior to the procedure if possible.

Due to swelling of the prostate, obstructive voiding symptoms and urinary retention represent another complication. Sometimes a temporary indwelling catheter is inevitable. Complication rates differ between transrectal and transperineal biopsy pathways. Hematuria is described more frequently in transrectal biopsies, which might be explained by the core direction, which potentially "crosses" the urethra leading to a higher risk of injury. In contrast, transperineal biopsies and large prostate volumes are associated with increased urinary retention. The reported rate of urinary retention for transperineal biopsies is 4.2% vs. 0.9% for transrectal biopsies (Hara et al. 2008).

A rare complication is a temporary erectile dysfunction that is reported for both entry paths. Generally, it is less impairing and regresses spontaneously within a few weeks.

Antibiotic Management

The burden of increasing post-biopsy infections and antibiotic resistance requires a precise individual management prior to and during the procedure. In general, a urine culture should be compiled for each patient to exclude an acute urinary infection. It has been proven that a targeted antimicrobial therapy reduces both urinary tract infections and sepsis in comparison to a single antibiotic prophylaxis (4.55% and 2.21% vs. 0.72% and 0.48%) (Cussans et al. 2016) when using a pre-procedural rectal swab or stool culture. A targeted antibiotic therapy according to the antibiogram has to be initiated at least 24 h before the biopsy and continued for 3 days.

Based on the potential risk of severe infectious complications, patients with a sterile urine should always receive antibiotic prophylaxis during the biopsy as well. Either oral or intravenous application of a fluoroquinolone is still recommended as the preferred antibiotic because of its broad spectrum. Ciprofloxacin was shown to be superior to others. However, the number of fluoroquinolone resistance is described as up to 23% (Cussans et al. 2016). Moreover, current guidelines also mentioned that the increase in quinolone resistance leads to more severe post-biopsy infections (American Urological Association 2013; European Association of Urology 2016).

Effective strategies to avoid complications due to resistant species should include the following: As already indicated, an assessment of risk factors is obligate. A recent fluoroquinolone therapy within the past 6 months and international travel to countries with a known high rate of resistance should trigger a rectal swab culture in addition to the urine culture. In case of a resistant species, another targeted antimicrobial therapy should be elected. Beyond that, a change in general first-line antibiotic therapy should be considered. Studies evaluating different antibiotic regimens have shown superiority for an augmented antibiotic prophylaxis, e.g., combining a cephalosporin and an aminoglycoside. However, this strategy might be preserved for complex bacteria or patients with risk factors. In uncomplicated patients, a third-generation cephalosporin is an appropriate alternative to fluoroquinolones.

Some studies proposed the use of rectal disinfectants like enemas in addition to antibiotic prevention. The incidence of bacteremia declined when compared to antibiotic prevention only. Disinfection of biopsy needles and a reduced number of biopsy cores may lead to a further decrease. However, reliable data is recently missing.

Indications and Future Perspective

Current international guidelines still recommend a systematic 10- to 12-core biopsy as a baseline biopsy in case of prostate cancer suspicion (American Urological Association 2013; Deutsche Gesellschaft für Urologie 2016; European Association of Urology 2016). European guidelines state that the biopsy can be either performed through a transrectal or transperineal entry path since cancer detection rates are identical when using the same number of cores. Additional cores should be obtained from suspect digital rectal examination/TRUS areas.

Although patient demand for imaging modalities prior to the first prostate biopsy increases rapidly, fusion biopsy in this setting is not part of the current guidelines. This is based on randomized controlled trials showing no benefit in the initial biopsy setting for fusion biopsy (Baco et al. 2016; Panebianco et al. 2015). Nevertheless, many other series reported improved detection of significant cancers even in the initial biopsy. German guidelines recommend for MRI or ultrasound data gathered in primary setting its further use for targeted biopsy (Deutsche Gesllschaft für Urologie 2016). Potentially, within the next years, imaging and fusion biopsies will also be recommended for primary diagnosis.

In contrast, after an initial negative biopsy but persisting cancer suspicion, prostate imaging by mpMRI in the repeat biopsy setting is recommended (Deutsche 2016; European 2016). With mpMRI repeated systematic biopsies alone that harbor the risk to miss cancer lesions were aimed to be avoided. Innovative ultrasound modalities are not recommended for primary diagnosis in current guidelines. However, improvements in cancer detection can be derived from the published data. Thus, they can be used additionally to systematic biopsy, either instead of MRI if this modality is not available or in combination to increase diagnostic accuracy. Differences in the diagnostic performance between the several ultrasound techniques have to be considered.

Saturation biopsies have been compared to MRI/ultrasound fusion biopsies and revealed similar detection rates of clinically significant cancers but a lower efficiency and more insignificant cancers (Radtke et al. 2015). Consequently, saturation biopsies should only be applied in the biopsy cascade after negative image fusion biopsies.

In patients with previous positive biopsy, mpMRI improves risk stratification especially for

candidates to undergo active surveillance. It aids to rule out significant cancer and to monitor patients less invasively. Many trials showed that the presence of lesions in mpMRI leads to significant Gleason score upgrading in repeat biopsies. Conversely, the absence of mpMRI lesions comes along with a lower risk of reclassification and disease progression (Mullins et al. 2013).

Finally, in patients with expected relapse after primary radiation or focal therapy, mpMRI or positron emission tomography (PET) serves for early detection and localization of a local cancer recurrence. They can also be used for an image fusion-guided biopsy.

Future developments of prostate imaging and targeted biopsies will have to focus on an optimization of the predictive value of mpMRI and ultrasound modalities. New technologies and combinations of both mpMRI and functional ultrasound techniques may improve the sensitivity and specificity in cancer detection. Simultaneously, biopsy accuracy has to be further investigated independent of the type of imaging and the ongoing interpretation variety. In the wide field of biopsy techniques, comparative studies have to ascertain the technique with the most accurate targeting and clinical applicability as a standardized technique, not only for a small expert group of users but for urologists of all educational levels. Although fusion biopsies already gained an outstanding role in risk adjustment and focal therapy planning, they will probably be complemented by novel blood and/or urine biomarkers and risk nomograms in order to appropriately select patients for the respective therapy.

Cross-References

- Local and Systemic Staging by Modern Imaging Modalities in Prostate Cancer
- Management of Nonmetastatic Failure Following Local Prostate Cancer Therapy
- Natural History of Untreated Localized Prostate Cancer: Rational for Active Surveillance
- Risk Assessment Based on Molecular and Genetic Markers in Prostate Cancer
- Screening of Prostate Cancer

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Pathological Assessment of Prostate Cancer

9

Sven Perner, Verena Sailer, and Anne Offermann

Contents

Abstract

In the first instance, the diagnostic approach of prostate cancer (PCa) requires histopathological assessment of tumor tissue, and subsequent immunohistochemical analysis, if needed. In part I of this chapter, methods of PCa diagnosis based on differently obtained prostate tissue as well as essential information that have to be reported from pathologists are described. In addition, histomorphological basics for the diagnosis of PCa and, most importantly, features to differentiate PCa from non-neoplastic prostatic lesions are given. One of the most important information provided by pathologists is the current grading of PCa whose morphological basis is described in more detail.

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Part II summarizes immunohistochemical markers that are frequently used for diagnostic purposes and of potential prognostic value. In part III, the molecular signature of PCa is described by highlighting the most important characteristics of PCa including heterogeneity of primary PCa, genomic lesions affecting androgen receptor signaling and main changes during progression to metastatic disease.

Part I: Histopathological Assessment of Prostate Cancer

Classification of Prostate Cancer

Prostate cancer comprises several malignancies dependent on the cellular origin. By far the most common malignant tumors arise from epithelial origin, with acinar adenocarcinoma being the most common type of prostatic carcinoma. Other carcinomas include ductal adenocarcinoma, urothelial carcinoma, squamous cell neoplasms, basal cell carcinoma, as well as neuroendocrine carcinomas.

Prostatic mesenchymal tumors are rare neoplasms arising from the prostatic stroma.

In addition, there are several miscellaneous benign and malignant prostatic tumors having identical counterparts elsewhere.

Very rarely, hematological neoplasias can affect the prostatic gland forming hematolymphoid prostate tumors.

Besides cellular origin, these tumors possess marked differences regarding incidence, epidemiology, histomorphology, molecular profile, clinical course, and treatment (Holger Moch et al. 2016).

This chapter will focus on acinar adenocarcinoma of the prostate accounting for more than 90% of all diagnosed prostatic tumors. Both conventional morphology and immunohistochemistry of prostate cancer will be discussed.

Methods of Prostate Cancer Diagnosis

If prostate cancer is clinically suspected based on elevate serum PSA, abnormal digital rectal examination, suspect imaging findings, or presence of distant metastases, needle core biopsy is the standard procedure for histological diagnosis of PCa. Current standard is to obtain 10–12 systematic core biopsies from predefined prostate regions. Additional image-guided, targeted core biopsies may be obtained as well. The development of precise biopsy sampling guided by MRI or ultrasound-MRI fusion might improve cancer detection in the future. Biopsies are histologically assessed in several levels (Holger Moch et al. 2016; Grignon 2018; Verma et al. 2017).

Tissues obtained from transurethral resection of the prostate or prostate enucleation from patients with benign prostatic hyperplasia are embedded completely (tissue weight < 12 g) or representatively (tissue weight > 12 g) allowing the detection of incidental PCa, classified as T1 tumors (Holger Moch et al. 2016).

Radical prostatectomy specimens are systematically and completely assessed in order to identify several tumor characteristics guiding postoperative patient management. In particular, surgical margins, pathological stage, and definitive grading are important prognostic factors which partially influence clinical management (Holger Moch et al. 2016; Grignon 2018) (Fig. 1). Representative images for different methods of prostate cancer tissue diagnnosis are shown in Fig. 1.

Macroscopy

As described above, radical prostatectomy specimens are completely assessed; thus, the macroscopic aspect plays a minor role in the diagnostic process. While some tumors are not grossly visible, especially clinical T1c tumors, other tumors show a discrete tan, white, or yellow cut surface and may be conspicuous upon palpation (Holger Moch et al. 2016).

Histopathology

The diagnosis of prostate cancer is based on a constellation of several criteria including histomorphological architectural and cellular

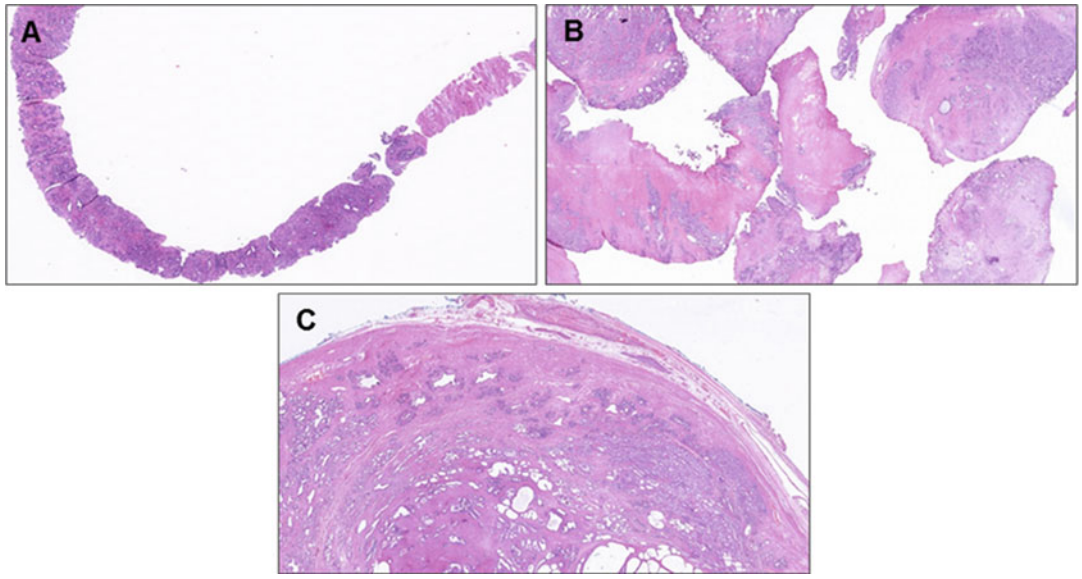

Fig. 1 Methods of prostate cancer tissue diagnosis. (**a**) Needle core biopsy, (**b**) transurethral resection of the prostate, (**c**) radical prostatectomy specimen. (**a**–**c**) x 1

features as well as stratifying immunophenotypes. It is essential to identify features that are diagnostic for cancer allowing to distinguish benign mimickers of prostate cancer. In addition to the diagnosis of cancer, histopathological assessment includes the identification of histological variants, eventual treatment effects, prognostic factors, as well as prostate cancer grading. Obviously, it is necessary to distinguish prostate cancer from other cancers infiltrating the prostate.

Generally, the diagnosis of prostate cancer is based on a constellation of several features supporting malignancy which are interpreted together. However, some features are sufficient for the diagnosis of cancer, because they are not observed in benign conditions. These features may be seen in needle biopsies: mucinous fibroplasia, glomerulation, and perineural invasion (Baisden et al. 1999). Mucinous fibroplasia (or collagenous micronodules) is characterized by loose fibrous tissue with an ingrowth of fibroblasts and eventually with blue mucinous secretion (Baisden et al. 1999). Cribriform gland formations with epithelial proliferation projecting into the gland lumen and single attachment to one edge of the gland resemble a renal glomerulus and are called glomerulations (Baisden et al. 1999). Perineural invasion requires complete circumferential cancer growth around the nerve if used as key diagnostic feature, but might be also diagnosed in the context of prostate cancer if perineurial tracking, intraneural involvement, or partial circumferential growth is seen (Fig. 2a) (Holger Moch et al. 2016). Perineurial invasion is identified in the majority of prostatectomy specimens.

Architectural features of prostate cancer are reflected in the Gleason score which is defined by growth patterns of the tumor and described separately in this chapter. A specific feature of prostate cancer in contrast to benign mimickers is the observation of atypical glands with a single row of lining epithelial cells on both sides of a benign gland. Mimickers of cancer might also seem to be infiltrative, but do not appear as isolated glands around benign glands (Holger Moch et al. 2016; Epstein 1995; Iczkowski and Bostwick 2000). Growth patterns of higher-grade tumors include crowded and fused glands, cribriform and glomerular patterns, as well as solid and single cell infiltrates (Pierorazio et al. 2013).

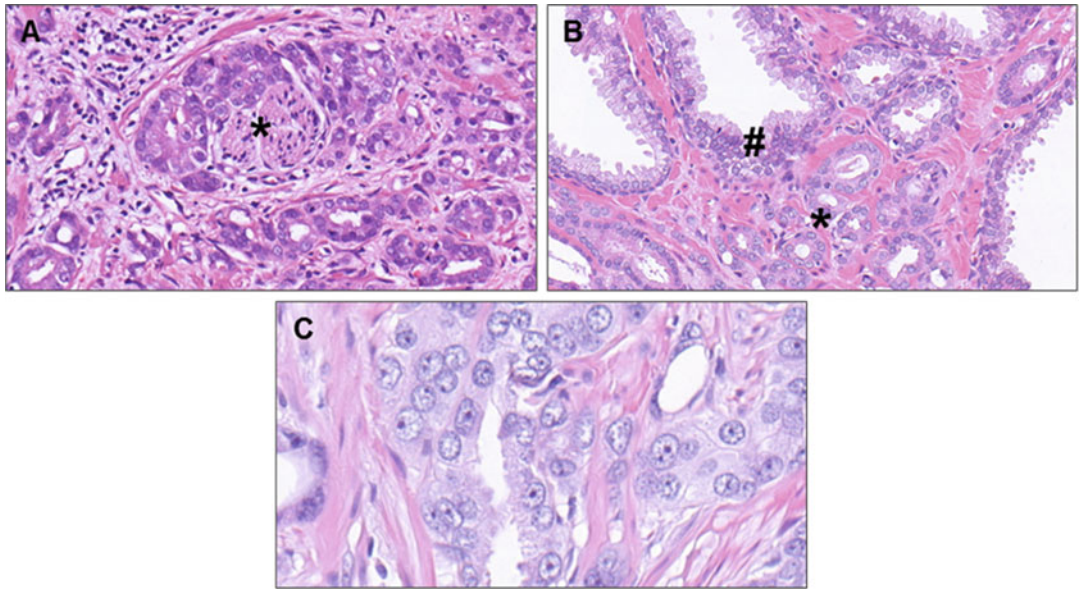

Fig. 2 Features of prostate cancer. (**a**) Perineural invasion *. (**b**) Atypical glands with a single row of lining epithelial * compared to nonneoplastic glands # with basal cell and luminal cell layer and (**c**) cytological features suspicious for prostate cancer: prominent nucleoli and nuclear enlargement, (**a**–**c**) x 40

Cytological features of malignancy relate to nuclear and cytoplasmic characteristics of tumor cells which should not be solely used as diagnostic criteria. Prominent nucleoli are suspicious for prostate adenocarcinoma (Fig. 2c) but might also been seen in a subset of benign mimickers or are lacking in certain tumor areas (Epstein 1995; Varma et al. 2002). Additional nuclear features of prostate cancer are nuclear enlargement and nuclear hyperchromasia as well as mitotic figures and apoptotic bodies, while the latter are more common in high-grade prostate cancer (Holger Moch et al. 2016; Iczkowski and Bostwick 2000).

Importantly, a high degree of pleomorphism regarding nuclear form and size should lead to a diagnostic algorithm ruling out a malignant tumor from elsewhere infiltrating the prostate (Fig. 3).

In addition to features regarding cellular appearance, the characterization of intraluminal contents may aid in the differential diagnosis of cancer and benign mimickers. While intraluminal corpora amylacea characterized by well-circumscribed round to oval structures are common features in benign prostatic glands (Fig. 4a), so-called prostatic crystalloids are more commonly seen in prostate cancer (Fig. 4b). Prostatic crystalloids are eosinophilic crystal-like structures with various geometric forms (Holger Moch et al. 2016; Epstein 1995; Ro et al. 1986; Christian et al. 2005). These structures may also be seen in adenosis which is morphologically distinct from prostatic adenocarcinoma. Other intraluminal contents supporting the diagnosis of cancer are blue-tinged mucinous and pink amorphous secretions (Holger Moch et al. 2016).

Histological Variants of Acinar Adenocarcinoma

There are several histological variants of acinar adenocarcinoma of the prostate that might be challenging to distinguish from benign prostatic glands. Most variants are observed in association with acinar adenocarcinoma. Adenocarcinoma with atrophic pattern characteristically shows cytoplasmic volume loss and eventual flattened nuclei and usually contains areas of usual acinar adenocarcinoma. However, if solely observed,

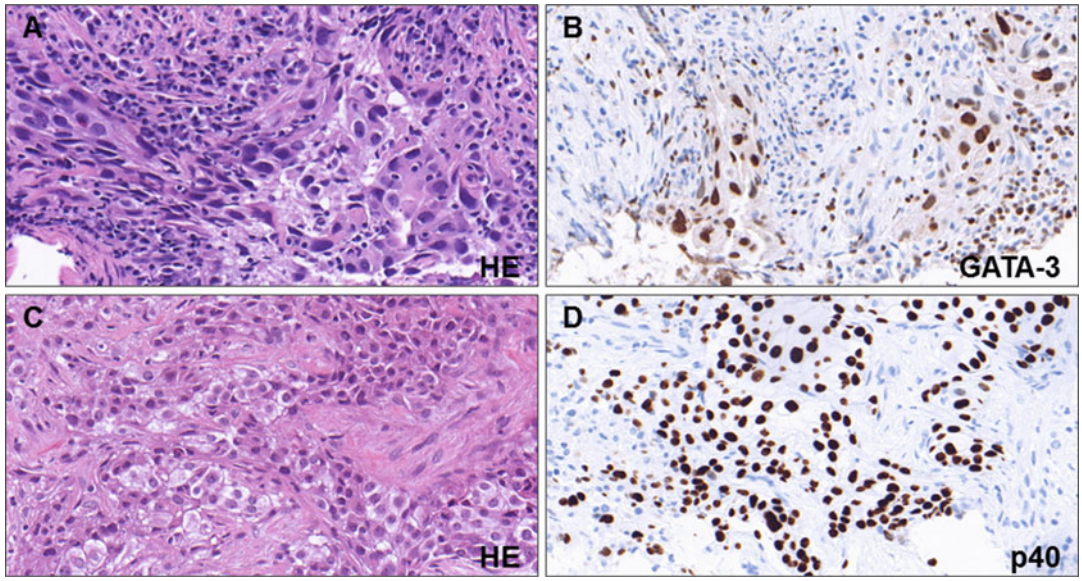

Fig. 3 Non-prostatic neoplasms infiltrating the prostate. (**a**) Urothelial carcinoma infiltrating the prostate diagnosed on needle biopsy showing high degree of nuclear pleomorphism and (**b**) expression of urothelial marker GATA-3. (**c**) Squamous cell carcinoma infiltrating the prostate diagnosed on needle biopsy (**d**) which was confirmed by immunohistochemistry against p40. (**a**–**d**) x 40

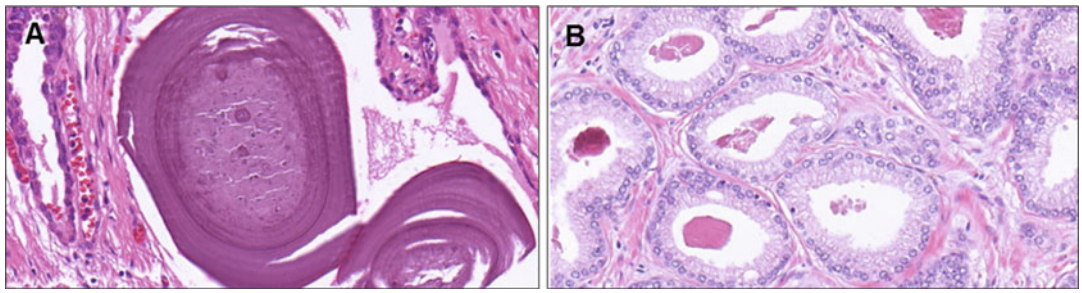

Fig. 4 Intraluminal contents. (**a**) Corpora amylacea in the lumen of a benign prostatic gland compared to (**b**) prostatic crystalloids suspicious for prostate cancer. (**a**–**b**) x 40

it might be challenging to differ this variant from benign atrophic glands requiring immunohistochemical detection of basal cells (Holger Moch et al. 2016; Kaleem et al. 1998). Pseudohyperplastic patterns of adenocarcinoma may appear similar to benign hyperplastic glands with papillary infoldings and branching as well as absence of infiltrative growth. Diagnosis is mostly made in the context of associated acinar adenocarcinoma or verification of basal cell loss (Holger Moch et al. 2016; Humphrey et al. 1998). A small proportion of acinar adenocarcinoma exhibits areas with microcystic patterns of malignant glands characterized by enlarged, cystic dilated glands with atrophic appearance. Detection of cytoplasmic AMACR expression and absence of basal cells support this diagnosis (Holger Moch et al. 2016; Yaskiv et al. 2010). Foamy gland adenocarcinoma is associated with acinar adenocarcinoma and contains malignant cells with abundant cytoplasm and pyknotic nuclei without nuclear enlargement or prominent nucleoli (Hudson et al. 2012) (Fig. 5a).

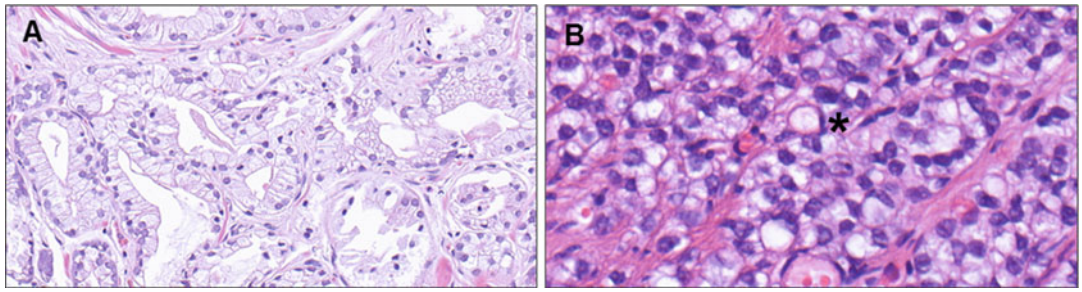

Fig. 5 Histological variants. (**a**) Foamy gland variant of acinar adenocarcinoma of the prostate and (**b**) signet ringlike cells * within a Gleason pattern 5 cancer. (**a**–**b**) x 40

In addition, there are four rare variants with distinct histological features that have been associated with worse clinical outcome of patients. The mucinous variant is composed of malignant glands within extracellular mucin pools and mostly associated with Gleason score 7 or 8 (Holger Moch et al. 2016). Published data are incongruent regarding prognosis compared to usual acinar adenocarcinoma (Marcus et al. 2012). In contrast, the signet ringlike cell variant (Fig. 5b), the pleomorphic giant cell variant, and the sarcomatoid variant are associated with an aggressive clinical course of patients (Holger Moch et al. 2016; Marcus et al. 2012).

Treatment Effects

After radiation or hormonal therapy, both cancer cells and normal prostatic tissue including the stroma and benign glands may exhibit characteristic features. The prostate that has been irradiated may contain atypical appearing benign glands with variably paucicellular and scarred stroma. Indeed, cancer cells are often inconspicuous showing vacuolated cytoplasm and small nuclei (Goldstein et al. 1998). Similarly, effects of androgen deprivation therapy may also be recognized in both benign and malignant cells. Benign glands exhibit a diffuse atrophy with prominent basal cells and may be with immature metaplasia. Malignant areas are composed of clusters, rows, or single cancer cells with inconspicuous cytology (Holger Moch et al. 2016).

Until now, there are no routinely used biomarkers that predict response to therapy or reflect the degree of response.

Prostate Cancer Grading

Grading of prostate cancer is solely based on the architectural pattern of the tumor presenting the basis for assigning the Gleason score and WHO grade groups. Gleason pattern 3 includes variably sized individual and well-formed glands. Poorly formed and fused glands, cribriform patterns, and glomeruloid structures are interpreted as Gleason pattern 4. Gleason pattern 5 is defined as tumors comprised of individual cells, cords of cells and solid growth patterns, as well as comedonecrosis within solid or cribriform tumor areas (Pierorazio et al. 2013). Ductal adenocarcinoma shows most commonly a cribriform or papillary growth pattern and is be graded as Gleason score $4 + 4 = 8$, except if there are comedonecrosis which is then be interpreted as pattern 5 (Holger Moch et al. 2016) (Fig. 6e).

Due to its heterogeneity and multifocality, grade is defined as the sum of the two most common grade patterns (Holger Moch et al. 2016). If there is limited cancer of lower grade (<5%) on both needle biopsy and radical prostatectomy specimen, the lower grade is ignored, and the two most predominant patterns are reported (Epstein et al. 2005). Indeed, higher-grade tumor on needle biopsy should be included into the Gleason score regardless of its quantity. Thus, the most and the worst patterns are added to establish the Gleason score (Holger Moch et al. 2016; Epstein et al. 2005). For needle biopsies, the grade of each core is reported separately followed by an overall score. Since 2016, it is recommended to report the Gleason score

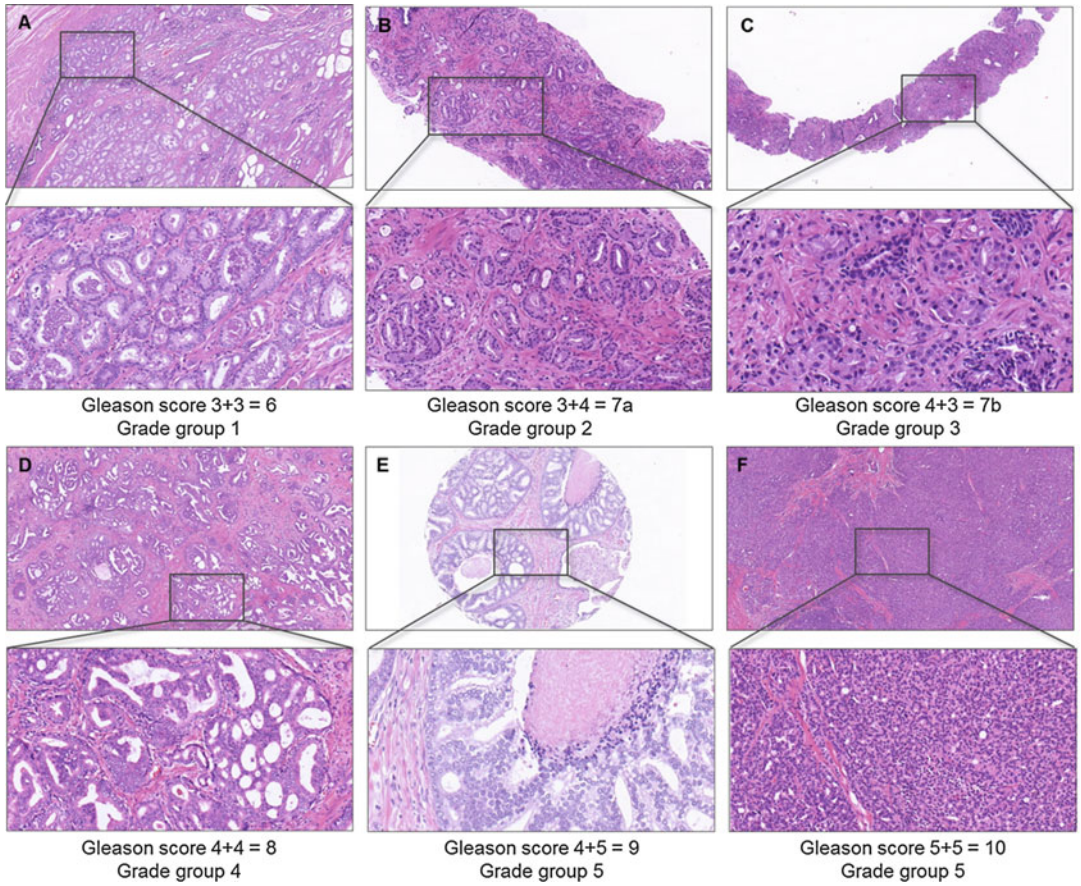

Fig. 6 Prostate cancer grading based on the architectural pattern of the tumor. Upper, x 10; lower, x 40

and, in addition, the WHO grade group (Holger Moch et al. 2016; Pierorazio et al. 2013) (Figure 6). A major recommendation of the 2016 WHO is to report the percentage of pattern 4 of WHO grade group 2 and 3 tumors in order to achieve consistency in reporting cancers including Gleason 4 patterns, to improve individual treatment selection for patients as well as achieve highest prognostic value (Choy et al. 2016).

Reporting of Needle Biopsies

There are several histological parameters that predict postoperative tumor stage, disease progression, and disease-specific survival, thus serving as important information for clinical management. On needle biopsies, it is recommended to report the histological type of cancer, Gleason score, extraprostatic extension, seminal vesicle invasion, and quantification of the tumor. The latter includes reporting the number of cores positive for cancer in relation to total number of cores and a measure of linear extent of cancer (percentage or length per core) (Holger Moch et al. 2016; Srigley et al. 2009).

Reporting of Radical Prostatectomy Specimen

In addition to the histological type of cancer, Gleason score, and tumor quantitation, pathological stage and surgical margins are important

parameters to predict disease recurrence and mortality (Holger Moch et al. 2016). Of note, upgrading from needle biopsy to radical prostatectomy specimen is common, (Epstein et al. 2012) strengthening the importance of definitive Gleason score after surgery. Organ-confined carcinomas are classified as pT2 with pT2a for unilateral cancers involving <50% of one side, pT2b for unilateral cancers involving >50% of one side, and pT2c for bilateral cancers. While these pT2 substages have similar outcomes thus lacking clinical significance, tumor extension beyond the boundaries of the prostate is associated with disease recurrence. Tumor extension into periprostatic adipose tissue or microscopically into bladder neck tissue is classified as pT3a, while infiltration into the seminal vesicle is defined as pT3b (Fig. 7). Reports should include the extent of extraprostatic extension and distinguish between focal and non-focal extension. Tumors that are fixed to or invade adjacent structures including external sphincter, rectum, elevator muscles, or pelvic wall are defined as pT4 (Holger Moch et al. 2016).

The surgical margin status associates with the risk of postoperative biochemical recurrence. Reports should include information about the location and the extent of positive margin (focal or extensive and length in mm) as well as Gleason grade at the margin (Holger Moch et al. 2016; Stephenson et al. 2014). If lymphadenectomy is performed, the number of positive lymph nodes relative to all lymph nodes is reported (Holger Moch et al. 2016) (Fig. 8).

Prostatic Intraepithelial Lesion (PIN)

Prostatic intraepithelial lesion (PIN) defines neoplastic epithelial cells of prostatic glands and is generally categorized into low and high grade; however, only high-grade lesions are reported (Egevad et al. 2006). Isolated high-grade PIN (HGPIN) lacking concomitant prostate cancer (PCa) is present in up to 16% of needle biopsies. In contrast, needle biopsies harboring PCa show associated HGPIN in 80–100%. The median risk of PCa following diagnosis of HGPIN is approximately 21%; thus, patients are more closely monitored (Netto and Epstein 2006).

Histologically, PIN is characterized by glands of medium to large size lined by atypical epithelial cells showing nuclear hyperchromasia and enlarged nuclei with prominent nucleoli and amphophilic cytoplasm (Fig. 9). PIN might exhibit diverse architectural patterns including structures comprising of stratified and folded epithelial cells as well as micropapillary, cribriform, or flat structures. Importantly for differentiating from low-grade PCa, PIN harbors a basal cell layer which might be intact or discontinuous and can be highlighted using basal cell markers, e.g., p63 or high-molecular-weight cytokeratin (Holger Moch et al. 2016).

On molecular level, *TMPRSS2-ERG* fusion can be detected in 19% of HGPIN adjacent to PCa,(Perner et al. 2007) while it occurs much less common in isolated PIN, providing evidence for a genetic association between HGPIN and PCa. Other molecular alterations including aneuploidy DNA, deletions of chromosome 8p, and aberrations of oncogenes and tumor-suppressor genes occur in a subset of HGPIN, while PTEN is intact expressed and might distinguish between HGPIN and intraductal PCa (Lotan et al. 2013).

Atypical Small Acinar Proliferation (ASAP)

Atypical small acinar proliferation (ASAP) is a descriptive term for a lesion that has some features of carcinoma, but lacks sufficient criteria for a diagnosis of prostate cancer (Srirangam et al. 2017). In general, atypia and some degree of architectural distortion are present in a very small focus of acinar structures (Fig. 10). The report might state “suspicious, but not sufficient for a diagnosis of carcinoma.” A diagnosis of ASAP is correlated with a risk of a carcinoma

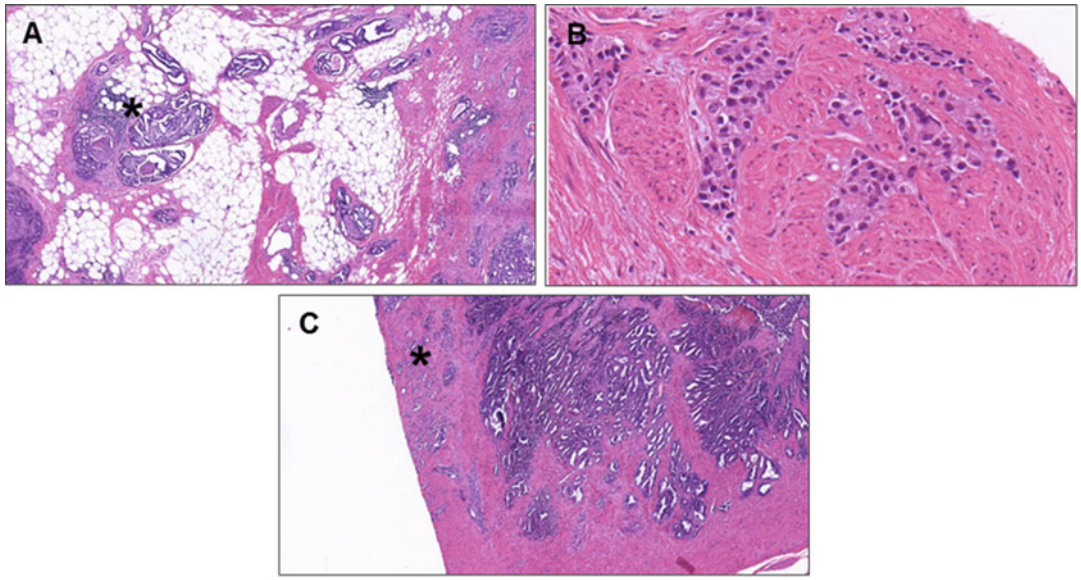

Fig. 7 Extraprostatic extension of prostate cancer. (**a**) Extension into periprostatic adipose tissue (cancer tissue *) and (**b**) smooth muscles of the bladder neck (pT3a), (**c**) infiltration into the seminal vesicle (cancer tissue *) (pT3b). (**a**–**c**) x 20

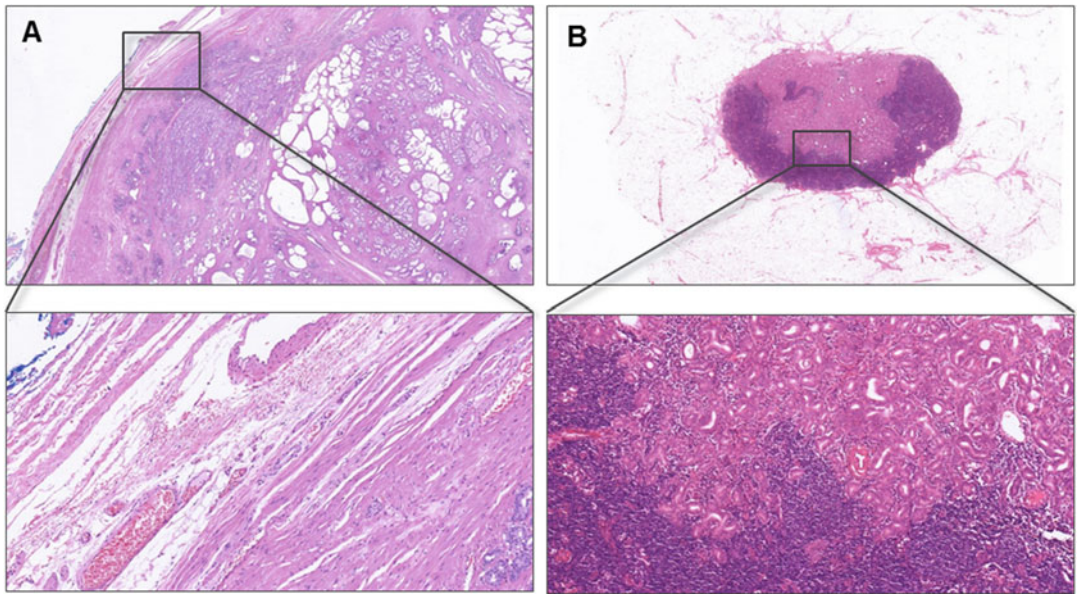

Fig. 8 Surgical margin and lymph node assessment. (**a**) R0-resected prostate cancer, (**b**) lymph node metastasis. Upper: x 10, lower: x 40

diagnosis on subsequent biopsy in 30–60% of cases with the carcinoma being in general low grade and low volume (Ericson et al. 2017; Iczkowski et al. 1997). However, 8% of patients with a diagnosis of ASAP will subsequently be diagnosed with high-grade disease. Thus, current guidelines recommend a repeat biopsy within 3–6 months (Leone et al. 2016).

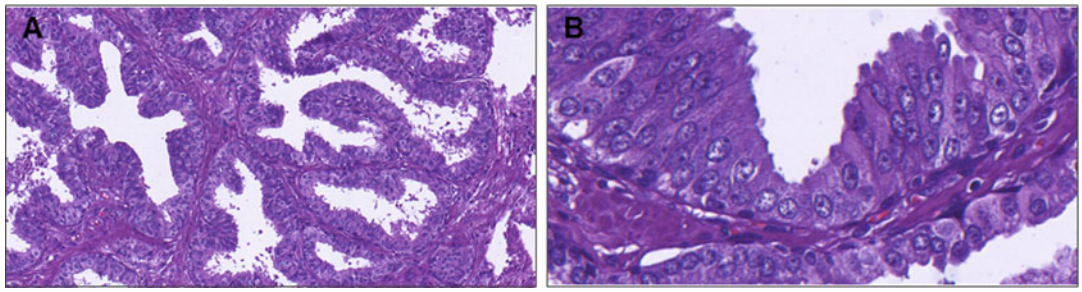

Fig. 9 High-grade prostatic intraepithelial neoplasia (PIN) in low power showing stratified and folded atypical epithelial cells (**a**) and in high power showing nuclear atypia (**b**)

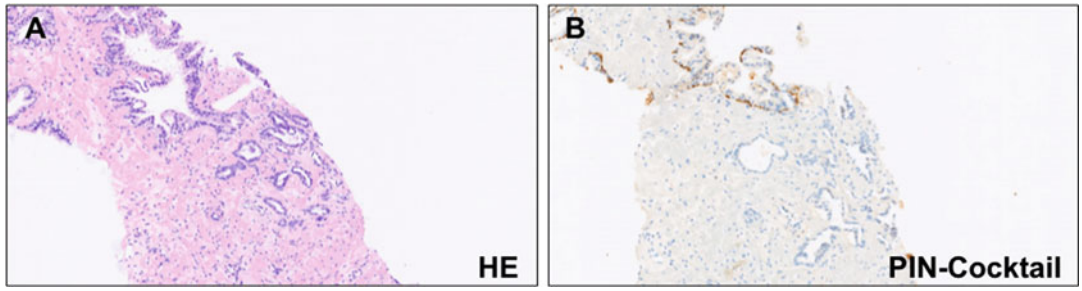

Fig. 10 **ASAP**: Small acini without significant architectural distortion (**a**), but loss of basal cells without AMACR expression (**b**)

Part II: Immunohistochemistry in the Diagnosis of Prostate Cancer

Immunohistochemistry (IHC) is a widely used additional method to stain certain cytoplasmic, nuclear, or membranous proteins. Thus, IHC helps to distinguish cells of different origins, e.g., epithelial vs. mesenchymal.

The following paragraph pertains to core needle biopsies of the prostate gland, but herein presented methods can be used in resection specimen, i.e., transurethral resection or prostatectomy specimen, as well. In general, the International Society of Urological Pathology (ISUP) does not recommend the use of additional immunohistochemical stains in the event of overt prostate carcinoma or obvious benign glands in a needle biopsy (Amin et al. 2014). However, IHC might aid in assessing small foci of suspicious glands and thus reducing the rate of re-biopsies.

As mentioned above, the absence of basal cells is one of the hallmarks of infiltrating acinar adenocarcinoma of the prostate gland and can be assessed best by employing additional immunohistochemical stains. Since basal cells display a different immunophenotype than luminal epithelial cells, immunohistochemistry can be employed to highlight basal cells or the lack thereof (Hameed and Humphrey 2005). This can be very valuable in particular in small (<less than 1 mm) clusters of atypical glands. The most commonly used antibodies for basal cells are directed against high-molecular-weight cytokeratins (e.g., 34βE12) or against the transcription factor p63, a homolog of TP53, or its isoform, ΔNp63 (p40 antibody) (Sailer et al. 2013). Care has to be taken when evaluating basal cell stains, and additional criteria for malignancy such as infiltrating growth and nuclear atypia should be taken into account as well. Benign conditions like atrophy, partial atrophy, and adenosis might also show a

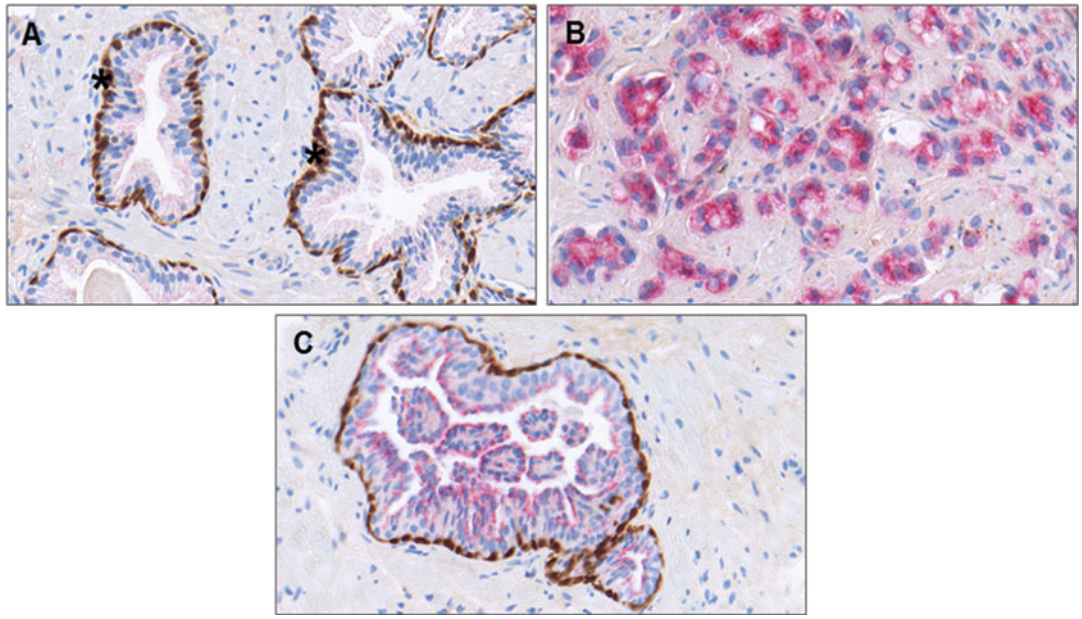

Fig. 11 Immunohistochemical assessment of PCa. (**a**) Normal gland with surrounding basal cells (brown, *), x 40. (**b**) Loss of basal cells in tumor glands, which stain positive (red) for AMACR, x 40. (**c**) High-grade PIN with positive staining for AMACR (red) and retained basal cells (brown), x 40

loss of basal cells (Giannico et al. 2017). Of note, some tumors can show p63 positivity, albeit in a pattern, that is distinctly different from a basal cell distribution (Tan et al. 2015).

One or two basal cell markers can be combined with a stain that highlights malignant epithelium, like alpha-methylacyl-CoA racemase (AMACR or p504s). AMACR shows 97% sensitivity and 100% specificity for detecting prostate cancer (Rubin et al. 2002). Thus, a loss of basal cells and positive staining for AMACR can assist in evaluating small atypical glands in a prostate core needle biopsy (Fig. 11). The ISUP therefore recommends using a double or triple cocktail, which can achieve a specificity of 100% and a sensitivity of 93.8–100% (Ng et al. 2007; Molinie et al. 2004).

Additional IHC for Diagnostic and Prognostic Purposes

Apart from these established and widely used markers, a plethora of markers has been evaluated in prostate tissue samples to identify prostate cancer and/or to provide prognostic information. These markers might be of value as adjunct markers in particularly challenging situations.

One of the most prominent is the ERG protein, which can be upregulated in prostate cancer as result of the prostate-specific gene fusion of *TMPRSS2* with members of the *ETS* family (see below) (Tomlins et al. 2005). The latter is found in approximately 40% of all prostate tumors and in 10–20% of high-grade prostatic intraepithelial neoplasia (HGPIN) adjacent to prostate cancer (Carver et al. 2009a). Therefore, if a small cluster of suspicious glands expresses ERG, it can be attributed to a malignant disease. Shah et al. found that in conjunction with p63 and AMACR, positive ERG staining helped establish a diagnosis of prostate cancer in an additional of 28% of cases of atypical small glands (Shah et al. 2013). However, ERG negativity does not exclude prostate cancer. While the prognostic relevance of the *TMPRSS2-ERG* fusion is still largely unclear, ERG expression seems to have prognostic value in patients undergoing active surveillance in that positive ERG status is prognostic of tumor progression (Bostrom et al. 2015; Berg 2016).

PTEN is a negative regulator of the PI3KI/AKT pathway and lost in up to 17% of primary prostate cancer due to deletion or inactivating mutation (The Molecular Taxonomy of Primary Prostate Cancer 2015). It might be of use in distinguishing intraductal prostate carcinoma from HGPIN (Morais et al. 2015). In addition, loss of PTEN expression is associated with worse overall survival in patients with low-risk tumors (Lokman et al. 2017).

In approximately 10% of *ETS*-negative tumors, the serine peptidase inhibitor, Kazal type 1 (SPINK1), is overexpressed and acts as independent predictor of biochemical recurrence after resection (Tomlins et al. 2008). It can be evaluated with ERG in a double immunostain (Fontugne et al. 2016). As to date, no systematic analysis had been performed to evaluate its role as a diagnostic marker in prostate core needle biopsies. However, since SPINK1 expression is mutually exclusive with ERG expression, the double stain might help identify molecularly distinct, i.e., separate primary tumors, in the prostate and thus influence clinical management.

Fatty acid synthase (FASN) is overexpressed in prostate cancer and has shown promising potential as a prognostic marker in prostate cancer (Epstein et al. 1995). Since FASN can be expressed in AMACR-negative tumors, it might provide additional information in challenging cases (Tischler et al. 2010).

In the event of a tumor in a prostate core needle biopsy without overt prostate differentiation, an infiltrating urothelial carcinoma or colorectal carcinoma should be excluded. The transcription factors GATA-3 and p63 have been shown to be highly sensitive in urothelial carcinoma, and these proteins are not expressed in prostate cancer(Hoang et al. 2015) (Fig. 3). The ISUP therefore recommends their use when faced with the need to distinguish prostate cancer from urothelial cancer (Amin et al. 2014). Colorectal carcinoma can be excluded by using a marker panel of CDX2 and CK20, which should in general be negative in prostate cancer, but positive in colorectal cancer (Owens et al. 2007). Rarely, elsewhere located primary tumors will metastasize to the prostate, or lymphoma might be suspected in a prostate biopsy. These cases should be worked up by immunohistochemistry taking into account the patients' history and radiological and clinical findings. Prostate cancer metastases can be a diagnostic challenge, particularly if they occur before a diagnosis of prostate cancer has been established. A combination of immunohistochemical markers prostate-specific antigen, androgen receptor, and prostate-specific membrane antigen can diagnose a prostate cancer metastasis with a sensitivity up to 98% for lymph node and up to 100% for distant metastases (Queisser et al. 2015).

Part III: Molecular Signatures of Primary and Metastatic Prostate Cancer

Molecular Signatures of Primary Prostate Cancer

Rapidly evolving sequencing techniques have provided a unique insight into the molecular underpinnings of cancer. Localized prostate cancer is characterized by complex structural chromosomal alterations including copy number variations and chromosomal rearrangements. Indeed, recurrent non-synonymous point mutations occur markedly less frequently in localized, hormone-naive prostate cancers than in other cancers (Beltran et al. 2013).

Molecular Complexity and Heterogeneity

There is a high degree of inter- and intratumoral genetic heterogeneity providing molecular evidence for the clinically variable behavior of prostate cancer. Several studies observed a high grade of genetic and transcriptomic diversity between different cancer foci within one patient as well as tumors of different patients (Tosoian and Antonarakis 2017). This heterogeneity gives evidence to define molecular subgroups of prostate cancer with characteristic genetic/transcriptomic profiles, clinical courses, and treatment responses. With the aim to identify subgroups with high risk of developing metastases and disease recurrence, several models of molecular subtyping have been proposed as clinically useful prostate cancer classifiers (Walker et al. 2017).

Genome-wide sequencing of prostate cancer has led to the identification of complex and highly interdependent genomic rearrangements termed "chromoplexy." This model describes coordinate genomic derangement based on a few genetic events supporting the model of clonal evolution in carcinogenesis (Baca et al. 2013). Complementary to this report, several other studies confirmed the highly complex nature of prostate cancer genetics.

Chromosomal Alterations

Recurrent gene fusions affecting members of the erythroblastosis virus E26 transformation-specific (ETS) family of transcription factors are observed at high prevalence in localized prostate cancers (Tomlins et al. 2009). Fusion between *ETS* members acting as oncogenic transcription factor and androgen-regulated genes serving as 5′ fusion partner results in androgen-mediated overexpression of oncogenes. Among the ETS transcription factors, family members, *ERG* (21q22.2), *ETV1* (7p21.2), and *ETV4*, are fused to the androgen responsive gene *TMPRSS2* (Tomlins et al. 2009; Barros-Silva et al. 2013). Other androgen response 5′ fusion partners of *ERG* are *SLC45A3*, *HER-PUD1*, and *NDRG1* (Barros-Silva et al. 2013; Pflueger et al. 2009; Rubin and Demichelis 2018). The most common gene fusion in localized prostate cancer is the *TMPRSS2-ERG* fusion observed in approximately 50% of prostate tumors (Tomlins et al. 2005). Several functional models showed that ETS members promote prostate cancer pathogenesis supporting their putative oncogenic role (Klezovitch et al. 2008).

In addition, gene fusions that do not involve ETS family members have been identified as driver fusions and, however, occur at much lower frequency than ETS rearrangements. In ETS rearrangement-negative prostate cancer, paired-end transcriptome sequencing has led to the identification of recurrent rearrangements in the RAF pathway including gene fusions between *SLC45A3-BRAF* and *ESRP1-RAF1* (Rubin and Demichelis 2018; Palanisamy et al. 2010). Interestingly, its expression in prostate cells induced a neoplastic phenotype that was sensitive to RAF and mitogen-activated protein kinase (MAPK) inhibitors (Palanisamy et al. 2010).

Mechanistically, recent findings give insights into the underlying molecular mechanisms driving genomic rearrangements. Androgen receptor signaling including involved downstream transcription factors recruit the enzyme topoisomerase 2B (TOP2B) to target gene promotors resulting in locus-specific double-strand breaks and subsequent gene transcription (Ju et al. 2006). Concordantly, the androgen receptor and TOP2B are co-expressed in prostate cancer precursor lesion in which the *TMPRSS2-ERG* fusion occurs. Other mechanisms include recruiting DNA break-inducing enzymes to translocation breakpoints in an androgen receptor-dependent manner (Mani et al. 2009; Haffner et al. 2010).

In conclusion, transcription factors and pathways known to be altered in localized prostate cancer contribute to the formation of locus-specific genomic rearrangements.

Already in early studies, loss of heterozygosity of genes located on 10q and 8p has been described in a subset of human prostate cancer samples. Distinct loci as sites for recurrent deletions were identified to cause inactivation of tumor-suppressor genes (Rubin and Demichelis 2018).

Genomic Lesions Affecting the Androgen Receptor Signaling

The androgen receptor axis belongs to the most relevant pathways critically involved in prostate cancer. Genomic alterations of the androgen receptor itself including gene amplification, point mutations, and splice variants are restricted to metastatic castration-resistant prostate cancer (Taylor et al. 2010). Indeed, genetic alterations in several androgen receptor-modulating factors have been identified in both metastatic and localized hormone-naïve tumors (Rubin and Demichelis 2018). Comprehensive analyses revealed that about 50% of primary tumors harbor genetic alterations affecting the androgen receptor signaling axis. Dysregulation of transcription factors, androgen receptor coactivators and corepressors, interacting molecules, and chromatin regulatory elements have been identified to modulate the androgen receptor axis (Taylor et al. 2010).

Among the most affected genes, *NCOA2*, a nuclear receptor coactivator, has been identified to be significantly amplified and to exhibit somatic mutations in about 8% of localized tumors. Similarly, the nuclear receptor corepressor 2 (NCOR2) gene is mutated in primary tumors with mutation frequencies in up to 23% (Holger Moch et al. 2016; Barbieri et al. 2012).

Other components include the non-tyrosine kinase TNK2, the adenovirus E1A-associated cellular p300 transcriptional coactivator protein EP300 (p300), and the androgen receptor interaction partner FOX1A showing point mutations and chromosomal aberrations in localized tumors (Barbieri et al. 2012; Ren et al. 2017).

Collectively, these data support the central importance of the androgen receptor signaling in both metastatic castration-resistant and localized hormone-naïve prostate cancer.

Recurrent Somatic Mutations

Recurrent mutations that occur at high frequency in various other cancer types are observed at much lower frequency in localized prostate cancer. Indeed, markable higher frequencies of recurrent mutations are observed in metastatic- and castration-resistant tumors.

The most common mutated gene in localized prostate cancer is the speckle-type POZ protein (SPOP) gene located at chromosome 17 (Barbieri et al. 2012). In treatment-naïve localized tumors, *SPOP* is recurrently mutated at frequencies ranking from 6 to 14% (Holger Moch et al. 2016; Blattner et al. 2014). Based on the observations that SPOP is mutated in intraepithelial neoplasia (high-grade PIN) adjacent to invasive carcinoma, *SPOP* mutation is thought to be an early event in prostate tumorigenesis.

SPOP serves as an E3 ubiquitin-protein ligase adaptor to recruit substrates for ubiquitination. Missense mutations of *SPOP* affecting its efficiency or specificity lead to differential degradation of proteins with potential oncogenic or tumor suppressive functions (Zhuang et al. 2009; Theurillat et al. 2014).

Distinct patterns of co-occurring genetic events define *SPOP*-mutated tumors as individual prostate cancer subtype. *SPOP* mutations are mutually exclusive or inverse correlated to ERG rearrangement supporting their roles as distinct driver events in prostate carcinogenesis. Indeed, recurrent 5q and 6q deletions that result in the loss of tumor-suppressor genes correlate with the presence of SPOP mutation (Rubin and Demichelis 2018).

Inactivation of the tumor-suppressor gene phosphatase tensin homolog (PTEN) (10q23) by gene deletion can be observed in approximately 50% of localized prostate cancers (Barbieri et al. 2013). Loss of *PTEN* by loss-of-function mutations or somatic indels occurs at much lower frequencies (5–10%). Alterations in *PTEN* significantly correlate with TMPRSS2-ERG fusion in primary tumors, and functional studies support their cooperative effect on prostate cancer pathogenesis (Barbieri et al. 2012; Carver et al. 2009b).

In addition to PTEN, TP53 belongs to the most commonly altered tumor-suppressor gene in cancer. Inactivation of TP53 through gene deletions and point mutations occurs in approximately 50% of primary prostate cancers with significant overlap with *PTEN* deletion and *ETS* rearrangement (Holger Moch et al. 2016).

Several genes that are involved in chromatin regulation are altered in diverse cancer types. In prostate cancer, the most commonly affected gene is the tumor-suppressor chromodomain-helicase-DNA-binding (CHD) protein 1 (5q21) (Taylor et al. 2010). Its inactivation is mainly based on homozygous gene deletion and associates with additional copy number losses predominantly on 2q, 5q, and 6q. Further studies found somatic point mutations in CHD1 at lower frequencies.

Molecular Signatures of Metastatic Prostate Cancer

Primary prostate cancer is often multifocal, but only one, morphologically indistinct, clone gives rise to metastatic disease (Liu et al. 2009). Thus, molecular alterations in prostate cancer metastases from patients with metastatic castration-resistant disease (mCRPC) differ significantly from those found in primary tumors (The Molecular

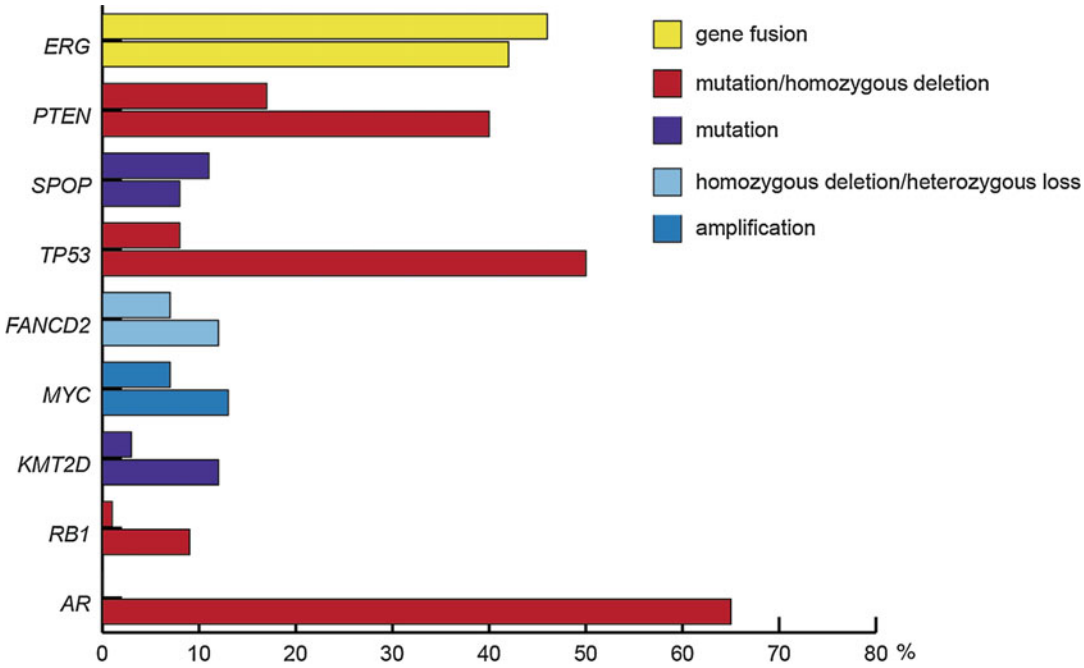

Fig. 12 Comparison of molecular alterations in primary (upper bar) and metastatic (lower bar) prostate cancer. (Adapted from TCGA (The Molecular Taxonomy of Primary Prostate Cancer 2015))

Taxonomy of Primary Prostate Cancer 2015). For instance, a significant higher burden of copy number alterations and mutations are found in metastatic specimen. Some alterations, like *TMPRSS2-ERG* fusions, occur in similar frequency both in primary and metastatic samples (Fig. 12).

Several pathways are altered in mCRPC, e.g., AR signaling, PI3K, cell cycle, and DNA repair. Interestingly, while alterations of the androgen receptor (AR) gene are infrequent in primary prostate cancer, they occur in more than 70% of metastatic prostate cancer by amplification of mutation, and mutations of *AR* are not found in primary prostate cancer at all (Robinson et al. 2015). This probably reflects a selection pressure introduced by antiandrogen therapy. In addition, genes involved in AR signaling like the transcription factor *FOXA1* and the AR-regulator *NCOR1/2* also frequently altered (Robinson et al. 2015). Interestingly, *SPOP* mutations occur to a lesser degree in metastatic samples (The Molecular Taxonomy of Primary Prostate Cancer 2015). Of clinical use is the detection of the AR splice variant AR-V7. AR-V7 acts as a transcription factor and lacks a ligand-binding domain, which is targeted by enzalutamide and arbiraterone. AR-V7 remains constitutively active despite treatment with and thus predicts resistance to treatment with enzalutamide and arbiraterone (Antonarakis et al. 2014).

PI3K pathway alterations are more frequent in metastatic samples, as are *TP53* and *RB1* alterations (The Molecular Taxonomy of Primary Prostate Cancer 2015). *RB1* alterations resulting in loss of the tumor suppressor are found in around 20% of mCRPC samples. Additionally, focal amplifications of *CCND1*, which encodes the cell cycle regulator cyclin D1, are found in almost 10% of cases (Robinson et al. 2015). Concurrent loss of *TP53* and *RB1* results in lineage plasticity from a high-grade adenocarcinoma to a neuroendocrine phenotype in appr. 25% of mCRPC patients (Mosquera et al. 2013). This process is mediated by the transcription factor *SOX2* (Mu et al. 2017). Transdifferentiation to a neuroendocrine, androgen-independent phenotype is a response mechanism to androgen deprivation therapy and is accompanied by

amplification of the cell cycle regulator *AURKA* and the transcription factor *MYCN* (Mosquera et al. 2013). Trials with *AURKA* inhibitors in mCRPC have so far not shown to be promising (Lin et al. 2016).

Almost half of mCRPC samples harbor alterations in the PI3K pathway in the form of deletions and amplifications, activating mutations, and fusions(Robinson et al. 2015). This is of particular interest, since these alterations might be clinically actionable, but efficacy of drugs targeting the PI3K pathway has not been proven yet (Statz et al. 2017; Armstrong et al. 2017).

It is worth pointing out, that germline defects in DNA-repair genes are found in around 12% of men with metastatic prostate cancer (Pritchard et al. 2016). Somatic alterations in the same pathway are found in almost 20% of all cases, most frequently in *BRCA2*, *BRCA1*, and *ATM* (Robinson et al. 2015). Both germline and somatic defects in DNA-repair genes compromise the homologous recombination pathway, thus providing a treatment rationale for PARP inhibitors. In pretreated patients with metastatic disease and DNA-repair defects, 88% responded to therapy with the PARP inhibitor Olaparib (Mateo et al. 2015).

Other alterations occur less frequent than the aforementioned ones, but are potentially actionable like mutations in *FGFR2* and *RAF* (Beltran et al. 2016).

In summary, while the same molecular pathways are activated both in primary and metastatic prostate cancer, monoclonal evolution results in distinct variances in the frequency in which these alterations occur. Some of the differences might also be attributable to selective pressure by antitumor therapy.

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Natural History of Untreated Localized Prostate Cancer: Rational for Active Surveillance

10

Peter C. Albertsen

Contents

Abstract

The treatment of localized prostate cancer remains controversial, especially for tumors detected by prostate-specific antigen (PSA) testing. Although the lifetime risk of receiving a prostate cancer diagnosis is about 17%, the risk of dying from this disease remains around 3%. This suggests that many men are unlikely to benefit from treatments. When assessing the value of any intervention, men must first understand the threat posed by their disease and then determine how likely interventions will alter this outcome.

The most powerful predictor of the natural history of prostate cancer continues to be the

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Gleason score. Men with high-grade disease (Gleason 8–10) have a high probability of disease progression and often die from prostate cancer 5–10 years after diagnosis depending upon whether the disease is localized or metastatic at diagnosis. Men with screen-detected, high-grade, localized disease often have an additional 5 years before they succumb to their disease. Men with screen-detected, low-volume, low-grade prostate cancer have the best prognosis. In the absence of intervention, many are likely to survive at least 15–20 years without symptoms or evidence of disease progression. Prostate cancer mortality is less than 5%. These are the men who may want to consider active surveillance. Men diagnosed with screen-detected intermediate-grade disease (Gleason 7) are the most difficult to counsel. Clinical symptoms are unlikely to occur for at least 10 or possibly 15 years. As a consequence older men may wish to monitor their disease, while younger may wish to seek intervention.

Historical Background

During the past 150 years, prostate cancer has risen from a relatively rare clinical entity to the most commonly diagnosed malignancy in men aside from skin cancer (Siegel et al. 2017). In a classic monograph on the enlarged prostate published in 1852, Thompson reported on 18 cases of prostate cancer (Thompson 1852). Improvements in the microscope in the late 1800s resulted in multiple additional case series reports from Germany and France. In 1891, von Recklinghausen recognized that the primary lesion in the prostate was often small and that metastatic disease had a predilection for bone. By the turn of the last century, physicians such as Pasteau and Degrais in France and Barringer in the United States were aggressively treating prostate cancer by placing radium needles into the prostate in order to ablate malignant cells. Hugh Hampton Young developed a perineal approach to the prostate to facilitate biopsies, place radium needles, and occasionally remove the prostate. By the early 1900s, most clinicians viewed prostate cancer as a lethal disease that often caused obstructive voiding symptoms and almost always led to metastatic progression. For this reason, Young advocated screening by rectal examination in order to diagnose this disease earlier and hopefully to provide a cure (Young 1905).

Pathologists and some internists had a different perspective of this disease. They recognized that men with a firm prostate often had prostate cancer but that in many cases the disease would progress slowly if at all so that men often died with their prostate cancer rather than from their prostate cancer. In a 1996 paper, Sakr estimated that as many as 30% of men in their 30s and more than 70% of men in their 70s harbored prostate cancer (Sakr et al. 1996). Donald Gleason recognized that prostate cancer presented in many histologic forms ranging from minor changes in glandular structure to sheets of cells that were barely recognizable as arising from the prostate. He documented nine different histologic growth patterns that were presented schematically in a classic diagram as Gleason patterns 1–5 (Gleason 1966). He then went on to show that classifying the primary growth pattern and the secondary growth pattern would result in a Gleason score that was highly predictive of subsequent prostate cancer-specific mortality. One of the most important outcomes of the Veterans Administration Cooperative Urological Research Group was the validation of the Gleason scoring system for establishing a prostate cancer patient's prognosis (Gleason and Melinger 1974).

For the past century, most patients and clinicians have believed in the Halsted paradigm of cancer progression (Welch et al. 2015). Specifically, cancers arise within a target organ, grow there for a while, and eventually migrate via blood and lymphatics to distant sites. This paradigm implies that prostate cancer can be cured if the disease is found early enough so that it can be removed by surgery or ablated by either radiation, cryosurgery, or some other techniques. Urologists have utilized these methods for over 100 years with mixed results. For Barringer, only 36 of

352 patients receiving radon implants lived over 5 years following treatment. Huggins' discovery that prostate cancer was an endocrine-dependent tumor revolutionized treatment of this disease (Huggins et al. 1941). By the early 1950s, antiandrogen therapy was commonplace, and discussion ensued whether this treatment was simply palliative or resulted in improved survival (Byar and Corle 1988). Efforts to identify other effective chemotherapeutic agents were unsuccessful.

Until three decades ago, most patients with clinically significant prostate cancer presented with back pain, weight loss, and cancer cachexia. Patients were usually offered antiandrogen therapy to palliate symptoms. Unfortunately these men usually died within 3–5 years of diagnosis. For men who appeared to have disease localized to the prostate, Bagshaw began promoting external beam radiation therapy in the 1960s as an effective treatment for localized prostate cancer. In the 1970s, Whitmore promoted brachytherapy through a lower abdominal incision, and in the 1980s, Walsh promoted the nerve-sparing radical prostatectomy. All of these men recognized the importance of effective disease staging prior to treatment. Radiation and surgery were limited to men presenting with a prostate nodule or following transurethral resection of the prostate. These therapies were usually aborted if lymph node involvement was identified.

These diagnostic and treatment paradigms are important to understand in order to appreciate the enthusiasm that greeted Stamey's 1987 report of prostate-specific antigen (PSA) and Catalona's 1991 recommendation to use this test as a screening tool to identify localized disease (Stamey et al. 1987; Catalona et al. 1991). Within 3 years of adopting PSA testing, the incidence of prostate cancer in the United States tripled (Siegel et al. 2017). In view of their previous experience with prostate cancer, most urologists and radiation therapists recommended treatment since the prevailing view held that prostate cancer was uniformly fatal if allowed to progress (Welch and Albertsen 2009). While this perspective of prostate cancer dominated prostate cancer management in the United States, it was not accepted worldwide. Researchers and clinicians in Sweden recognized the variable natural history of this disease and published several key studies that have shaped the contemporary understanding of prostate cancer progression.

Estimates of the Natural History of Prostate Cancer from Population-Based Case Series Data

Beginning in 1977, Johansson et al. began recruiting consecutive patients with early-stage (T0–T2, Nx M0) prostate cancer and tracked their outcomes (Johansson et al. 2004). By 1984, they had accrued 223 patients and subsequently followed them for an additional 21 years, publishing their findings in 2004. They found that most low- to intermediate-grade prostate cancers diagnosed at an early stage have an indolent course but local tumor progression and aggressive metastatic disease may develop in the long term. Half of these patients were detected following transurethral resection of benign prostatic enlargement, and half were detected because of a palpable nodule. None were identified by PSA testing. Two thirds (148/223) of the patients had well-differentiated tumors, and 30% (66/223) had moderately differentiated disease. Only nine patients had poorly differentiated disease of which five subsequently died from prostate cancer. The mean age at diagnosis was 72 years. Johansson concluded that radical treatment is indicated for men with well and moderately differentiated disease provided that they had an estimated life expectancy exceeding 15 years.

In the United States, Potosky et al. also recognized that the rising incidence of prostate cancer was associated with the increasing rates of transurethral resection for benign disease (Potosky et al. 1995). It was unclear, however, if these tumors posed a clinical threat and whether men benefited from surgical or radiation therapies. A computer simulation of the natural history of prostate cancer published in 1993 concluded that intervention carried at best a relatively modest benefit within 10–15 years following diagnosis (Fleming et al. 1993). This analysis inspired a population-based observational study that documented the

critical importance of Gleason score in predicting the likelihood that localized disease will become clinically significant during a patient's lifetime (Albertsen et al. 2005). The study population consisted of 767 men identified from the Connecticut Tumor Registry database who were Connecticut residents when diagnosed with prostate cancer between January 1, 1971, and December 31, 1984. Of these men, 717 died before October 8, 2004, after a median observation of 24 years (range 16–33 years). Eighty-seven percent were followed for more than 20 years. Charts were abstracted onsite to confirm the date of diagnosis, metastatic evaluations completed, method of treatment, and any associated comorbidities. Patients who had undergone surgery, received either external beam radiation or brachytherapy, or were known to have metastatic disease at the time of diagnosis were excluded. Patients with other concomitant cancers and those surviving less than 6 months following diagnosis were also excluded. Study personnel performing chart abstraction were blinded to the long-term outcome of the patients as recorded in the tumor registry. Original histology slides that were used to secure the patients' diagnoses were retrieved from hospital pathology departments and mailed to a referee pathologist, Dr. Gleason, who was also blinded to the long-term outcome. Standardized grading was performed using the original Gleason classification system. Accurate staging information was lacking for many men, and none had information concerning PSA concentrations. Approximately 71% of patients were diagnosed with prostate cancer following transurethral resection or simple open prostatectomy, 26% were diagnosed by needle biopsy, and 3% were diagnosed by other or unknown methods.

Results of this study were published in JAMA in 2005 including a figure that has since been widely reproduced (Fig. 1) (Albertsen et al. 2005). Few men with low-grade tumors had disease progression leading to prostate cancer death within 20 years of diagnosis. Conversely, most men with high-grade disease died from prostate cancer regardless of their age at diagnosis. Among relatively healthy men, 26%, 15%, and 8% survived at least 15, 20, and 25 years, respectively. Among men with Charlson comorbidity scores greater than 1 at diagnosis, 11%, 6%, and 3% survived at least 15, 20, and 25 years, respectively. The prostate cancer mortality rate was 33 per 1000 person-years during the first 15 years of follow-up and 18 per 1000 person-years after 15 years of follow-up. These values were not statistically different after adjusting for the more favorable histology profiles among men who survived more than 15 years following diagnosis.

Both the Johansson study and the Albertsen study agreed that men with well-differentiated prostate cancers rarely die from their disease, while men with poorly differentiated tumors frequently die within 5–10 years of diagnosis, often despite aggressive interventions. Men with moderately differentiated tumors (contemporary Gleason 7 tumors) have the greatest variation in outcomes. Counseling men who have moderately differentiated disease and a life expectancy greater than 15 years poses the greatest challenge. A majority of these men will die from competing medical conditions during a period of 15–20 years. Unfortunately, repeated PSA testing is exacerbating the problem by introducing a lead time of many years. Data from the Johansson study and the Albertsen study were derived from patients diagnosed with prostate cancer before the advent of PSA testing. Draisma has estimated that for a single PSA screening test at age 55 years, the estimated lead time is 12.3 years and the likelihood of detecting clinically insignificant disease is 27% (Draisma et al. 2003). At age 75 years, the estimated lead time is only 6.0 years, but the likelihood of detecting clinically insignificant disease could be as high as 56%.

Estimates of the Prevalence of Prostate Cancer in Healthy Men

While pathologists have long recognized that localized prostate cancer is a common finding at autopsy among older men, our understanding of the prevalence of prostate cancer was dramatically advanced by data gathered for the Prostate Cancer Prevention Trial (PCPT) (Thompson et al. 2003). The PCPT was a phase 3, randomized, double-

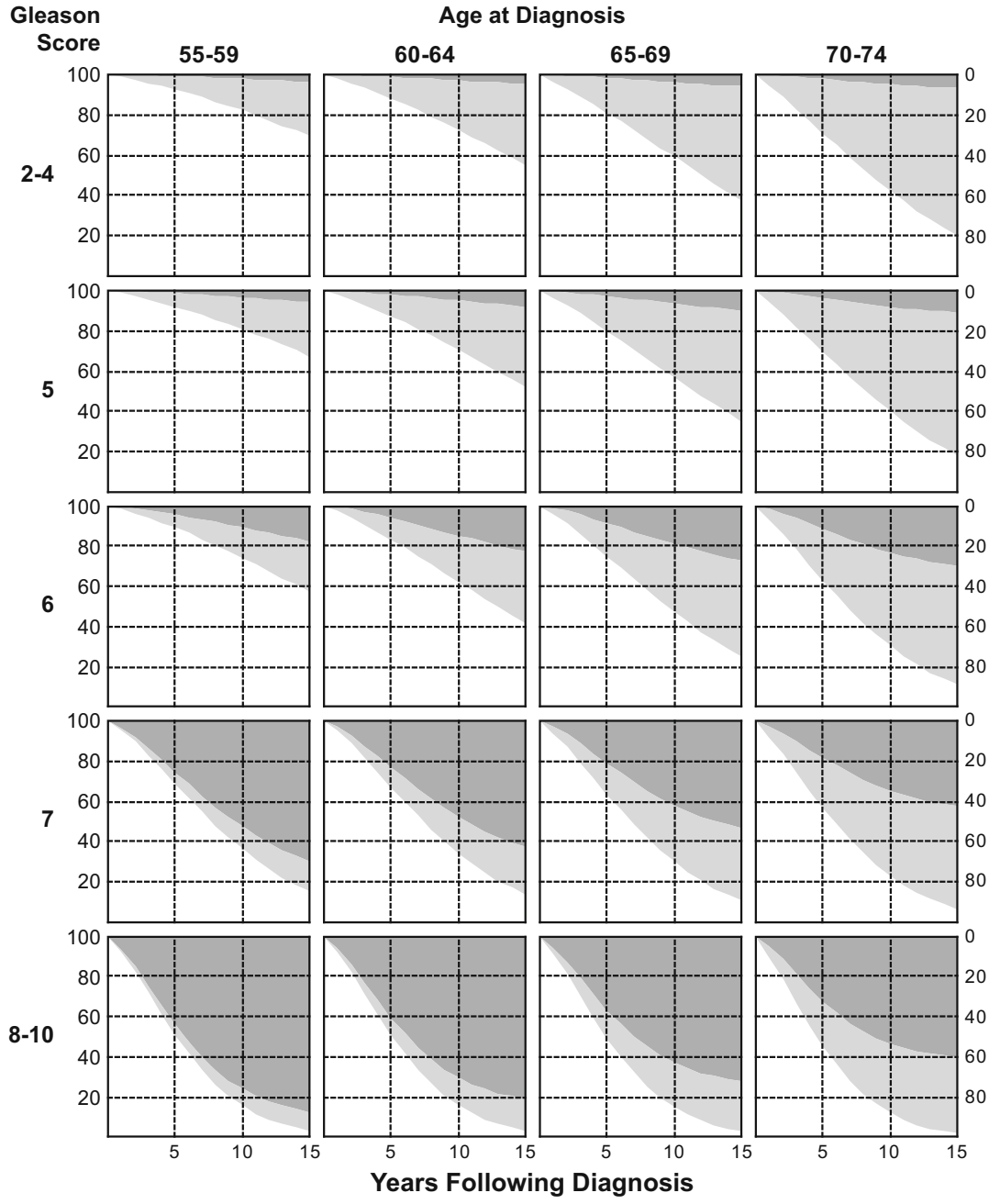

Fig. 1 Survival and cumulative mortality from prostate cancer and other causes up to 20 years after diagnosis, stratified by age at diagnosis and Gleason score (Reproduced with permission from Albertsen et al. (2005). Copyright ©2005 American Medical Association. All rights reserved)

blind, placebo-controlled study that evaluated whether finasteride could reduce the prevalence of prostate cancer during a 7-year period of treatment. Fortunately, the study protocol called for all participants to undergo an end-of-study prostate biopsy if they had not previously been

diagnosed with cancer. The original study was powered to detect a 25% reduction in prostate cancer and assumed the prevalence of disease to be 6% within the study population. At the conclusion of the trial, 24% of the men in the control arm had been diagnosed with prostate cancer; most of these men had no clinical evidence of disease and were biopsied per study protocol. Of the 449 men identified as having cancer on their end-of-study biopsy, 361 (80%) had Gleason score 6 or less, while 60 (13%) had Gleason score 7, and 7 (1.6%) had Gleason score 8 or 9. This study revealed the extensive pool of well-differentiated prostate cancers that exist in a normal, healthy male population. Furthermore, the authors demonstrated that biopsy-detectable prostate cancer was not rare among men with PSA levels of 4.0 ng/mL or less, a level historically considered normal (Thompson et al. 2004). The prevalence of prostate cancer was 6.6% among men with a PSA level of up to 0.5 ng/mL, 10.1% among men with values 0.6–1.0 ng/mL, 17% among men with a PSA level 1.1–2.0 ng/mL, 23.9% among men with a PSA value 2.1–3.0 ng/mL, and 26.9% among those with values 3.1–4.0 ng/mL. In hindsight, this probably should have come as no surprise. Pathologists have long known that many men harbor prostate cancer that is not clinically apparent. Sakr et al. examined prostate glands of 525 men who died from accidental deaths (Sakr et al. 1993). They showed that the pool of subclinical prostate cancer is highly age dependent and is probably within the range of 30–70% in men older than 60 years.

Estimates of the Natural Progression of Prostate Cancer from Prostate-Specific Antigen Screening Trials

Another source of estimates of the natural history of prostate cancer comes from screening trials evaluating the efficacy of PSA to identify clinically significant disease. The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a multicenter, randomized, screening trial with the main aim to compare mortality from prostate cancer in an intervention group invited to screening with a control group where no intervention was offered (Schroder et al. 2014). The trial was initiated in 1993 in the Netherlands and in Belgium. Five other centers (Sweden, Finland, Italy, Spain, and Switzerland) joined the study between 1994 and 1998. Eligible participants were men aged 50–74 years at the time of randomization who were subsequently screened every 4 years (2 years in Sweden). The median age at randomization was 60.2 years. Screening was discontinued after three screening rounds in Belgium, Finland, and Spain but continued up to five rounds in the Netherlands and ten in Sweden.

The most recent trial update reported 7408 prostate cancer cases were diagnosed in the intervention group and 6107 cases in the control group. Of the screen-positive men who underwent a biopsy, 4883 (24%) were diagnosed with prostate cancer within 12 months of testing. During the same period, 355 (4.8%) men died from their disease in the intervention group and 545 (8.9%) in the control group. While many of these men underwent treatment for their disease, many men with low-grade disease did not. Although follow-up from randomization was 13 years, the median follow-up from diagnosis of prostate cancer was only 6.4 years in the intervention group and 4.3 years in the control group. Results from the ESRSPC study showed that 41% of the screen-detected cases were low-volume, low-grade prostate cancers that are unlikely to result in prostate cancer mortality.

The US-based Prostate, Lung, Colon, and Ovary (PLCO) trial was initiated in 1993 and randomized 76,683 men age 55–74 years in ten centers (Andriole et al. 2009). Half were assigned to an intervention, and half were assigned to the control arm. Men in the intervention arm received a PSA blood test and digital rectal examination at baseline, an annual digital rectal examination for 3 more years, and an annual PSA for 5 more years. PSA results were classified as abnormal if they were greater than 4 ng/mL. Participants and their physicians were notified in writing of any suspicious abnormality on screening. The diagnostic process following a positive screen was managed by participants' primary care physicians and was not dictated by the trial.

Extended 15-year mortality results were reported recently. A total of 38,340 and 38,343 men were randomized to the intervention and control arms, respectively. A total of 4250 prostate cancers were diagnosed in the intervention arm and 3815 in the control arm. Of these men 255 (6.0%) died of prostate cancer in the intervention arm and 244 (6.4%) in the control arm. The median duration of follow-up is 18 years. Just as in the ERSPC trial, many of the men in the PLCO trial underwent treatment, while others did not. Overall the likelihood of death from prostate cancer within 13 years of diagnosis is well under 10%.

Estimates of the Natural Progression of Prostate Cancer from Randomized Clinical Trials

Probably the best estimates of the natural progression of prostate cancer come from the control arms of randomized clinical trials. Results from three independent trials conducted in three different countries have been published for prostate cancer: the Scandinavian Prostate Cancer Group 4 trial, the US-based Prostate Cancer Intervention versus Observation trial, and the UK-based ProtecT trial. Each should be viewed independently since the method of disease identification differed in each of these three trials.

The Scandinavian Prostate Cancer Group 4 Trial (SPCG-4)

Between 1989 and 1999, 695 men with early prostate cancer were randomly assigned to either watchful waiting or radical prostatectomy and were followed through 2012 (Bill-Axelson et al. 2014). During the 23 years of follow-up, 200 of the 347 men assigned to surgery and 247 of the 348 assigned to watchful waiting died. Of these deaths 63 in the surgery group and 99 in the watchful waiting group were due to prostate cancer. The study showed that radical prostatectomy reduced the incidence of prostate cancer mortality by 11%, but this benefit was concentrated primarily among men younger than 65 years of age and in those with intermediate-risk disease. Furthermore, a large proportion of long-term survivors in the watchful waiting group have not required any palliative treatment.

A closer look at the study population shows that most patients were diagnosed clinically following a transurethral resection of the prostate or following a rectal examination that revealed a prostate nodule. Only 12% of the patients had a non-palpable T1c tumor at the time of enrollment. Patients' tumors had to be well to moderately differentiated in order for the patient to be included in the study, but a substantial number were upgraded to high-risk disease once PSA testing became available. Low-risk disease was defined as a Gleason score < 7 and a PSA level less than 10. Men with high-risk disease had a Gleason score > 7 and PSA level greater than 20. All other patients were considered to have intermediate-risk disease.

Among the men with low-risk disease, a group of patients now considered potential candidates for active surveillance, none had evidence of lymph node metastases at the time of surgery. Twenty men (14%) on watchful waiting died from prostate cancer after a median 18 years of follow-up compared with 11 men (10%) that died from prostate cancer following surgery. Androgen deprivation therapy was given to 235 of the 348 men on watchful waiting and 145 of the 347 undergoing surgery. However, the majority of these men harbored intermediate- and high-grade tumors. Among men with low-grade disease, only 63 men (18%) on watchful waiting and 32 men (9%) following surgery were placed on androgen deprivation therapy. The remaining patients did not require any palliative treatments. There was no significant difference in the rate of death from prostate cancer in the two groups, although the risk of metastases was lower by 10.6% among men undergoing surgery. The authors concluded that "the large proportion of long-term survivors in the watchful waiting group who never required palliative treatment provide support for active surveillance as an alternative in adequately selected groups."

The Prostate Cancer Intervention Versus Observation Trial (PIVOT)

The Prostate Cancer Intervention versus Observation Trial was organized in the early 1990s and began enrollment in November 1994 and ended enrollment in January 2002 (Wilt et al. 2012). A total of 731 men were recruited from 44 Department of Veterans Affairs sites and 8 National Cancer Institute sites. Patients had to be medically fit for radical prostatectomy and to have histologically confirmed, clinically localized prostate cancer. During the median follow-up of 10 years, 171 of 364 men (47%) assigned to radical prostatectomy died as compared with 183 or 367 men (50%) assigned to observation. A prostate cancer death claimed 21 men (5.8%) assigned to radical prostatectomy as compared with 31 men (8.4%) assigned to observation. The effect of treatment on all-cause and prostate cancer mortality did not differ according to age, race, coexisting conditions, patient performance status, or tumor grade.

A closer look at the study population shows that that the mean age at diagnosis was 67 years, one third of the patients were African-American, and half were diagnosed on the basis of an elevated PSA value (T1c). The median PSA value was 7.8 ng/mL. Based upon central pathological review, 52% of the patients had Gleason 6 disease or less, and 33% were classified as having low-risk disease. After 12 years of follow-up, the radical prostatectomy group was associated with a nonsignificant absolute reduction in mortality of 3.0% points as compared with observation (4.4 vs. 7.4%). Bone metastases occurred in 17 men assigned to radical prostatectomy (4.7%) as compared with 39 (10.6%) assigned to observation.

Among the 148 men with low-risk tumors (Gleason score less than 7 and a PSA value less than 10.0) assigned to radical prostatectomy and the 148 men with low-risk tumors assigned to observation, 6 and 4 men, respectively, died from prostate cancer during the 12-year follow-up. During the same period, 56 (38%) and 50 (34%) died from other causes. When compared to the Scandinavian Prostate Cancer Group 4 study, the PIVOT trial enrolled a higher percentage of men with non-palpable tumors and PSA values less than 10%, criteria used to identify men appropriate for active surveillance. The overall percentage of men who died from prostate cancer was considerably lower in the PIVOT study (7.1%) as compared with the Scandinavian study (19.6%). Treatment adherence was similar in the two trials. The PIVOT trial findings were particularly robust for men with a PSA value less than 10 ng/mL; a group that was less well represented in the Scandinavian study. The authors concluded their study by stating "our findings support observation for men with localized prostate cancer, especially those who have a low PSA value and those who have low-risk disease."

The Prostate Testing for Cancer and Treatment Trial (ProtecT)

The ProtecT trial is a combined screening and treatment trial that recruited men between 1999 and 2009 (Hamdy et al. 2016). A total of 82,429 men aged 50–69 years underwent a single PSA screening; 2664 were diagnosed with localized prostate cancer, and 1643 (62%) agreed to undergo randomization to active monitoring (545), radical prostatectomy (553), and radiation therapy (545). After a median 10-year follow-up, 17 men have died from prostate cancer: 8 in the active monitoring group, 5 in the surgery group, and 4 in the radiation therapy group. No significant differences were noted in the number of deaths from prostate cancer or the number of deaths from any cause. Metastases developed more frequently in the active monitoring group (33 men) when compared to the surgery group (13 men) or the radiation therapy group (16 men). Overall the incidence of prostate cancer deaths and development of metastases at 10 years in the entire cohort was low (1.0% and 3.8%, respectively).

A closer look at the study population reveals several important differences when compared to the SPCG-4 trial and the PIVOT trial. First, all of the men recruited to the trial had cancers identified

as a result of PSA testing. None presented clinically. Second, most men harbored low-volume, low-grade disease. The majority (77%) had Gleason 6 disease, and 76% were stage T1c. Ninety percent had a PSA value less than 10.0 ng/mL. Men participating in the ProtecT trial are much more typical of contemporary patients who might consider active surveillance. Treatment adherence differed between study arms. A total of 482 of the 545 men assigned to active monitoring (88%), 391 of the 553 men assigned to surgery (71%), and 405 of the 545 men assigned to radiation therapy (74%) received their assigned treatment within 9 months of randomization. After 10 years of follow-up, 85% of the men assigned to surgery or radiation therapy had received radical intervention. Of the 545 men assigned to active monitoring, 291 (55%) had abandoned active monitoring and had received a radical treatment by the end of November 2015.

A total of 204 men (12.4%) had disease progression including metastases during the 10-year follow-up. The incidence was higher in the active monitoring group than in the surgery or radiation groups (112 in the active monitoring, 46 in the surgery group, and 46 in the radiation therapy group). Metastases were observed in 33 men in the active monitoring group, 13 men in the surgery group, and 16 men in the radiation therapy group. Androgen deprivation therapy was initiated in 6.3% of the patients including 47 men in the active monitoring group, 26 men in the surgery group, and 30 men in the radiation therapy group.

All-cause and prostate cancer-specific mortality were much lower in the ProtecT trial when compared to the SPCG-4 trial or PIVOT trial. This may be related to recruitment of a healthier cohort through population-based PSA testing but is more likely due to the substantial lead time associated with PSA testing. Screening has also likely preferentially selected for men with low-grade disease. As a consequence there is a lower probability of disease progression. Almost half of the men in active monitoring arm have received no intervention during the 10-year follow-up.

Estimates of the Natural Progression of Prostate Cancer from Active Surveillance Case Series

Another source for estimating the natural progression of prostate cancer comes from the several case series following men with low-volume, low-grade prostate cancers. While reports concerning case series suffer from the usual selection biases, they still offer some information concerning the natural progression of prostate cancer. A systematic review of active surveillance case series identified seven large series located in the United Kingdom, the Netherlands, Canada, and the United States (Dall'Era et al. 2012). Each series differs somewhat in their inclusion criteria. Most require that patients harbor Gleason 3 + 3 disease or less. Most require a PSA value less than 10 and clinical stage T2 or less. Finally, most require less than three biopsy cores positive or less than 33% of the tissue submitted involved with cancer. Table 1 lists common criteria for very low-risk and low-risk prostate cancer. Follow-up in most of these series is still relatively short and often less than 4 years. All-cause mortality ranges from 2% to 21%, but prostate cancer-specific mortality in all of these series is 0–1%.

The largest active surveillance case series is located in Toronto and has recruited 993 men as of the last update (Klotz et al. 2014). Most patients

Table 1 Commonly used criteria for low-risk and very low-risk prostate cancer

	PSA (ng/mL)	Clinical stage	Gleason score	Positive cores	Percent cancer per core	PSA density
Very low risk (Epstein et al. 2005)	<10	T1c	≤6	≤2	<50%	<0.15 ng/mL
Low risk (Dall'Era et al. 2012)	<10	T1-2a	≤6	≤33%	≤50%	

have Gleason 6 disease, but a few patients older than age 70 at entry were diagnosed with Gleason 7 disease or had a PSA value up to 15. Two hundred six patients have been observed for more than 10 years and 50 patients for more than 15 years. Among all 993 patients, 149 have died, 819 are alive, and 25 have been lost to follow-up. Three quarters of the patients had their diagnosis made by PSA testing and were staged T1c. To date there have been 15 deaths (1.5%) from prostate cancer. The 10- and 15-year cause-specific survival rates are 98.1% and 94.3%, respectively. An additional 13 patients (1.3%) developed metastatic disease of which 9 are still alive with confirmed metastatic lesions and 4 have died from other causes. At 5, 10, and 15 years, 75.7%, 63.5%, and 55.0% of patients remained untreated and on surveillance. The authors conclude that for selected patients, low-volume low-risk prostate cancer remains a relatively benign disease. During 15 years of follow-up, only 2.8% of the patients developed metastatic disease, and 1.5% died from prostate cancer.

Godtman et al. recently updated the outcomes of men followed in the Goteborg arm of the ERSPC trial (Godtman et al. 2016). Of the 1050 men who were diagnosed with screen-detected prostate cancer between January 1, 1995, and December 21, 2014, 480 (46%) did not receive immediate curative therapy, and 474 were felt to be suitable for active surveillance. The tumor risk distribution was 244 men with very low-risk disease, 126 men with low-risk disease, and 104 men with intermediate-risk disease. During a median follow-up of 8 years, 202 (43%) discontinued active surveillance. The primary reasons were cancer volume increase or Gleason score progression 108 (53%) and PSA progression only 50 (25%). To date, 54 men have failed active surveillance, and six men have died from prostate cancer. Metastases-free survival at 10 and 15 years is 99% and 93%, respectively, and prostate cancer-specific survival at 10 and 15 years is 99.5% and 96%. During the same period, 108 men (23%) have died from other causes. Four of the six deaths occurred among men with Gleason 3 + 4 disease. These rates are consistent with the mortality rates observed in other large clinical trials including those offering definitive intervention. They remind us that a few men with very low- and low-risk disease may progress during a 20-year follow-up. Younger men must carefully weigh the potential risk of disease progression before selecting a strategy of active surveillance.

Summary

The treatment of localized prostate cancer remains controversial, especially for tumors detected by prostate-specific antigen (PSA) testing. Although the lifetime risk of receiving a prostate cancer diagnosis is about 17%, the risk of dying from this disease remains around 3% (SEER 2007). This suggests that many men are unlikely to benefit from treatments. When assessing the value of any intervention, men must first understand the threat posed by their disease. Only then can they estimate the value of different interventions. Based upon information gathered from several sources including population-based studies, randomized trials, and case series analyses, a more accurate picture is emerging.

The most powerful predictor of long-term outcome continues to be the Gleason score. Men with high-grade disease (Gleason 8–10) have a high probability of disease progression. Those diagnosed clinically often survive 5–10 years before succumbing to their disease depending upon whether the disease is localized or metastatic at diagnosis. Men with screen-detected, high-grade, localized disease often have an additional 5 years before experiencing symptoms of disease progression. Men with screen-detected, low-volume, low-grade prostate cancer have the best prognosis. In the absence of intervention, they are likely to survive at least 15–20 years without symptoms or evidence of disease progression. Prostate cancer mortality is likely less than 5%. These are the men who may wish to consider active surveillance.

Men should also recognize that the evidence supporting treatment efficacy is still modest. The

SPCG-4 trial provides the strongest support for surgery but is based upon a study population that had more clinically advanced disease at the time of diagnosis when compared to contemporary screen-detected patients. The ProtecT trial has accrued patients more typical of contemporary patients, and as a result the incidence of prostate cancer death is only 1% at 10 years and the incidence of progression only 12%. Similar results are reflected in data from population-based reports, other randomized trials, and case series analyses of active surveillance cohorts. While high-grade prostate cancer often progresses rapidly and is often lethal, the natural progression of low-volume, low-grade prostate cancer is very slow and results in a disease-specific mortality of 0.1–1.5% over a 15-year period. Estimates at 20 years are not much higher. These are the men most likely to benefit from active surveillance. Patients with intermediate-risk disease, especially men with small volumes of Gleason 3 + 4 disease, are the most difficult to counsel. They will probably experience disease progression if their life expectancy exceeds 15–20 years.

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Surgical Management of Localized and Locally Advanced Prostate Cancer

11

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Abstract

Localized prostate cancer can be managed with different treatment options based on the risk of progression of the disease and the patient morbidities and preferences. The most accepted treatment options include watchful waiting, external beam radiation therapy, brachytherapy, cryosurgery, high-intensity focused ultrasound, and radical prostatectomy. Radical prostatectomy is associated with excellent oncological outcomes in the localized setting but also with a variable degree of functional adverse events, mainly impotence and incontinence. Modification of the surgical technique with preservation of the neurovascular bundles improves postoperative sexual outcomes and continence. The advent of minimally invasive surgery has contributed to the emergence of many studies investigating the potential benefits on oncological and functional outcomes.

While surgery used to be offered mainly in the low-risk setting and rarely to high-risk patients, it has recently gained importance in the latter group, sometimes as part of a multimodal approach. The main advantages over other treatment options are the pathologic confirmation of the primary tumor grade and the regional staging provided with the pelvic lymph node dissection.

Introduction

Prostate cancer (PCa) is a heterogeneous disease with a wide range of different treatment options for the localized stage. The introduction of prostate-specific antigen (PSA) testing has been associated with modest reductions in mortality and large increases in the number of men overdiagnosed with and overtreated for PCa.

The current international guidelines consider watchful waiting, external beam radiation therapy, brachytherapy, cryosurgery, high-intensity focused ultrasound (HIFU), and radical prostatectomy (RP) as treatment options for localized low-risk PCa. Recent accumulating data also supports the use of RP for locally advanced PCa.

In this chapter, we will explore the rationale for RP in the localized and locally advanced setting and focus on the surgical technique and the importance of pelvic lymph node dissection for accurate staging of the disease.

Radical Prostatectomy Versus Watchful Waiting

SPCG-4

The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomly assigned 695 patients with early PCa from 1989 to 1999 to either watchful waiting ($n = 348$) or RP ($n = 347$) (Bill-Axelson et al. 2008; Bill-Axelson et al. 2011; Bill-Axelson et al. 2014). Definition of early PCa included clinical T1 or T2, well or moderately differentiated tumors, PSA below 50 ng/ml, and negative bone scan. Gleason score was graded in 1999 for all specimens. Of note, inclusion of patients in this study was before the use of PSA as a screening tool.

This multicenter trial gathered patients from 14 hospitals from Sweden, Finland and Iceland. Their primary endpoints were death from any cause, death from PCa and risk of metastases. As secondary endpoints they studied the need to initiate androgen deprivation therapy.

Recurrences in the RP group were treated with androgen deprivation therapy, even if local recurrence was suspected.

Table 1 SPCG-4 and PIVOT results

	SPCG-4	PIVOT
n	695	731
Median follow-up (years)	13.4	10
PSA inclusion criteria	<50 ng/ml	<50 ng/ml
Age inclusion criteria	<75 years	<75 years
Primary endpoints	Overall mortality PCa mortality Risk of metastases	Overall mortality
Secondary endpoints	Androgen deprivation therapy	PCa mortality
Age (mean)	65 years	67 years
PSA (mean)	13 ng/ml	7.8 ng/ml
Risk distribution	37.8% low risk	40% low risk 34% intermediate risk 21% high risk
Absolute death from any cause risk reduction with RP	12.7% ($p < 0.001$)	2.9% ($p = 0.22$)
Absolute death from PCa risk reduction with RP	11% ($p = 0.001$)	2.6% ($p = 0.09$)
Absolute metastases risk reduction with RP	12.2% ($p < 0.001$)	6% ($p = 0.001$)
Absolute use of ADT risk reduction with RP	25% ($p < 0.001$)	Not studied
NNT to prevent one death	20 at 10 years of follow-up 8 at 18 years of follow-up	N/A

The overall absolute risk reduction of death from PCa with RP at 23 years of follow-up was 11% ($p = 0.001$). When stratifying for D'Amico tumor risk groups, the intermediate-risk group benefited more with a 15.5% risk reduction in overall mortality, 24.2% risk reduction in cancer-specific mortality, and 19.9% risk reduction in development of metastases. The low-risk group had a significant risk reduction of overall mortality (15.6% risk reduction) and risk of metastases (10.6% risk reduction) but did not have any difference in cancer-specific mortality. No significant risk reduction was seen for any outcome in the high-risk group. Also, an age-based stratified study showed a stronger benefit of surgery for patients younger than 65 years old.

Inclusion of patients to the study was done during the early era of PSA screening. The primary outcome was all-cause mortality, and the secondary one was PCa mortality.

The overall absolute risk reduction of death from PCa with RP was a nonsignificant 2.6% ($p = 0.09$).

All-cause mortality was reduced with RP for men with PSA >10, with an absolute risk reduction of 13.2% ($p = 0.02$). Also, a 12.6% absolute risk reduction was significant for those patients with intermediate-risk tumors (PSA 10–20, Gleason 7 or cT2b). However, no significant differences were detected after central pathological review and in an analysis focused on Gleason score only.

Pivot

The Prostate Cancer Intervention versus Observation Trial (PIVOT) randomly assigned 731 patients from 52 institutions with localized PCa from 1994 to 2002 to RP ($n = 364$) or observation ($n = 367$) (Wilt et al. 2012). Definition of localized PCa included clinical T1 or T2 NxM0.

SPCG-4 Versus PIVOT

Table 1 summarizes the main differences from the two studies. These differences may be due to different factors. First of all, the negative result in PIVOT is especially in the low-risk group, which is underrepresented in the SPCG-4 trial. For instance, in the PIVOT study, 50% of patients had stage T1c disease, which means that they

were diagnosed because of elevated PSA with normal digital rectal examination. In the SPCG-4, because it was initiated before the PSA era, only 12% had T1c tumors. Also, PIVOT did not reach the prespecified enrollment targets, limiting the statistical power to detect a significant difference in the primary endpoint.

Finally, adherence to the treatment arm assigned was lower in the PIVOT study, with only 77% of patients in the RP group finally undergoing surgery. In contrast, adherence to RP was 94% in the SPCG-4 trial (the remaining 6% did not undergo RP because they were found to have lymph node involvement at the time of surgery).

Patient Selection for Radical Prostatectomy

Selecting candidates for RP is a challenging process for both physician and patient. When debating the risks and benefits of surgical treatment, it is paramount to consider the life expectancy of the patient, the natural history and curability of the PCa, and the morbidity of the treatment.

Since clinically localized PCa does not represent an immediate life threat, treatment benefits will only be visible if the patient lives long enough to avoid future consequences of untreated disease. Experts in the surgical treatment of PCa advocate that RP should be offered only to men younger than 70 years or those patients with a life expectancy of 10 years or more (Lepor 2000). Instead of a chronologic age-based decision, radical treatment should be considered for men with a life expectancy greater than the potential survival of the untreated disease (Droz et al. 2010).

Another factor that should be taken into consideration when deciding the optimal candidates for surgical treatment is the aggressiveness of the tumor. Not all men with PCa are at the same risk from their malignancy. For instance, based on a population-based retrospective study, men with PCa aged 65–75 not treated or treated in a delayed manner with hormones will only experience loss in their life expectancy if they have tumors Gleason 5 or more (Albertsen et al. 1995). Similarly, the risk of dying of a localized disease not treated with curative intent decreases with age, being of 100% before being 50 years, of 50% at 70 years, and of 40% at 75+ years (Aus et al. 1995). Based on that, assuming that PCa is not a clinically relevant disease for men older than 70 years is an underestimate of its natural history.

Functional Outcomes after Radical Prostatectomy

The excellent oncological outcomes of RP for localized PCa have raised increasing interest in the evaluation of the relative side effects of surgery in an attempt to reduce related morbidity, mainly continence and sexual function. Lower stage and younger age migration of PCa since the introduction of PSA testing have amplified the importance of reducing these complications that negatively impacts on quality of life. Few data is available on comparative outcomes between treatment options. Moreover, extrapolation of reported outcomes from referral centers to general population is limited because most of the series do not report pretreatment status and/or do not use validated instruments to analyze functional outcomes. The latter is of upmost importance because significant differences have been found between physicians' and patients' assessments using validated tools, with physicians likely to underestimate the symptoms (Litwin et al. 1998).

Potency and Sexuality

A wide range of erectile dysfunction rates (14–90%) following RP have been reported over the last two decades (Tal et al. 2009). The disparities among different studies are influenced by the definition of erectile dysfunction, the measuring tools, the characteristics of surgery, the patient selection criteria, and the rehabilitative protocols adopted by each group (Salonia et al. 2012). Bilateral nerve preservation, young age, and preoperative potency have been described as predictive factors of post-prostatectomy potency (Rabbani et al. 2000).

Table 2 Potency rate 1 year after surgery

Author		*n*	Potency rate 1 year after surgery[a] (%)
Ficarra et al. 2009b	Open	41	49[b]
	Robotics	64	81[b]
Kim et al. 2011	Open	122	28
	Robotics	373	57
Di Pierro et al. 2011	Open	47	26
	Robotics	22	55
Haglind et al. 2015	Open	144	25
	Robotics	366	29

[a]Defined as erection sufficient for intercourse
[b]Sexual Health Inventory for Men score > 17

Based on the International Index of Erectile Function (IIEF) questionnaire on a sample size of 1236 patients, 85% of men had some grade of erectile dysfunction 4.3 years after surgery (Schover et al. 2002). Similarly, data from the Prostate Cancer Outcomes Study revealed that 87% of patients undergoing RP were unable to have erections sufficient for intercourse 15 years after surgery (Resnick et al. 2013). Likewise, erectile dysfunction rate among patients undergoing RP from the SPCG-4 was 84%. However, a similar rate of 80% was described among patients undergoing watchful waiting, and 46% of men from a matched by region and age control group also reported erectile dysfunction (Johansson et al. 2011). Since the neurovascular bundle preservation was described by Walsh and Donker in 1982 (Walsh and Donker 1982), better outcomes have been pursued applying their technique. Also, the advent of minimally invasive surgery was expected to improve erectile results because of the increased surgical precision. However, while potency rates after open RP ranged from 31% to 86% at 12 months of follow-up with bilateral nerve preservation (Dubbelman et al. 2006), similar results of 42–76% have been reported after laparoscopic surgery (Ficarra et al. 2009a). A meta-analysis of robot-assisted RP reported potency recovery of 54–90% at 12 months after surgery and 63–94% at 2 years (Ficarra et al. 2012a). In an early outcome report of a randomized controlled phase 3 study comparing robotics versus open RP, no difference in terms of sexual recovery (Expanded Prostate Cancer Index Composite, sexual domain) was found between groups 4 months after surgery (35 vs. 38; $p = 0.18$) (Yaxley et al. 2016).

Because of the variable methodology among studies, a comparison of sexual outcomes between surgical techniques is difficult, and up to date there is no sufficient data from prospective studies to draw a definitive conclusion on which is the best technique to improve sexual outcomes. Some prospective studies comparing open prostatectomy with robotic-assisted surgery have reported slightly better sexual outcomes 1 year after surgery with the latter technique (Table 2). In addition, the cumulative analysis published by Ficarra et al. including 843 patients undergoing open surgery and 756 undergoing robotics surgery found a statistically significant advantage in favor of robotics (OR 2.84; 95% CI 1.48–5.43; $p = 0.002$). However, no advantage was seen when comparing laparoscopic versus robotic approach (OR 1.89; 95% CI 0.7–5.05; $p = 0.21$) (Ficarra et al. 2012a).

Taken together, robotic surgery has shown an advantage in terms of erectile function recovery in a meta-analysis. However, due to the lack of strong evidence coming from randomized controlled trials and the important role of the surgeon experience and skills, definitive conclusions regarding the gold standard technique for RP cannot be made. Longer follow-up of the randomized controlled trial is warranted to answer the question of which technique is better to recover erectile function after surgery.

Continence

Urinary incontinence after RP is an adverse event with high impact on quality of life (Miller 2005). Prevalence of this complication varies substantially depending on the definition, severity, impact on patient's quality of life, and the tool used to measure it. Urinary continence is usually defined as no need of pads. Some authors include patients using one pad in the continent group.

Reported continence rates 1 year after open surgery range from 60% to 93% (Ficarra et al. 2009a). Similarly, 66–95% rates are described

for the laparoscopic approach 1 year after RP (Ficarra et al. 2009a). In the robotic literature, reported continence rates range from 84% to 97% (Ficarra et al. 2009a). A cumulative analysis comparing robotic surgery with both open and laparoscopic approach showed a statistically significant advantage in favor of robotics (OR 1.53; 95% CI 1.04–2.25; $p = 0.03$ and OR 2.39; 95% CI 1.29–4.45; $p = 0.006$, respectively) (Ficarra et al. 2012b). However, the findings from retrospective data are in contrast to the early results of a randomized controlled trial which showed no statistically significant differences on Expanded Prostate Cancer Index Composite, urinary domain, and between open and robotic surgery 4 months after intervention (84 vs. 83; $p = 0.48$) (Yaxley et al. 2016).

The etiology of urinary incontinence is a complex issue. Several anatomic and biological factors have been investigated as possible contributing factors (Heesakkers et al. 2017). Anatomic components include the urethral sphincter complex and the supporting structures of the urethra. The urethral sphincter complex consists of an internal smooth muscle and an external skeletal muscle, innervated by pudendal nerve branches. The supporting structures of the urethra comprise the anterior pubourethral ligaments (pubovesical ligament, puboprostatic ligament, and tendinous arch of the pelvic fascia) and the posterior support (central perineal tendon, Denonvilliers' fascia, rectourethralis muscle, and levator ani complex). Biological factors include increasing age, increased BMI, previous TURP, preexisting LUTS, larger prostate size, and shorter membranous urethral length (Heesakkers et al. 2017).

The Role of Nerve-Sparing Techniques

Anatomical Background

Recent studies using neural immunostaining and computerized planimetry have shed light on the anatomy of the neurovascular bundles and their relationship to surrounding structures. Proximally, the distal branches of the lower part of the inferior hypogastric plexus lie within a plate between bladder and rectum, run close to the lateral aspect of the seminal vesicles, and continue dorsolaterally in the angle between the bladder neck and the prostate at its base (Alsaid et al. 2011). At the level of the seminal vesicles, the autonomic nerves represent the bulk of the pelvic plexus. Figure 1 shows the anatomy of the neurovascular bundles. Thus, gentle dissection close to the seminal vesicles during RP is critical during nerve-sparing procedures. At the level of the prostate, the proportion of autonomic periprostatic nerve surface is highest dorsolaterally, i.e., between the 7 and 9 o'clock positions. However, nerves are also found in the ventrolateral and dorsal positions (Ganzer et al. 2008). Furthermore, overall nerve surface area is largest at the base versus mid-level and apex. The ratios of periprostatic nerves over nerves entering the prostatic capsule is 1.9 at the apex and 3.6 at the base, meaning that for every nerve leaving the neurovascular bundle and branching out into the prostate, 2 to 4 may finally contribute to other functions such as continence and erectile function (Ganzer et al. 2008). Indeed, it has been shown that at the level of the prostatic apex and the urethra, some fibers innervate the urethral sphincter (Alsaid et al. 2010), while others reach the corpora cavernosa and the corpus spongiosum where they provide parasympathetic innervation (Alsaid et al. 2011). Beside the seminal vesicles, the apex represents another anatomical landmark where the neurovascular bundle can be damaged, as the latter is located very close to the urethral sphincter and the apex (Alsaid et al. 2011).

Nerve Sparing and Erectile Function

There is a general agreement that since the introduction of nerve-sparing techniques, potency rates after RP have increased significantly. Overall, potency rates after bilateral nerve-sparing RP range from 31% to 86%, after unilateral nerve-sparing RP from 13% to 56%, and after nonnerve-sparing RP from 0% to 17% (Dubbelman et al. 2006). In multivariable analysis, bilateral nerve sparing was associated with a significant 1.84-fold higher probability of potency than unilateral or nonnerve sparing (Marien et al. 2009). Thus, there is a clear correlation between the extent of

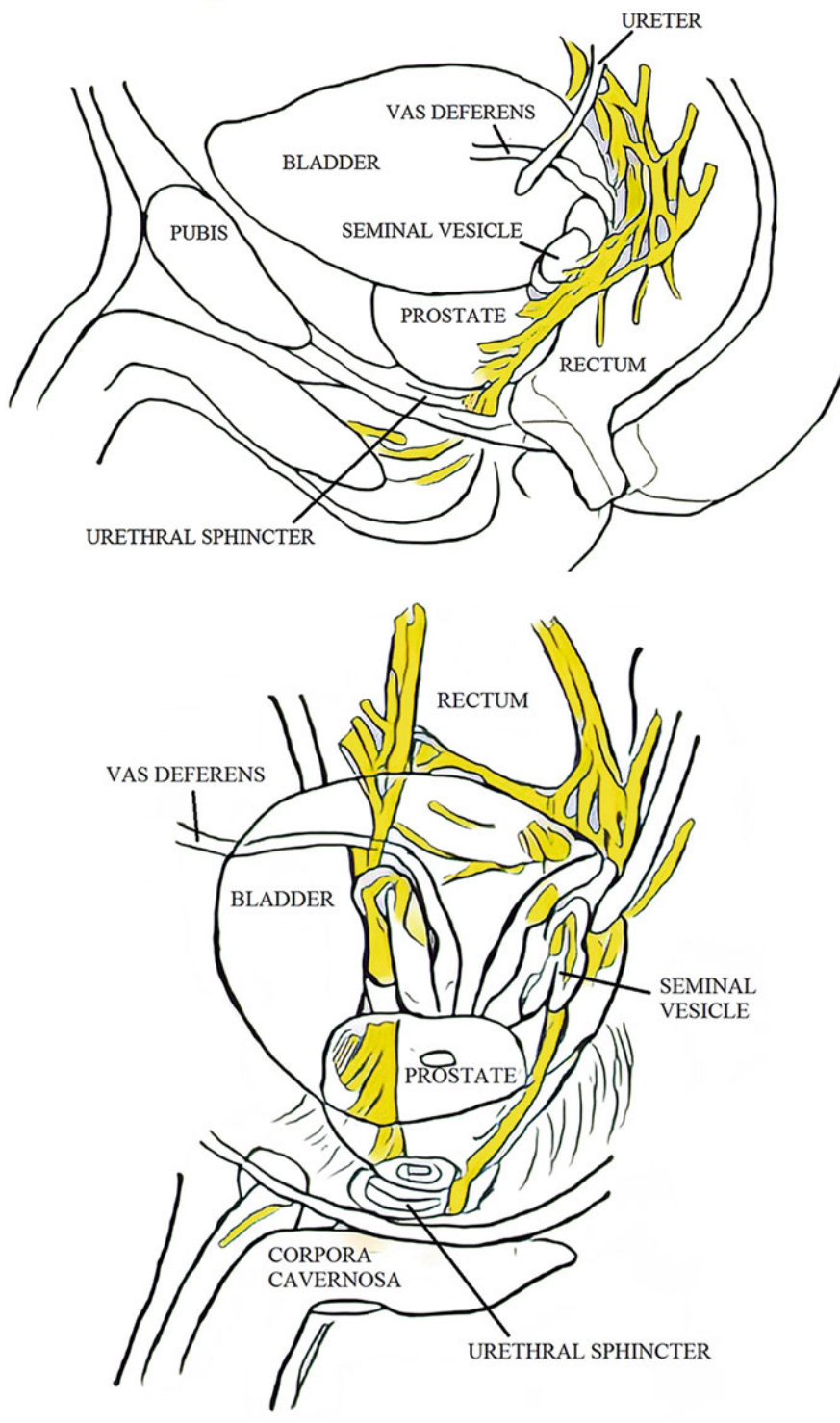

Fig. 1 Lateral (*top*) and oblique (*bottom*) view of the neurovascular bundles and their relationship with other pelvic organs

resection of the neurovascular bundles and the recovery of potency. The other major factor is age (Dubbelman et al. 2006; Marien et al. 2009).

Nerve Sparing and Urinary Continence

The role of nerve sparing with regard to continence outcomes is less clear than for erectile function. Eastham et al. (1996) found a significant association in multivariable analysis between the extent of resection of the neurovascular bundles and urinary continence in 581 RP patients. In a further study, attempted nerve sparing was associated with an almost fivefold higher probability of 1-year continence in 536 patients (Burkhard et al. 2006). Along the same line, a recent prospective study evaluated the association between the degree of nerve sparing at open or robot-assisted RP and 1-year urinary incontinence in 3148 Swedish men. Nerve sparing was categorized into seven groups according to the degree of bundle preservation, ranging from bilateral intrafascial dissection to no preservation. The authors found a significant association between the degree of nerve sparing and 1-year urinary incontinence, as patients with no nerve sparing had a more than twofold higher risk of incontinence at 1 year than those with bilateral intrafascial bundle preservation. Interestingly, this association was present regardless of preoperative erectile function (Steineck et al. 2015).

Positive results from observational data echoed those from experimental neurophysiological studies. Takenaka et al. (2007) demonstrated that electrical stimulation of the neurovascular bundle during RP resulted in a significant increase in urethral pressure. Along the same line, Kaiho et al. (2005) showed that intraoperative electrophysiological confirmation of nerve sparing at RP by monitoring intracavernous or intraurethral pressure changes was associated with postoperative continence status. In a prospective study, Catarin et al. (2008) found that impaired membranous urethral sensitivity was associated with incontinence after RP. These findings suggested that afferent innervation may play a role in urinary continence, hypothetically by inducing a spinal reflex or voluntary sphincter contraction upon sensation of urine entering the proximal urethra.

Nevertheless, in these series good results were achieved in the majority of patients even if no attention was given to nerve sparing. For instance, in the Swedish study, 68% of all men without any nerve sparing were still continent (Steineck et al. 2015). A recent meta-analysis of 27 studies found that nerve sparing improves early recovery of continence, however not long-term continence rates (Reeves et al. 2015). Unfortunately, this meta-analysis was limited by inherent bias including variability in study design, patient selection, surgical techniques, surgeon experience, and definitions used.

Michl et al. have recently hypothesized that the responsible for the better continence results of nerve-sparing surgery was the surgical technique and the accuracy of the apex dissection instead of the neurovascular bundle preservation themselves. To test their hypothesis, they compared three groups of patients. The first group underwent a nonnerve-sparing surgery upfront, the second group underwent a nerve-sparing surgery with a negative frozen section, and the third group underwent a nerve-sparing surgery followed by an immediate resection of the neurovascular bundles because of a positive frozen section. When comparing these three groups, the authors found a continence rate at 12 months after surgery of 70.5%, 85.4%, and 87%, respectively. These results support the idea that the continence is more dependent on the surgical technique and the meticulous dissection of the apex rather than the preservation of the neurovascular bundles (Michl et al. 2016).

Taken together, the available evidence suggests that even in men with preoperative declining erectile function, a certain degree of nerve sparing, preserving the autonomic nerves and/or leading to more meticulous dissection of the prostatic apex, should be attempted to optimize urinary continence outcomes. However, further research is warranted to better understand the neurological mechanisms governing urinary continence and the pathophysiology of incontinence following RP.

Nerve Sparing and Oncological Safety

It is evident that nerve sparing should be attempted while respecting the principles of oncological surgery. As of now, there is no data

showing that nerve sparing compromises oncological safety because of inadequate tumor resection. Indeed, although patient selection bias have to be taken into account, the incidence of positive surgical margins in patients undergoing nerve-sparing RP was not found to be significantly higher than that of patients undergoing nonnerve-sparing RP (Ward et al. 2004; Palisaar et al. 2005). Furthermore, in studies including multivariable analyses, nerve sparing was not associated with higher risk of positive surgical margins (Ward et al. 2004) or biochemical recurrence (Ward et al. 2004; Palisaar et al. 2005). Recently, the impact of nerve sparing on erectile function was evaluated in 584 patients with high-risk features (serum PSA $\geq$20 ng/ml, $\geq$cT3 stage, and/or biopsy Gleason score $\geq$ 8) who underwent RP. Bilateral nerve sparing was feasible in 73% of all patients. The positive surgical margin rate was an acceptable 24% in patients with either unilateral or bilateral nerve sparing, while 47% of preoperatively potent patients reported recovery of erectile function at 24 months (Recabal et al. 2016). These data showed that with careful preoperative planning using biopsy data and modern imaging, nerve sparing is feasible and safe in a good proportion of selected patients with high-risk features.

Performing a frozen section of the neurovascular bundles, also called NeuroSAFE (neurovascular structure-adjacent frozen section examination) increases the percentage of nerve-sparing surgeries in all stages (overall 97% vs. 81%) but especially in advanced disease (pT3b 88% vs. 40%). It also reduces the final positive surgical margin rates (22% vs. 15%), especially in <pT3b tumors, with no effect on biochemical recurrence rates at a median follow-up of 2–4 years (Schlomm et al. 2012). Using an intraoperative frozen section reveals 22–25% of positive margins that can be converted to negative margins in 86–92% of cases (Schlomm et al. 2012; von Bodman et al. 2013). The frozen section technique harbors a high rate of false-positive results, which account for around 75% of the cases, where the final pathology do not prove tumor in the secondary resected tissue, probably due to cauterization artifacts or undetected minimal residual tumor. Beyer et al. have tested the use of NeuroSAFE technique on robotic RP, with similar results. They showed an overall increase of nerve-sparing surgeries from 81% to 97%, reducing the final positive surgical margin rates from 24% to 16% (Beyer et al. 2014).

Thus, nerve-sparing techniques appear to be safe, provided risk stratification based on clinical examination, biopsy findings, and preoperative imaging is taken into account. For instance, in patients with suspicion of unilateral extracapsular extension, preservation of the neurovascular bundle should be limited to the non-tumor-bearing side. New techniques mainly based on intraoperative frozen section are being pursued to improve functional and oncological outcomes with promising results.

The Emergence of Minimally Invasive Radical Prostatectomy

History and Epidemiological Data

In 1997, the first laparoscopic RP was reported by Schuessler et al. (1997). In 1999, Guillonneau and Vallancien published an improved technique with promising results (Guillonneau and Vallancien 2000). Their original description of the surgical technique continues to represent the core of robotic-assisted laparoscopic RP as performed today. The transition to the robotic platform offers ergonomic advantages to the surgeon and allows for a much faster technical transition from an open to a laparoscopic platform (Artibani et al. 2008). However, the high economic cost of the system makes it available only in few institutions (Bolenz et al. 2014).

New advances in laparoscopy have been pursued, and three-dimensional view is now available with a lower cost than the robotic materials. Also, some devices with improved movement capability have been released, although they have not been widespread among urologists.

While long-term oncological outcomes of minimally invasive techniques are not yet available, indirect measures such as lymph node yield, positive surgical margins, use of adjuvant therapy,

and biochemical recurrence have been studied. Also, perioperative and functional outcomes have been keys to expand the diffusion of these techniques.

Oncological and Functional Outcomes

It is difficult to compare the open approach with the minimally invasive because the available data mostly comes from prospective, nonrandomized studies or from retrospective reviews, which provide a low level of evidence. Prospective randomized controlled trials are difficult to perform as many patients would not accept the idea of not undergoing the most modern surgical procedure or would like to choose a specific surgeon. In addition, in those centers where they can perform several techniques, patients with low-risk disease are more often operated using minimally invasive techniques, whereas open surgery is more likely to be used for those patients with high-risk disease where an extended lymph node dissection is required.

The most used and reported variable for indirect oncological outcomes are the positive surgical margins. However, margin rates are subject to cancer extent, technical error, surgical artifact, and pathologic processing, remaining a problematic endpoint for oncological outcome comparisons. De Carlo et al. systematically reviewed 44 comparative studies including open, laparoscopic, and robotic approaches and only found slightly better results with robotic approach (De Carlo et al. 2014). The overall positive margins for open, laparoscopic, and robot approaches were 22.5%, 22%, and 21%, respectively. While positive surgical margins rates were lower with robotics for pT2 stage tumors, pT3 tumors had less positive margins with the open approach. A match comparison of biochemical progression-free survival between open and robotic approach at 3 years of surgery found no differences between the two techniques (Krambeck et al. 2009). Due to the controversial outcomes, final conclusions cannot be drawn, and randomized trials are necessary to answer which one technique is superior to the other.

The evaluation of functional outcomes is difficult because of the lack of standardization between series. Regarding continence, there is no uniform definition (no pads/no leak/one safety pad) and use of validated questionnaires. The continence rates described at 12 months for the open, laparoscopic, and robotic approaches are 83.22%, 70.7%, and 92.78%, respectively (De Carlo et al. 2014). However, the lack of validated questionnaires in many studies does not allow for any conclusive statement of superiority of any technique. Potency after RP is also under the same limitations as continence, with few studies reporting outcomes based on validated questionnaires. The 3-month potency rates for open, laparoscopic, and robotic approaches are 22.34%, 35.12%, and 32.53%, respectively. At 12 months, the rates were 55.85% for the open approach and 60.93% for the robotic technique (De Carlo et al. 2014).

To date, a randomized controlled phase 3 study comparing open versus robotic RP reported no difference in terms of continence and erectile function 12 weeks after treatment. Longer follow-up is expected to clarify the potential benefits of minimally invasive surgery on functional outcomes after RP (Yaxley et al. 2016).

High-Risk Prostate Cancer: The Role of Surgical Management

Clinical and Biological Rationale for Radical Prostatectomy

Although the patients with high-risk disease has declined with the introduction of PSA testing, about 15% of the newly diagnosed patients will present with some of these high-risk features (Kane et al. 2007; Cooperberg et al. 2008). The exact definition of high-risk prostate cancer remains uncertain, and a consensus has yet to be reached. Table 3 summarizes the most commonly used definitions.

The optimal management for these patients remains controversial. Traditionally, RP was not considered a viable treatment option for high-risk prostate cancer. However, good oncological

Table 3 Definition of high-risk prostate cancer

Author	Definition
D'Amico	PSA > 20 ng/ml and/or GS ≥ 8 and/or clinical stage ≥ T2c
European Associaion of urology	PSA > 20 ng/ml and/or GS ≥ 8 and/or clinical stage ≥ T3a
National Comprehensive Cancer Network (NCCN)	PSA > 20 ng/ml and/or GS ≥ 8 and/or clinical stage ≥ T3a or any two of the fol- lowing: PSA 10–20 ng/ml, GS 7, cT2b/c

survival rates encouraged further use of surgery for some high-risk patients, as shown in Table 4. One of the most important benefits of RP compared to other treatment options is the pathologic confirmation of the primary tumor grade and the regional nodal staging. In a study published by Abern et al., up to 39% of patients with clinical high-risk PCa were downstaged after surgery because there were no extracapsular or seminal vesicle extension and no lymph nodes and Gleason score was <8. Those patients had similar oncological outcomes as those with intermediate- and low-risk disease (Abern et al. 2014).

Radical Prostatectomy Versus Radiotherapy

Available therapeutic options for high-risk localized PCa include RP or combined therapies with radiation therapy as a local treatment plus androgen deprivation therapy as a systemic treatment of the potentially micrometastatic disease. Some studies report comparable oncological outcomes for both options. For instance, a retrospective review of 1238 patients undergoing surgery and 609 receiving radiotherapy (some of them with adjuvant hormonal therapy) found no differences regarding clinical progression and cancer-specific mortality (Boorjian et al. 2011). Surprisingly, they found that overall mortality was higher within the radiation plus hormones group, probably because of the unbalanced groups in terms of comorbidities. A small study randomized 95 patients to RP plus androgen deprivation therapy or 60–70Gy radiation therapy with androgen deprivation therapy. With a follow-up of 102 months, the authors found no differences between the two groups regarding progression or survival (Akakura et al. 2006).

Other studies suggest that RP may be more effective for these patients. A retrospective review of 68,665 patients found lower cancer-specific mortality rates at 10 years in the RP group compared to radiation therapy. The difference was greater within the high-risk group when a stratified analysis was done, with almost a 5% difference (Abdollah et al. 2012). Petrelli and colleagues performed a meta-analysis including 17 studies with more than 13,000 patients and concluded that RP improved overall survival and cancer-specific and noncancer-specific mortality over radiation therapy for high-risk PCa (Petrelli et al. 2014). In line with these results, Zelefsky et al. compared the risk of metastasis between surgery and radiation therapy. This retrospective study comprised 2380 men treated at Memorial Sloan Kettering Cancer Center. Those who were treated with surgery had a significantly lower risk of metastasis at 8 years than patients who received radiation therapy. The scope of the risk reduction increased as the risk of the disease increased. There was 7.8% risk reduction in the high-risk group vs. 3.3% in the intermediate and 1.8% in the low-risk group (Zelefsky et al. 2010).

The Role of a Multimodal Approach

RP or radiation therapy for high-risk localized PCa may provide benefit, but a considerable number of patients will experience disease recurrence and progression and will need further treatments (Yossepowitch et al. 2007). Multimodal approaches for these high-risk patients have shown survival benefit when adding adjuvant androgen deprivation therapy to radiation therapy, with a 5-year overall survival benefit of 18% (hazard ratio 0.46; $p = 0.0001$) and a cancer-specific survival benefit of 16% (hazard ratio 0.23; $p = 0.0001$) (Bolla et al. 2002). Similar results are sought for additional treatment to

Table 4 Oncological outcomes in high-risk prostate cancer series treated with radical prostatectomy

Author	Location	n pts	High-risk definition	PSA, median	Follow-up, median	BPFS	CPFS	Definition CPFS	CSS	OS	Note
Joniau et al. 2012	Germany	51	cT3b-T4	16,9	108 mo	53% 5y	78% 5y	Local recurrence or metastasis	92% 5y	88% 5y	35% did not receive neoadjuvant/ adjuvant treatment
											22% did not receive salvage treatment
						46% 10y	73% 10y		92% 10y	71% 10y	63% ≥ pT3b
											22% N+
Freedland et al. 2007	United States	62	cT3a	9,5	13 y	62% 5y	90% 5y	Metastatic	98% 5y	NA	44% biopsy Gleason ≥7
											74% pathological Gleason ≥7
											29% ≥ pT3b
						49% 10y	80% 10y		91% 10y		31% N+
						49% 15y	73% 15y		84% 15y		
Hsu et al. 2007	Belgium	235	Unilateral cT3a	14,88 (mean)	71 mo (mean)	60% 5y	96% 5y	Local recurrence or metastasis	99% 5y	96% 5y	22% adjuvant treatment
											34% salvage treatment
											20% ≥ pT3b
						51% 10y	85% 10y		92% 10y	77% 10y	9% N+
Carver et al. 2006	United States	176	cT3	12,7	6,4 y	48% 5y	86% 5y	Metastasis or CRPC	94% 5y	NA	36% neoadjuvant treatment
											34% ≥ pT3b
						44% 10y	76% 10y		85% 10y		19% N+
									76% 15y		
Xylinas et al. 2009	France	100	cT3	11,6 (mean)	69 mo	45% 5y	NA	NA	90% 5y	NA	31% adjuvant/salvage treatment
											26% ≥ pT3b
											17% N+

Ward et al. 2005	United States	843	cT3	10,2	14.3 y	58% 5y	90% 5y	Metastasis	95% 5y	90% 5y	58% neoadjuvant/adjuvant treatment
Mitchell et al. 2012											24% ≥ pT3b
						43% 10y	82% 10y		90% 10y	76% 10y	27% N+
						38% 15y	72% 20y			53% 15y	
Kaushik et al. 2016	United States	87	pT4	12,2	9,8 y	48% 5y	77% 5y	Metastasis	NA	91% 5y	89% adjuvant ADT
											37% adjuvant radiation therapy
						37% 10y	64% 10y			70% 10y	46% N+
Loeb et al. 2010	United States	175	D'Amico	NA	8 y	68% 10y	84% 10y	Metastasis	92% 10y	NA	5% ≥ pT3b
											14% N+
Furukawa et al. 2016	Japan	382	D'Amico	15,9	48 mo	60% 5y	NA	NA	NA	NA	16% ≥ pT3b
											5,5% N+
Briganti et al. 2012	Europe	1366	EAU	21.3	10.5 y (BPFS mean)	69% 5y	NA	NA	96% 5y	NA	40% ≥ pT3b
											48% adjuvant treatment
					15.5 y (CSS mean)	54% 10y			91% 10y		23% N+
Boorjian et al. 2011	United States	1238	NCCN	20,5	10,2 y	NA	85% 10y	Metastasis	92% 10y	77% 10y	41% adjuvant treatment

RP. Boorjian et al. analyzed 507 patients with nodal involvement on RP and found that immediate adjuvant hormonal therapy improved biochemical recurrence-free survival. However, no such effect was seen regarding cancer-specific survival (Boorjian et al. 2007). A Cochrane systematic review of three randomized trials comparing adjuvant radiotherapy versus salvage radiotherapy for locally advanced PCa treated surgically showed a biochemical recurrence-free survival benefit with adjuvant treatment. An overall survival benefit was seen at 10 years of follow-up, but no differences appeared at 5 years. Of note, the survival benefit was accompanied with an increased risk of urethral and bladder neck stricture and with worse incontinence (Daly et al. 2011).

Neoadjuvant hormone therapy has been used in an attempt to improve oncological outcomes after RP. A meta-analysis of these studies reported reduced positive surgical margins, extraprostatic involvement, and lymph node invasion with no impact on overall or disease-free survival rates (Shelley et al. 2009). Recently, interest in investigating the value of neoadjuvant therapies before RP has been renewed, particularly with the advent of new therapies such as abiraterone acetate and enzalutamide. A phase II trial of patients with intermediate- and high-risk PCa comparing neoadjuvant LHRH agonists versus neoadjuvant LHRH agonists plus abiraterone acetate showed significantly reduced intraprostatic androgen levels in the abiraterone group, with unknown clinical relevance of this finding to date (Taplin et al. 2014). With the recent publications of the CHAARTED and the STAMPEDE trials (Sweeney et al. 2015; James et al. 2015), which showed a survival advantage of ADT plus docetaxel over ADT alone in hormone-naïve metastatic PCa, assessing combined treatment for high-risk localized disease has also gained interest. To answer the question of whether chemohormonal neoadjuvant treatment improves biochemical progression-free survival in localized high-risk PCa, the Cancer and Leukemia Group B (CALGB)/Alliance 90,203 trial (NCT00430183) has finished accrual and will soon report the results.

The Role of Pelvic Lymph Node Dissection

The necessity and extent of pelvic lymph node dissection (PLND) at the time of RP remains a topic of much debate. There is general consensus that an extended template increases staging accuracy. However, survival benefit of extended PLND has not been evaluated in a well-designed, prospective, randomized study. Single-center experiences suggest a benefit of PLND on survival in a subset of patients with minimal lymph node disease or even in lymph node-negative patients. Figure 2 shows the limited and extended PLND templates.

Lymph Node Staging

Several mapping studies on the lymphatic drainage of the prostate have recently shown that primary landing sites of the prostate are found beyond the external iliac region and the obturator fossa. Indeed, approximately 25% of all primary landing sites were located in the internal iliac regions (Weckermann et al. 2007; Mattei et al. 2008). A mere 38% of all primary landing sites would be included within a template including the external iliac region and the obturator fossa only (Mattei et al. 2008), while 63% of lymphatic landing sites were located inside the boundaries of an extended template up to the bifurcation of the common iliac artery. By extending the dissection more proximally to include the common iliac regions up to the ureter crossing, approximately 75% of all nodes potentially harboring metastases would be removed. These findings have been supported by a mapping study using indocyanine green that documented that common iliac regions contain up to 23% of all primary landing sites (Nguyen et al. 2016). The same study demonstrated that a prostatic lobe can drain into the contralateral group of pelvic lymph nodes.

Thus, a bilateral, extended PLND is the only variant that considers findings from anatomic and mapping studies, and it has become evident that limited PLND misses a substantial number of primary landing sites. Yet, accurate tumor staging

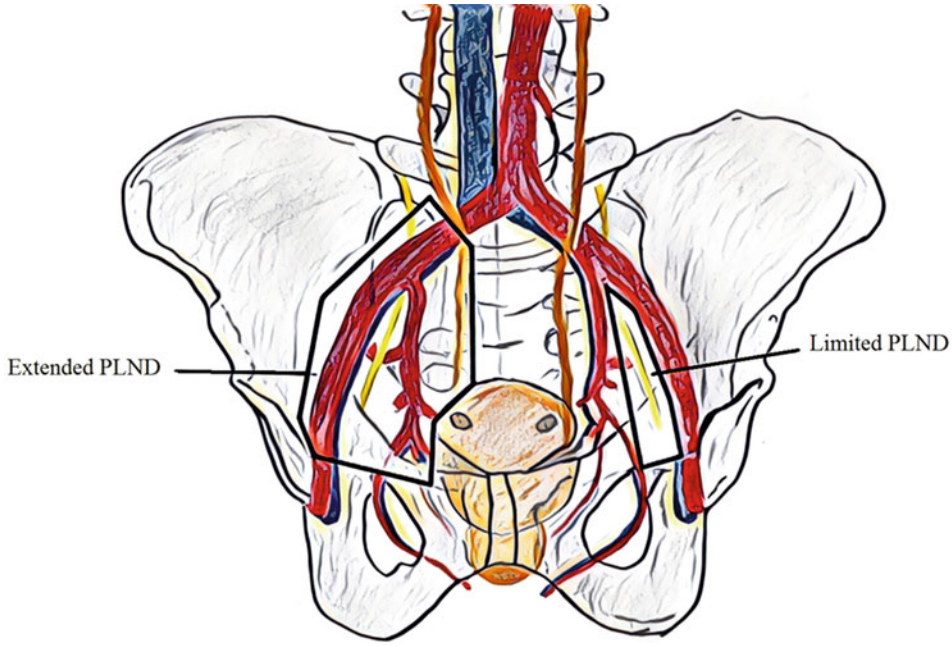

Fig. 2 Limited and extended PLND templates

identifies extent and location of the malignancy, helps define the biology of the tumor, and forms the basis for optimal therapeutic management. Preoperative prediction models of lymph node invasion based on patient and tumor characteristics have inherent limitations that question their reliability. In addition, modern imaging techniques still lack diagnostic accuracy in the staging of pelvic lymph nodes. For all of these reasons, histopathologic examination of a meticulously performed PLND remains for the time being the most accurate and cost-effective staging procedure.

Detection of Lymph Node Metastases

Extended PLND template detects a higher proportion of patients with lymph node invasion than a limited template. Heidenreich et al. found twice as many positive nodes using the extended versus the limited template (26% vs. 12%; $p < 0.03$) (Heidenreich et al. 2002). In agreement, Wawroschek et al. detected an additional 35% of patients with lymph node metastases when including the internal iliac region (Wawroschek et al. 2003). Touijer et al. reported a more than eightfold higher risk of lymph node metastases for extended versus limited PLND after adjusting for other prognostic factors (Touijer et al. 2007). In the Bern and Leuven series, 58–59% of all lymph nodes metastases were found along the internal iliac vessels, alone or in combination with other sites (Bader et al. 2002; Joniau et al. 2013). Taken together, these studies indicate that a limited PLND template misses at least 40% of all metastatic lymph nodes, under-staging patients and leaving them with tumor disease.

Oncological Outcomes with Regard to PLND

Lymph node involvement at RP is commonly associated with poor survival. However, there is evidence that a subset of node-positive patients have good outcomes, even without adjuvant hormonal therapy. Touijer et al., evaluating 369 node-positive patients at RP, reported that 28% of these

men remained disease-free at 10 years. The presence of ≥3 positive nodes conferred a significantly higher risk of biochemical recurrence (Touijer et al. 2014). In the Bern cohort, cancer-specific survival probabilities were 85% at 5 years and 60% at 10 years in 122 node-positive patients after a median follow-up of 5.6 years. For patients with 1, 2, and ≥3 positive nodes, cancer-specific survival at 10 years was 72%, 79%, and 33%, respectively. The number of lymph node metastases was the most significant predictor of cancer-specific death (Schumacher et al. 2008). Thus, a robust number of node-positive patients have a good chance of long-term survival in the presence of minimal lymph node disease. These results would not seem possible if metastatic lymph nodes had been left in.

Interestingly, extended PLND has proved to confer survival benefit to pathologically node-negative patients. Masterson et al. showed a significant correlation between number of nodes removed and freedom from biochemical recurrence for node-negative patients (Masterson et al. 2006). Heidenreich et al. reported biochemical recurrence rates of 23% and 8% in node-negative patients who underwent limited and extended PLND, respectively (Heidenreich et al. 2007). These data suggest that extended PLND may remove micrometastases that are not detected by routine pathologic processing. Indeed, molecular techniques detect micrometastases in up to 30% of all patients (Pagliarulo 2006). The principal finding of these studies is the importance of an accurate staging of the nodal metastatic burden, allowing for a more precise correlation with oncological outcomes.

Collectively, the available evidence suggests that not only the detection of positive nodes but also the removal of as many nodes as possible should be the main objective for PLND to optimize staging.

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Radiotherapy for Localized and Locally Advanced Prostate Cancer

12

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Abstract

Radiotherapeutic management encompasses all stages of prostate cancer. Conformal and intensity-modulated techniques have made possible dose-escalated external radiotherapy improving survival outcomes in localized disease and reducing toxicity in the postoperative adjuvant setting. Stereotactic techniques, under rigorous conditions, permit moderate and extreme hypofractionation which shortens the overall treatment time. In the curative setting, this can be a tool for dose escalation by taking advantage of the radiobiologic properties of prostate cancer. In the palliative setting, this allows for shorter regimens and, more importantly, re-irradiation. Finally, with the advent of transrectal ultrasonography, prostate brachytherapy has emerged as a versatile tool, either as a monotherapy in the treatment of low- or intermediate-risk disease, as a boost to external radiotherapy in high-risk disease, or as salvage treatment.

Introduction

The use of conventional external beam radiation therapy (EBRT) for early-stage prostate cancer entailed two-dimensional planning using bony landmarks and contrast to identify the prostate and organs at risk on radiographs and standard four-field (anteroposterior and laterals) irradiation. This limited the dose deliverable to the prostate and resulted in poor survival outcomes (cancer-specific survival rates of 55–80% and 35–70% at 5 and 10 years, respectively) and considerable toxicity.

Advances in EBRT techniques starting in the late 1980s, namely, three-dimensional conformal and intensity-modulated techniques and proton beam therapy, accompanied by advances in imaging, have led to better target volume and organ-at-risk delineation and radiation delivery, leading to a safe delivery of higher radiation doses. EBRT dose of at least 72 Gy to the prostate was shown to achieve outcomes comparable to radical prostatectomy (RP) (Kupelian et al. 2004), and dose escalation yielded improvement in biochemical progression-free survival in early prostate cancer (Dearnaley et al. 2007; Kuban et al. 2008; Al-Mamgani et al. 2008; Zietman et al. 2010; Beckendorf et al. 2011). The recently published results of the only randomized clinical trial comparing active monitoring, RP, and EBRT showed no significant difference in prostate-cancer-specific mortality but lower incidences of disease progression and metastases with RP and EBRT (Hamdy et al. 2016).

Image-guidance techniques improved management of target and organ motion and treatment verification but made EBRT more complex and expensive. Hypofractionation was seen as a solution, especially that prostate cancers have been shown to have low alpha-beta ratios. This ushered the use of moderately hypofractionated radiotherapy (2.2- to 4.0-Gy fractions), stereotactic external radiotherapy techniques (greater than 5.0-Gy fractions), and brachytherapy either as a monotherapy or boost to EBRT.

Several randomized trials investigate the non-inferiority or even superiority of moderate hypofractionation regimens (e.g., 3 Gy X 20, TD 60 Gy) for curative prostate EBRT (Wilkins et al. 2015; Yeoh et al. 2006; Arcangeli et al. 2011; Aluwini et al. 2015). The results are promising in terms of toxicity and PSA progression-free survival, and these regimens will probably become the new standard very soon. However, nowadays the standard remains the classic regimen of EBRT with fractions of 2 Gy.

Stereotactic techniques entail the delivery of even bigger fraction sizes and thus require even

more intensive patient immobilization and prostate and organ motion management. Brachytherapy, by delivering radiation from inside the prostate using interstitial needles, overcomes problems with prostate, rectal, and bladder motion and, by allowing highly conformal and localized doses, permits delivery of higher radiobiologically equivalent doses. The advances in brachytherapy techniques, including real-time planning, have greatly shortened treatment times, simplified treatment planning and delivery, and reduced overall treatment costs.

The role of androgen deprivation therapy (ADT) in intermediate-risk (short-term neoadjuvant) and in high-risk (neoadjuvant, concurrent, and long-term adjuvant) disease has been established, and whether elective nodal irradiation (ENI) is necessary, especially in the setting of dose escalation, is currently being addressed by ongoing trials.

The role of adjuvant radiotherapy for operated prostate cancer with high-risk pathologic features has been established, although the optimal timing (immediate postoperative, or delayed until biochemical failure) in order to reduce toxicity remains controversial. The same advances in EBRT and brachytherapy, paralleled by advances in imaging, have rendered these modalities effective and safe options for salvage treatment for local recurrences.

Finally, EBRT as palliative treatment can be safely given in shorter courses or in a single session, according to the clinical status and needs of the patient.

Advances in External Beam Radiotherapy

Conformal three-dimensional radiotherapy (*3DCRT*) is characterized by three elements: (1) the use of CT-based treatment planning allowing 3D target volume and organs-at-risk definition, (2) the consequent generation of more individualized or conformal treatment beams, and (3) the calculation of 3D dose distributions and dose-volume histograms for purposes of plan evaluation and further optimization. MR image co-registration may be used to better guide volume delineation. 3DCRT techniques are the minimum requirement to deliver adequate external radiotherapy doses (at least 72 Gy) without increased bowel or bladder toxicity.

Intensity-modulated radiotherapy (*IMRT*) differs from 3DCRT in two essential aspects: (1) the use of beams with nonuniform fluence (intensity modulation), thus allowing for simultaneous delivery of different dose levels, and (2) the use of planner-specified optimization criteria (dose-volume constraints and weights) to effectuate computer-generated optimal fluence profiles for a given set of beam directions (inverse planning). This requires a treatment planning computer system capable of inverse planning and a system of delivering the nonuniform fluences as planned, that is, linear accelerators (LINACs) equipped with multi-leaf collimators (MLCs) or tomotherapy machines.

MLC-equipped LINACs can deliver IMRT in three different ways: (1) *static or step-and-shoot delivery*, which employs beams segmented into subfields with the radiation being turned off in between transition, (2) *dynamic or sliding window delivery*, which employs nonuniform fluence beams with continuously sweeping collimator pairs and continuous irradiation, and (3) *arc therapy*, which employs the MLCs to dynamically shape the field and modulate the intensity, and at the same time gantry rotation, such that radiation is delivered in arcs rather than discrete beams.

Tomotherapy employs intensity-modulated beams that irradiate the patient slice-by-slice (hence, *tomo-*) such as during CT imaging.

While image-guidance techniques may be employed in the various stages of radiotherapy planning and treatment (such as MRI co-registration during imaging and patient simulation), the term *image-guided radiotherapy* (IGRT) signifies the use of image guidance for target localization before and during treatment to reduce and manage inter- and intra-fractional variations in patient setup and anatomy. For prostate treatments, cone beam CT, rather than radiographs, is used to better verify and correct patient setup during treatment. The use of fiducial markers facilitates image co-registration and setup verification and correction. Helical tomotherapy combines features of a LINAC and a helical CT scanner.

Stereotactic body radiotherapy (SBRT) is defined as a method of EBRT that accurately delivers a high irradiation dose to an extracranial target in one or few treatment fractions. This implies the utilization of advanced techniques of imaging and simulation, treatment planning, treatment setup and delivery, as well as the most modern RT accelerators. This allows for more precise radiation delivery, smaller treatment margins, and the delivery of bigger fraction sizes with higher equivalent doses.

While the above advances pertain to improvements in the delivery of external radiotherapy using photons, these techniques (3DCRT, IMRT, IGRT) can be employed in *proton beam therapy.* Protons differ from photons in having a slightly greater radiobiologic effect dose-per-dose (relative biologic effectiveness of 1.1, relative to photons) and in having a dose deposition characterized by a slow increase in dose with depth initially, culminating in a sharp increase or peak in dose deposition (Bragg peak) at the end of its range, and thus lacking exit dose deposition.

Advances in Brachytherapy

The advent of transrectal ultrasound (TRUS) and three-dimensional planning systems surmounted the need for laparotomy for the implant and lack of dose optimization capability, thus ushering in the era of modern prostate brachytherapy in the 1980s. The emergence of appropriate isotopes (I^{125}, Pd^{103}) and the afterloading technology led to the development of *low-dose-rate brachytherapy* (LDRBT, or permanent seed implant, PSI) and *high-dose-rate brachytherapy* (HDRBT). Both techniques require a coordinate-system-based instrument and accessories for needle insertion, a multi-planar transrectal probe for needle guidance, and a three-dimensional planning system, which may be ultrasound- or CT-based.

The use of ultrasound-based planning coupled with inverse-planning optimization software system made possible *intraoperative planning techniques* for PSI, which include *intraoperative preplanning*, *interactive planning*, *and dynamic dose calculation* (Nag 2001). *Intraoperative planning* is similar to the conventional preplanned technique but allows acquisition of TRUS images and planning on the same day as the implantation, thus eliminating the need for a preplanning session, the need for patient repositioning and setup, and problems with changes in prostate anatomy during the interval.

Interactive planning entails intraoperative generation of an optimized plan, needle placement, registration of actual needle placement, plan re-optimization, and seed deposition. On the other hand, *dynamic dose calculation* allows for plan re-optimization based on actual seed deposition rather than needle placement. For instance, peripheral needles are loaded with seeds first, and subsequent placement and loading of central needles are optimized according to the deposited seed positions.

High-dose-rate brachytherapy (HDRBT) entails irradiation for a shorter period of time using high-dose-rate point sources and afterloading systems. Unlike in *PSI*, HDRBT allows for greater freedom in optimization (such as loading of needles around and outside the prostate) and is not subject to dosimetric distortion due to prostate or tumor shrinkage or fibrosis.

The arrival of multiparametric MRI and 3D color flow power Doppler ultrasound has allowed for better precision of intraprostatic lesions leading to the concept of partial gland treatments (hockey stick, hemi-gland, focal), including *focal brachytherapy*, either as monotherapy or boost. These treatments remain investigational.

Localized Disease

Low-Risk Disease

For low-risk disease, dose-escalated radiotherapy using modern EBRT techniques and brachytherapy alone are both associated with biochemical control rates comparable to surgery.

Long-term outcomes from phase 3 trials on dose escalation using 3DCRT, IMRT, or proton therapy (Michalski 2012a; Zelefsky et al. 2011; Zietman 2005) have all demonstrated biochemical control benefit for low-risk disease. Furthermore, a

retrospective monocentric comparison between surgery and radiotherapy reported that for low-risk disease treated to ≥72 Gy, biochemical failure-free survival is comparable to that treated with radical prostatectomy (Kupelian et al. 2004). The European Association of Urology (EAU) considers IMRT, with or without IGRT, as the gold standard for EBRT for localized prostate cancer and recommends treating to a minimum dose of 74 Gy (Mottet et al. 2016). The National Comprehensive Cancer Network (NCCN) guidelines recommend treating to 75.6–79.2 Gy (NCCN 2016).

A recent clinical trial that randomized patients with localized disease to active monitoring, RP, or EBRT reported similar prostate-cancer-specific mortality among the three groups, with lower rates of disease progression and metastases in patients who underwent RP or EBRT (Handy 2016). The NCCN recommends active surveillance, EBRT, brachytherapy, or RP as equally preferable options for patients with low-risk prostate cancer and life expectancy of ≥10 years (NCCN 2016).

The use of IGRT has rendered prostate radiotherapy more precise yet more complex and more expensive. Hypofractionation, from the radiobiological perspective an advantageous approach due to the known low α/β ratio of prostate adenocarcinoma, emerged as a logical solution. Furthermore, moderate hypofractionation (2.5–4.0-Gy fractions) using 3DCRT and IMRT has been shown to be safe, but long-term efficacy has yet to be demonstrated (Koontz et al. 2015). Extreme fractionation (5–10 Gy), on the other hand, requires IGRT and stereotactic techniques, and data on long-term efficacy and toxicity are still lacking. The EAU recommends restricting practice of combined moderate hypofractionation and dose escalation to experienced teams with rigorous RT quality assessment and strict optimization constraints and restricting extreme hypofractionation to prospective clinical trials (Mottet et al. 2016). The NCCN considers moderate hypofractionation as an acceptable alternative if clinically indicated and if done with image guidance and IMRT; extreme hypofractionation and SBRT are considered cautious alternative and only at clinics with appropriate technology, physics, and clinical expertise (NCCN 2016).

There are no randomized clinical trials comparing brachytherapy alone against other modalities. Long-term biochemical failure-free survival rates ranging from 82% to 98.6% have been reported for low-risk disease treated with PSI. Higher biologically effective dose, a dose to 90% of the prostate (D90) >130 Gy, lower pretreatment PSA levels, and lower PSA nadir values at 3 years after treatment were associated with better biochemical control rates. Using real-time intraoperative planning and inverse planning optimization, 5-year PSA relapse-free survival rate of 98% was achieved for low-risk disease, with improved biochemical control outcomes in patients treated to D90 >140 Gy (based on post-implant day 0, rather than day 30, CT dosimetry). The benefit of adding neoadjuvant or adjuvant ADT to PSI is unclear.

The ESTRO/EAU/EORTC consensus on the eligibility criteria for LDR monotherapy is as follows: stage cT1b-T2a N0, M0; Gleason 6 with <50% of biopsy cores positive, or Gleason 3 + 4 with <33% of biopsy cores positive; an initial PSA level of <10 ng/mL; a prostate volume of <50 cm^3; and an International Prostatic Symptom Score (IPSS) <12 (Ash et al. 2000). The American Brachytherapy Society (ABS) consensus guidelines consider PSI monotherapy as appropriate for low-risk disease and that combination with EBRT is unnecessary, as with ADT except for purposes of prostate downsizing (Davis et al. 2012). Furthermore, the following are cited as absolute contraindications to TRUS-guided PSI, limited life expectancy, unacceptable operative risks, distant metastases, the absence of rectum, large TURP defects precluding seed placement and acceptable radiation dosimetry, and ataxia telangiectasia, and relative contraindications, high IPSS (>20), prior pelvic radiotherapy, TURP defects, large median lobes, gland size >60 cc at time of implantation, and inflammatory bowel disease.

HDRBT as monotherapy is associated with low acute toxicity and high biochemical control rates, but data are from limited series, and long-term data are lacking. The GEC/ESTRO does not recommend its practice outside of a formal study (Hoskin et al. 2013).

Intermediate-Risk Disease

Intermediate-risk disease may be appropriately treated with EBRT, brachytherapy, or a combination of the two, with or without short-term ADT, according to perceived risk of nodal metastasis. However, the need for nodal irradiation is unclear in the setting of hormonal therapy and/or dose escalation, more so for intermediate-risk disease.

Intermediate-risk disease, by definition, remains prostate-confined clinically although with higher probability of occult extracapsular extension (ECE), seminal vesicle involvement (SVI), and, to a lower degree, nodal metastasis. This requires irradiation of at least the prostate and the proximal portion of the seminal vesicles. This is often achieved with dose-escalated EBRT or with EBRT followed by brachytherapy boost, with the latter capable of delivering more conformal and much higher doses of radiation. HDRBT, compared to PSI, allows implantation of the immediate external periphery of the prostate and a portion of the seminal vesicles (Davis et al. 2012). The NCCN recommends either PSI or HDRBT in combination with EBRT.

For select low-volume intermediate-risk disease, the NCCN considers PSI monotherapy as appropriate. The ABS recommends PSI without EBRT or ADT for select intermediate-risk disease with otherwise low-risk features such as low-volume disease, predominant pattern 3, and only one adverse feature. The initial report of the NRG Oncology/RTOG 0232 trial comparing PSI with and without EBRT for intermediate-risk disease (T1c-T2b; Gleason 2–6 and PSA 10–20, or Gleason 7 and PSA<10; and prostate volume <60 cc) showed no control benefit at 5 years with addition of EBRT. Patients were stratified according to T-stage, Gleason score, PSA, and neoadjuvant ADT; final results are pending.

Locally Advanced Disease

High-Risk Disease

Radical prostatectomy is associated with high recurrence, and definitive dose-escalated EBRT combined with long-term androgen deprivation therapy (LTADT) is the preferred treatment (Mottet 2016; NCCN 2016) in order to avoid the need for postoperative adjuvant radiotherapy, which is associated with increased toxicity.

Dose-escalation trials have demonstrated that at least 74 Gy should be given and that improved outcomes are seen with increasing doses up to 80 Gy (Zietman 2010; Beckendorf et al. 2011; Dearnaley et al. 2014; Kuban et al. 2011; Heemsbergen et al. 2014). The NCCN guidelines recommend doses up to 81 Gy in conventional fractions. These doses are best delivered with IMRT, with or without image guidance. Alternatively, lower doses (45–50 Gy) may be delivered by EBRT and combined with an HDRBT boost in single or multiple fractions. A randomized clinical trial has demonstrated superiority of HDRBT boost over EBRT alone; however, the dose used in the EBRT-alone arm was significantly lower than the current standard. A systematic review found that the use of HDRBT boost is associated with superior biochemical control and overall survival compared to either EBRT alone or PSI boost (Zietman et al. 2005).

High-risk disease is characterized by extraprostatic extension (ECE or SVI), or by features that are associated with increased risk for extraprostatic extension or nodal metastasis. Thus, at least the prostate and the proximal part of the seminal vesicles (entire, if with SVI) are irradiated. However, the benefit of ENI remains unclear. While the RTOG 94-13 study showed advantage with whole-pelvic irradiation combined with neoadjuvant and concomitant hormonotherapy (compared to a combination with adjuvant hormonotherapy, or to prostate-only or mini-pelvic irradiation with or without hormonotherapy), several randomized studies failed to show such a benefit (Liebel et al. 1994; Asbell et al. 1988; Pommier et al. 2007). Treatment may be guided by the estimation of risk for nodal involvement using Briganti tables and the Roach formula, or by a staging pelvic lymphadenectomy. Patients with occult nodal metastases on lymphadenectomy should receive ENI combined with LTADT (Pilepich et al. 2005; James et al. 2014).

The addition of LTADT, but not short-term ADT (STADT), to EBRT has been shown to

improve overall survival in high-risk prostate cancer (Roach et al. 2008; D'Amico et al. 2008; Lawton et al. 2007; Bolla et al. 2010; Denham 2011). LTADT can be initiated 2–3 months before (neoadjuvant) or at the same time as EBRT (concomitant) and continued for an overall duration of 2–3 years.

Postoperative Adjuvant Treatment

Radical prostatectomy, regardless of the technique used, is associated with excellent local control rates for intraprostatic disease. However, in those patients with extra-prostatic involvement (pT3–4, pN1), relapse rates are 15–40% per year. Other major risk factors include high Gleason score ($\geq$8), high initial PSA ($>$20), and involved resection margins (R1). Furthermore, adjuvant radiotherapy given $>$30 postoperative days is associated with an increased risk for relapse. Minor risk factors include an age $>$50 years, black race, perineural invasion, tumor involving $>$25% of the prostate volume, PSA density $>$0.7 ng/mL/cc, the number and percentage of positive cores in the preoperative biopsy, microvascular density, and ploidy. Patients with any of the major risk factors should receive and those with several minor risk factors should be considered for adjuvant radiotherapy (NCCN 2016).

Adjuvant radiotherapy refers to prophylactic irradiation of the surgical bed within 6 months from surgery without documented biochemical recurrence (or progression, in case of persistently detectable PSA after an R1 surgery) or local relapse. In contrast, salvage radiotherapy refers to a therapy that is being done in the setting of biochemical (defined as PSA $\geq$0.2 ng/mL) or locoregional relapse.

Adjuvant radiotherapy volumes and schedules vary in medical literature, but American guidelines recommend irradiation of the prostate bed in patients with low-intermediate-risk disease, as well as the pelvic nodal regions in case of high risk for nodal involvement, such as in the absence of adequate lymphadenectomy or in the presence of positive lymph nodes. Older series that used outdated techniques and doses report only a trend for better local control, but modern radiotherapy techniques allow the delivery of higher doses with acceptable toxicity. European guidelines recommend delivering a dose of at least 70 Gy to the prostatic bed at the lowest PSA possible (after two consecutive significant increments) as the PSA value at the time of postoperative RT relates to the biochemical relapse-free survival (King et al. 2012). IMRT is necessary if dose escalation (up to 76 Gy) is considered.

Delaying adjuvant radiotherapy until the first sign of relapse may decrease toxicity. However, this "wait-and-see" (WS) approach is associated with inferior biochemical control and relapse-free and overall survival when compared against immediate adjuvant radiotherapy in randomized clinical trials. Adjuvant RT improves biochemical relapse-free survival in patients with extracapsular extension or positive resection margins, as well as clinical relapse-free survival, in patients younger than 70. Furthermore, lower PSA ($<$0.2 ng/ml) at the time of RT is associated with longer metastasis-free survival.

While awaiting the results of three prospective randomized trials (RADICALS, RAVES, and GETUG 17), the EAU recommends WS approach as an option only in patients with PSA-only recurrence and with long PSA-DT ($>$12 months). Although the WS approach may avoid an unnecessary adjuvant RT, it may generate patient anxiety and, thus, a poor quality of life. The option should be thoroughly discussed with the patient.

Toxicity

Radiation toxicity may be categorized as acute and chronic. Acute toxicity occurs during the course of treatment and within 90 days from its completion and is secondary to radiation effects on early-responding tissues such as the intestinal, rectal, and bladder mucosa. Prevention and proper management of acute toxicity are important to prevent complications, avoid treatment interruption, and ensure its completion. These are frequent but are generally low-grade and tolerable, are easily managed with supportive care and medications, and subside after 2–4 weeks from treatment completion.

Chronic toxicity occurs >90 days from treatment completion and is secondary to radiation effects on late-responding tissues such as the connective tissues, vessels, and muscles in the rectal and bladder walls. Prevention is the best approach as these can be long-standing and may require long-term medication, hospitalization, or surgery. With current radiotherapy techniques and the availability of data on volume-dose organ tolerances guiding radiation dose optimization, high-grade chronic toxicities are infrequent to rare.

The RTOG-EORTC scoring criteria for acute and chronic toxicity for pelvic irradiation are summarized below (Table 1). In general, grade 1 late toxicity pertains to minor symptoms with no treatment required; grade 2, moderate symptoms not affecting performance status and responsive to simple outpatient management; grade 3, distressing symptoms affecting performance status and requiring hospitalization for diagnosis or minor surgical intervention; and grade 4, life-threatening symptoms requiring prolonged hospitalization and/or major surgical intervention.

In prostate treatment, radiation may be associated with intestinal-rectal, urinary, and sexual toxicities, as well as secondary malignancies.

Table 1 RTOG-EORTC radiation toxicity scoring criteria (Cox et al. 1995)

	Grade					
	0	1	2	3	4	5
GI	None	Increased frequency or change in the quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/ abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula, or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion	Fatal
GU	None	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain, or bladder spasm requiring regular, frequent narcotic/ gross hematuria	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Fatal
Chronic						
GI	None	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/ perforation fistula	Fatal
GU	None	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency and dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity <100 cc); severe hemorrhagic cystitis	Fatal

External Beam Radiotherapy

With the availability of 3DCRT and IMRT techniques and robust data on dose-volume organ tolerances, prostate EBRT is fairly well-tolerated with rare late complications, despite dose escalation. QUANTEC recommendations on organ dose-volume constraints are based on 3DCRT techniques and conventional fractionation (Table 2). Application of these constraints for hypofractionated and stereotactic techniques and proton treatment require calculations using radiobiologic models and careful clinical consideration.

Acute grade 2 intestinal or rectal toxicity (enteritis or proctitis, manifesting as abdominal discomfort or pain, flatulence, diarrhea, or tenesmus) and urinary toxicity (cystitis or urethritis, manifesting as dysuria, frequency, urgency, hesitancy, decreased stream or nocturia, or augmentation of these symptoms which commonly exist even prior to treatment), occur in 60% of patients, appear during the 3rd week of treatment, and subside within 2–4 weeks after treatment completion.

Chronic grade 3 toxicity is infrequent and grade 4 toxicity, rare, mostly manifesting within the first 4 years after treatment and rarely after 5 years.

With adherence to organ dose-volume constraints, the incidence of grade 2 chronic intestinal or rectal sequelae manifesting as persistent diarrhea, hematochezia, tenesmus, or proctitis can be diminished to 13% and grade 3 toxicity, including fecal urgency and incontinence, to 1–7%. Grade 3–4 complications, such as bowel ulceration, obstruction, or perforation and anal stricture, are observed in <1% with the use of IMRT and IGRT. Indeed, IMRT has been shown to diminish the risk of gastrointestinal toxicity from 13% to 5% when compared to 3DCRT.

Rectal toxicity correlates to the rectal volume receiving >70 Gy (V70) (Kuban et al. 2008). Rectal bleeding and high stool frequency were associated with the dose to the anorectal wall and fecal incontinence to the dose to the distal 3 cm of the anal canal wall. Advanced age, diabetes mellitus, hemorrhoids, inflammatory bowel disease, prior abdominal surgery, ADT, rectal

Table 2 QUANTEC organ-at-risk dose recommendations[a] (Marks et al. 2010)

Organ	Volume	Endpoint	Dose (Gy), or dose-volume parameters	Rate (%)
Small bowel	Individual small bowel loops	Grade ≥3 acute toxicity	V15 <120 cc	<10
	Entire potential space within peritoneal cavity	Grade ≥3 acute toxicity	V45 <195 cc	<10
Rectum	Whole organ	Grade ≥2 late toxicity	V50 <50%	<15
		Grade ≥3 late toxicity		<10
	Whole organ	Grade ≥2 late toxicity	V60 <35%	<15
		Grade ≥3 late toxicity		<10
	Whole organ	Grade ≥2 late toxicity	V65 <25%	<15
		Grade ≥3 late toxicity		<10
	Whole organ	Grade ≥2 late toxicity	V70 <20%	<15
		Grade ≥3 late toxicity		<10
	Whole organ	Grade ≥2 late toxicity	V75 <15%	<15
		Grade ≥3 late toxicity		<10
Bladder	Whole organ	Grade ≥3 late toxicity	Dmax <65	<6
	Whole organ	Grade ≥3 late toxicity	V65 ≤50%[b]	
			V70 ≤35%[b]	
			V75 ≤25%[b]	
			V80 ≤15%[b]	
Penile bulb	Whole organ	Severe erectile dysfunction	Mean dose to 95% of gland <50	<35
	Whole organ	Severe erectile dysfunction	D90 <50	<35
	Whole organ	Severe erectile dysfunction	D60–70 <70	<35

[a]Partial organ irradiation using 3DCRT and conventional fractionation (1.8–2.0-Gy fractions)
[b]Based on current RTOG 0415 recommendation

size, and severe acute rectal radiation toxicity are associated with increased chronic radiation proctopathy. Alternative treatments should be discussed with patients with a prior history of inflammatory bowel disease.

With 3DCRT, chronic urinary toxicity, in the form of cystitis, hematuria, urethral stricture, or bladder contracture, is <5%, and the incidence of grade 3 and 4 urinary-related complications requiring major surgical interventions or hospitalization is <1%. With dose escalation to 81 Gy using IMRT, the 10-year actuarial incidence of grade ≥2 urinary toxicity was 17% (Alicikus et al. 2011).

Unlike for rectal toxicity, a dose-volume cutoff for bladder toxicity is less well-defined, and little difference was seen in the urinary toxicity rates with 3DCRT and IMRT probably explained by the urethral dose which cannot be significantly decreased with IMRT or IGRT techniques. Pretreatment urinary symptoms, prior transurethral resection of the prostate, neoadjuvant androgen deprivation therapy, higher radiation doses, and acute urinary radiation toxicity predict chronic urinary toxicity.

Erectile dysfunction (ED) typically appears 1–2 years after EBRT, with 50–60% rate of potency preservation, according to a meta-analysis (Robinson et al. 2002). The assessment of the impact of EBRT on sexual function is complex and confounded by the effects of the natural aging process, existing comorbidities and medications, and the use of ADT. The penile bulb and the periprostatic neurovascular bundles are potential target tissues for ED. Among patients with ED post-EBRT, arteriogenic dysfunction was found in 63%, cavernosal dysfunction in 31%, and neurogenic impotence in 3%; improvement with sildenafil administration in 74% has been reported. The risk for ED has been associated to mean doses to the penile bulb. Decreased libido, decreased volume or absence of ejaculate, and decreased intensity of orgasm have also been described after EBRT.

Although the latency period for secondary malignancies is long (5–15 years), this is becoming more important due to younger age at diagnosis, earlier stage at presentation, improved treatment efficacy, and thus longer average life expectancy. The excess risk for solid tumors (bladder, rectum, lung, sarcoma) associated with radiation is small but significant (1/290, for all survivors, 1/125 for ≥5-year survivors, and 1/70 for ≥10-year survivors (Brenner et al. 2000).

Brachytherapy

As with EBRT and surgery, brachytherapy is associated with intestinal, rectal, and bladder toxicity; however, patients treated with PSI have been shown to have better sexual function performed better than those with EBRT or RP. While the association of EBRT to PSI boost has been shown to increase the risk for morbidity, early results from a more recent trial showed similar morbidities with definitive EBRT and EBRT and HDR boost (Hoskin et al. 2012).

While the emergence of intraoperative, real-time planning has diminished toxicity with brachytherapy, prevention of post-implant complications and radiation morbidity begins with proper patient selection. High initial IPSS (>7–10) and an enlarged prostate volume were associated with increased urinary morbidity. Short-course neoadjuvant ADT may reduce the prostate volume but not necessarily post-implant urinary morbidity. On the other hand, the use of prophylactic α-adrenergic blockers may diminish the impact of a high initial IPSS value. The option of definitive EBRT should be discussed with patients with enlarged prostates and high IPSS values. For patients with prior TURP, especially for those with large defects, a pre-implant ultrasound evaluation may be preferable to evaluate urethral trajectory and compatibility of the defect with planned seed locations. On the other hand, current PSI protocols (urethra-sparing by peripheral loading) are no longer associated with higher risk for prolonged post-implant dysuria and urethral necrosis risk after previous TURP.

Radiation toxicity after brachytherapy may be *acute* (immediate postoperative period), *subacute* (2–12 weeks after implant), or *chronic* (beyond 3 months). The temporal profile of radiation toxicity differs between PSI (associated with

continuous but decreasing irradiation) and HDR brachytherapy (associated with a more temporary, rapid irradiation) and among PSI sources, with sources having shorter half-lives (such as Pd-103) being associated with earlier and more intense peaking of acute symptoms, compared to those with longer half-lives (such as I-125).

Acute urinary toxicity manifesting as weak stream, dysuria, frequency, urgency, and hematuria is common, if not universal, in the immediate postoperative period. Alpha-adrenergic blockers, such as tamsulosin, terazosin, and doxazosin, can relieve weak stream and frequency, while urinary tract analgesics, such as phenazopyridine, can relieve dysuria, frequency, and urgency. Hematuria is generally self-limited but requires bladder irrigation to prevent urine retention, especially for HDR brachytherapy, where larger-bore needles are required.

Acute urinary retention is less common (5–15% in patients treated with PSI) and seems to be more related to acute prostate trauma, inflammation, and edema, as its incidence correlates with prostate volumes >35 cc (greater number of needles placed or seeds deposited) and higher baseline IPSS or AUA scores but not with dosimetric parameters, such as urethral dose and V150. Management may entail long-term catheter placement, with a reported median duration of retention of 70 days and a range of 0–469 days (Locke et al. 2002). Similarly, bloody ejaculate and painful orgasm due to intraoperative trauma may persist for several weeks.

Subacute urinary toxicity appears 1–2 weeks and peaks at 4–6 weeks after the implant, with most symptoms disappearing in 12 months. Neoadjuvant ADT, higher baseline IPSS, and greater number of needles were associated with increased rates of grade 2 acute toxicity. For persistent retention despite exhaustive medical management, transurethral incision or resection of the prostatic urethra can be performed after two to three half-lives of the isotope (Hu et al. 1998). Postoperative incontinence rate has been reported to be 26%.

Chronic urinary morbidity manifesting as frequency, incontinence, urethral strictures, and urethral necrosis appears at 6 months with 5-year rates of 24%, 6%, and <1% for grade 2, 3, and 4 toxicities, respectively. Risk factors for grade ≥2 toxicity were higher baseline IPSS, maximal post-implant IPSS, the presence of acute toxicity, and higher prostate V150. Urethra-sparing protocols by peripheral loading have resulted in lower chronic urinary toxicity. Nevertheless, toxicity remains greatest in those with large prostates in which peripheral loading should have the most significant impact. Large prostate volumes and neoadjuvant ADT are independent predictors of urinary retention, and a hypothesis is that prostate downsizing by ADT leaves mainly fibrous than glandular tissue, which does not permit accommodation to the inflammatory reaction to radiation (Michalski 2012).

With PSI, grade 2 rectal toxicity are common (4–12%), and grade 3–4 toxicity, unusual (<2%). Symptoms such as rectal bleeding, increased mucous discharge, diarrhea, constipation, tenesmus, or rectal pressure appear in the subsequent weeks and peak at 8–12 months. These are commonly self-limited and respond to conservative symptomatic management. Late rectal toxicity, most commonly self-limited proctitis, but also rectal ulceration, fistula formation, and incontinence, manifests 1–2 years after implantation. Proctitis is managed conservatively with stool softeners and local steroids; biopsies and laser treatments should be avoided when possible as these may precipitate ulceration and fistula formation.

Dose-volume effects have been demonstrated for rectal bleeding. The rates of grade 2 proctitis were 0% for those with rectal volume <0.8 cc receiving the prescription dose of 160 Gy; 8%, with 0.8–1.8 cc; and 25%, with >1.8 cc. The ABS recommends restricting the dose to 1 cm of the rectum to the prescription dose (Davis et al. 2012).

Potency preservation after brachytherapy has been reported to be as high as 80–85% of men aged <60 years old treated with PSI and as low as 29% after combination therapy with EBRT, ADT, and PSI, based on retrospective data. Age, diabetes, pretreatment erectile function, and implant dose were significant factors in potency preservation; the impact of STADT is less clear. Response rate to phosphodiesterase inhibitors was 62%, greater for patients treated with ADT.

The relative risk for second cancers after brachytherapy is lower or similar to that for EBRT (Abdel-Wahab et al. 2008).

Metastatic Setting

Retrospective data and a small prospective experimental cohort suggest that the treatment of the primary tumor in the form of surgery or radiotherapy may be beneficial in newly diagnosed patients with metastatic disease, in particular, those who have responded to ADT with only one to two metastases. An ongoing European phase III randomized trial (PEACE 1) aims to evaluate the efficacy of hormonotherapy in metastatic patients with or without abiraterone and/or prostate radiotherapy. Similarly, radiotherapy to nodal metastases has been proposed in order to delay systemic treatment, but this approach remains investigational.

Nevertheless, EBRT is an extremely useful tool for treating bone metastases, effecting pain relief in 80–90% of patients, permitting tapering down of pain medications, and reducing the risk of vertebral compression or fractures. For non-complicated bone metastases, a single dose of 8 Gy has been shown to be equivalent to fractionated schemes. Nevertheless, the dose and fractionation should be considered on a case-to-case basis. Radiometabolic therapy with Radium 223 dichloride can be a valid choice in multi-metastatic patients. In a metastatic lesion that is associated with neuropathic pain secondary to infiltration of a nervous plexus, leptomeningeal infiltration, cord compression, or significant risk for bone fracture, instability, or vertebral collapse, the treatment of choice is surgery followed by EBRT, or, in case of emergency, EBRT alone with steroid therapy. There is not a standard for dose and fractions; a single dose of 8 Gy, while effective in pain control, is associated with a higher number of re-irradiation.

Finally, EBRT has been shown to be effective in controlling symptoms of extended pelvic disease such as pain, bleeding, or visceral compression, especially in radio-naïve patients. There is not a standard dose or fractionation, but patients with longer life expectancy could benefit from higher doses.

Future Directions

Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, entails delivery of ablative doses using extreme hypofractionation (>5-Gy fraction sizes); this theoretically takes advantage of the low alpha-beta ratio of prostate adenocarcinoma. To limit toxicity, doses are confined to the target volume plus a tight margin. This requires intensive patient immobilization, careful bladder and bowel preparation, MRI co-registration, and image-guidance techniques including fiducial marker placement, prostate tracking, and online correction by (cone beam CT) CBCT imaging. The use of rectal protection techniques such as the endorectal balloon and rectal spacer has also been studied.

A pooled analysis of prospective phase 2 trials of SBRT monotherapy for localized prostate cancer, including 1100 patients, of which 58%, 30%, and 11% had low-, intermediate- and high-risk disease, respectively, reported 5-year biochemical failure-free survival rates of 95.2%, 84.1%, and 81.2%, respectively and no dose response within the range 35–40 Gy (given in 4–5 fractions). The authors concluded that outcomes for low- and intermediate-risk disease are comparable to those of other modalities and that escalation beyond 40 Gy is not warranted for these patients (King et al. 2013). Furthermore, better biochemical disease-free survival was noted with higher doses (37.5 Gy in five fractions versus 36.25–35 Gy in five fractions) and unacceptable toxicity with doses above 47.5 Gy in five fractions.

The HYPO-RT-PC trial, a non-inferiority trial concluded in 2015, randomized 1200 men with intermediate-risk (including cT3a) disease to equi-effective conventionally fractionated and extremely hypofractionated (seven 6.1-Gy fractions) regimens, with a primary outcome of freedom from PSA failure at 5 years posttreatment. At

2-year follow-up, early toxicity is comparable between the two regimens; mature data are pending.

The NCCN guidelines consider SBRT as a cautious alternative to conventional fractionation in settings with appropriate technology, physics, and clinical expertise; the American Society of Radiation Oncology considers it an appropriate alternative for select low- to intermediate-risk disease. In monotherapy SBRT series, high-risk disease is underrepresented, and conclusions are difficult to extrapolate to this group. The use of SBRT as boost after external radiotherapy in high-risk disease has been shown to be well-tolerated but remains controversial.

Finally, SBRT has also been used to escalate dose to the dominant intraprostatic lesion in low- and intermediate-risk disease with acceptable acute toxicity. However, longer follow-up is lacking.

Salvage Brachytherapy

With the recent increase in the use of radical prostatectomy even for intermediate- and high-risk disease and practice of delaying adjuvant radiation therapy until PSA reascension, postoperative local recurrence has been more common. Furthermore, 20–50% of patients treated with EBRT would develop failures within 10 years, even in the era of 3DCRT, IMRT, and IGRT techniques. Dose-escalation studies have demonstrated better outcomes with higher doses, and the doses deliverable by EBRT techniques are definitely less than the ablative doses delivered by highly conformal brachytherapy (Hoskin et al. 2012; Morris et al. 2016). While biochemical control has been consistently shown to be better with EBRT combined with brachytherapy boost compared to EBRT alone, there has been a recent decrease in the use of brachytherapy boost. Post-EBRT recurrences are perceived as secondary to inadequate dose and are thus not necessarily dose-resistant (Tetrault-Laflamme et al. 2016).

The advances in brachytherapy techniques combined with those of multiparametric MRI and Doppler US imaging have led to the use of salvage brachytherapy, whether whole gland, partial, or focal, in the treatment of local recurrences after EBRT or after RP. In all cases, the patient should have good life expectancy and, in case of re-irradiation, had grade 0–1 toxicity from the previous EBRT.

Salvage After EBRT

With salvage LDR brachytherapy, prescribed doses ranging from 110 to 145 Gy for I125 and from 100 to 120 Gy for Pd103 that have resulted in 5-year biochemical failure-free survival rates ranging from 34% to 77% have been reported. Among carefully selected patients (life expectancy >5–10 years, interval to biochemical failure >2 years, PSA <10 ng/mL, PSA doubling time >6–9 months), a rate of 83% has been reported (Tetrault-Laflamme et al. 2016). On the other hand, prolonged prior ADT use and castrate-resistant disease are associated with lower rates.

Acute toxicity is similar in nature (most commonly frequency and urgency) as that with primary treatment but persists for much longer (24–27 months) than during primary brachytherapy. Late toxicities are more frequent: grade 3 urinary toxicities (urethral strictures requiring dilatation or TURP, persistent hematuria) develop in 10–25%; rectal toxicities are less common (2–6%) but can be more problematic (grade 3–4) (ulcers, bleeding, or fistulae requiring a diverting colostomy). Hydrogel rectal spacers may be difficult to use due to adhesions and fibrosis and have not been effective in reducing rectal toxicity.

The following have all been associated with toxicity: re-irradiation interval (<4.5 years); high prostate D90 (>105%); bladder D2cc; urethral V100; rectal D0.1 cc, D1 cc, D2 cc, and V100; and dose inhomogeneity (reflected by V150 and V200). The following constraints have been proposed: bladder D2cc <70 Gy, urethral V100 <0.4 cc, and rectal D0.1cc <160 Gy, D1cc <120 Gy, D2cc <100 Gy, and V100 <0.35 cc (Peters et al. 2015, 2016). The RTOG 0526 phase 2 trial on salvage LDR brachytherapy after EBRT

defines dose (140 Gy), dose-volume (V100 ≥98%, D90 ≤125%), and dose homogeneity constraints (V150 <45%, V200 <10%); results are pending.

HDR techniques allow implantation of the seminal vesicles and extracapsular extension, greater freedom for dose optimization, and the opportunity to combine hyperthermia for salvage treatment. Control outcomes with salvage HDRBRT are comparable to LDRBT with lower grade 3 toxicity rates (urinary, 0–14%; rectal 0%) (Chen et al. 2013; Lee et al. 2007; Jo et al. 2012; Tharp et al. 2008; Yamada et al. 2014). A 5-year biochemical failure-free survival rate of 69% has been reported (Yamada et al. 2014).

Focal treatment entails use of multiparametric MRI, magnetic resonance spectroscopy, Doppler US, choline PET, and/or stereotactic biopsy mapping, to better define target volumes. Focal LDR salvage has resulted in 3-year biochemical failure-free survival rates of 60–71% with lower toxicity rates (no grade 3 or higher bladder, urethral, or rectal toxicity) (Hsu et al. 2013; Peters et al. 2014). Early results using focal HDR salvage showed 93% biochemical control rate with no grade 3 toxicity (Guerif et al. 2014). Phase 2 trials on focal HDR salvage and whole-gland HDR salvage with focal boost are ongoing (Chung 2016; Chung 2016).

Salvage After Radical Prostatectomy

Early studies have demonstrated the feasibility and safety of salvage brachytherapy with or without EBRT for TRUS-detectable local recurrences after RP with or without EBRT. No grade 3 toxicities were reported, but longer follow-up was lacking (Losa et al. 2003; Niehoff et al. 2005; Traudt et al. 2011).

A more recent series using real-time planning reported 5-year biochemical failure-free and cancer-specific survival rates of 89% and 97%, with acute grade 1–2 GU and GI toxicity rates in 49% and 17%, respectively, and late grade 1–2 GU and GI toxicity rates of 12% and 12%, respectively (Gomez-Veiga et al. 2012).

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Management of Nonmetastatic Failure Following Local Prostate Cancer Therapy

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Contents

Abstract

Biochemical recurrence (BCR) following curative surgery or radiation therapy in men with localized prostate cancer (PCa) is a common occurrence and one of the most challenging situations in urological oncology. Local recurrence or metastatic disease can be the underlying cause of rising prostate-specific antigen (PSA). The clinical course in these patients is highly variable, some patients requiring only observation, others needing local and/or systemic treatment. The decision to treat depends on various factors, including previous

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treatment, site of recurrence, individual tumor-specific parameters, PSA kinetics, comorbidities, and individual patient considerations. Observation is indicated in men with a favorable risk profile, elderly patients, or patients with severe comorbidities. Salvage radiation therapy and salvage prostatectomy are the preferred curative treatment options for men with local recurrence. Treatment should be based on the individual patient's history and selected after careful discussion in a multidisciplinary team to minimize treatment related side effects.

Keywords

Prostate cancer · Nonmetastatic failure · Biochemical recurrence · Rising PSA · Salvage radiation therapy · Salvage radical prostatectomy · Salvage pelvic lymph node dissection · Salvage brachytherapy · Salvage HIFU

Introduction

Although radical prostatectomy (RP) and radiation therapy (RT) is curative for most patients with low- and intermediate-risk prostate cancer (PCa), 20–40% will experience disease recurrence within 10 years after treatment. For patients with locally advanced/high-risk PCa (PSA >20 ng/mL and/or Gleason score of 8–10 and/or clinical stage T3/T4), the biochemical recurrence (BCR) rate is even higher, reported to be up to 70% (Grimm et al. 2012; Spahn et al. 2010; Yossepowitch et al. 2007). Local treatment of PCa consists of RP or RT either by external beam radiation therapy, or low-dose rate or high-dose rate brachytherapy, or any combination of these options. Alternative treatments, such as high-intensity focused ultrasound (HIFU) and cryosurgery, do not yet have validated PSA cutoff values defining BCR but follow the general principles for disease management as described in this chapter.

Management of rising PSA in patients after local PCa treatment is one of the most challenging situations in urological oncology. PSA recurrence can be caused by either local recurrence or metastatic disease. Currently no accurate diagnostic test is available to discriminate local from distant failure in patients with low PSA levels. Several parameters appear to be helpful in differentiating local from distant metastatic relapse: initial PSA level, tumor stage, Gleason score, time from RP/RT to PSA recurrence, PSA doubling time (PSA-DT), and PSA velocity (American Society for Therapeutic Radiology and Oncology Consensus Panel 1997).

Follow-up in these patients should assess immediate and long-term oncological results and include discussion of possible second-line treatments with curative intent, early hormone therapy (HT), or observation. Further follow-up should depend on various factors including previous treatment, site of recurrence, individual tumor-specific parameters, PSA kinetics, comorbidities, and individual patient considerations. Repeated measurement of PSA as an organ-specific tumor marker after local treatment for PCa is an apparently successful monitoring strategy. Current guidelines recommend routine follow-up of asymptomatic patients to include obtaining a disease-specific history and serum PSA measurement supplemented by digital rectal examination at 3, 6, and 12 months after treatment, then every 6 months until 3 years, and annually thereafter (Cornford et al. 2017). Imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, and positron emission tomography/computed tomography (PET/CT), should only be performed in patients with symptoms or whose BCR findings would affect treatment decisions. The recent recommendations for the use of imaging techniques are summarized in Table 1.

Optimal treatment of patients with a rising PSA after local therapy remains unclear due not only to the diagnostic limitations in discriminating local from distant cancer recurrence but also to the highly variable natural course of the disease. Furthermore, no prospective randomized trials have produced findings indicating when a local or systemic approach should be initiated and whether any treatment actually prolongs survival. Considering the variable course of recurrent disease, some patients might be at high risk of metastasis and cancer-related death while others will follow a rather benign course. High-risk patients might

Table 1 Guidelines for imaging in patients with nonmetastatic biochemical failure, modified by EAU-ESTRO-SIOG Guidelines on Prostate Cancer 2017 (Cornford et al. 2017)

	BCR after RP	BCR after RT
No imaging recommended for PSA <1 ng/mL (LE: 3, GR: A)		
PET/CT	PSA ≥1 ng/mL	Exclusion of lymph node involvement or metastases in patients fit enough for curative salvage treatment
	Choline- or PSMA-PET/CT	Choline-PET/CT
	(LE: 2b, GR: A)	(LE: 2b, GR: B)
Bone scintigraphy and abdominopelvic CT	PSA >10 ng/mL or in patients with adverse PSA kinetics:	PSA >10 ng/mL or in patients with adverse PSA kinetics:
	PSA-DT <6 months	PSA-DT <6 months
	PSA velocity >0.5 ng/mL/month	PSA velocity >0.5 ng/mL/month
	(LE: 3, GR: A)	(LE: 3, GR: A)
mpMRI	–	Localize abnormal areas and guide biopsies in patients considered candidates for local salvage therapy
		(LE: 3, GR: B)

BCR **biochemical** recurrence, *GR* grade of recommendation, *LE* level of evidence, *mpMRI* multiparametric magnetic resonance imaging of the pelvis, *PET* positron emission tomography, *PSA-DT* prostate-specific antigen doubling time, *RP* radical prostatectomy, *RT* radiotherapy

benefit from early "salvage" treatment to prevent metastasis and preserve quality of life (QOL) by delaying the occurrence of osseous lesions and ultimately prolonging survival. In other patients, observation might be appropriate because cancer-related disorders might be rare and not worth taking the risk of unprofitable treatment-related side effects. The PIVOT-trial found no survival benefit from surgery for patients with low- to intermediate-risk PCa compared to patients undergoing observation. Although the study was limited by an underpowered design, its findings raise the question of why BCR should matter in a patient cohort in which the same excellent long-term cancer-specific survival rate of >97% at 10 years can be achieved without any treatment (Wilt et al. 2012). The recently reported results from the ProtecT Trial further support a rather conservative approach to BCR in men with low- to intermediate-risk PCa. In the trial, patients were randomized for radical prostatectomy, radiation, or active surveillance. PCa-specific survival was at least 98.8% in all groups, with no significant difference among the three randomized groups ($P = 0.48$ by log-rank test) (Hamdy et al. 2016).

It should be borne in mind, though, that being diagnosed with recurrent PCa may provoke distress in patients greater than that experienced after the initial diagnosis of cancer (Cella et al. 1990). Both the fear of cancer and the fear of side effects associated with salvage treatment can provoke anxiety in patients and adversely impact their QOL.

The main issue, therefore, is not how to discriminate local from distant cancer recurrence, but rather how to identify patients at high risk of a clinically significant event: treating only those patients at high risk of metastasis and death would likely have the greatest impact on patient QOL and outcome.

In this chapter, the management of non-metastatic failure after local therapy for PCa is discussed.

Definition of Biochemical Recurrence

PSA progression often precedes clinical progression. Expectations for PSA levels differ after RP and RT (Horwitz et al. 2005; Stephenson et al. 2006). A solitary elevated serum PSA value must be confirmed before considering further therapy based solely on PSA elevation.

In patients treated with RP, serum PSA is expected to be undetectable within 6 weeks after successful treatment based on the PSA half-life of 2–3 days (Oesterling et al. 1988; Stamey et al.

1989). Persistently elevated PSA in these patients is considered due to either residual pelvic mass or micro-metastases. International consensus defines BCR after RP as two consecutive PSA values ≥0.2 ng/mL (Boccon-Gibod et al. 2004; Moul 2000). Ultrasensitive PSA assay is controversial for routine follow-up after RP.

Defining failure after RT is more complex due to the variability of posttherapeutic PSA values and interval to the nadir. Compared to RP, PSA levels fall slowly after RT, taking up to 3 years or more to reach the nadir and usually not reaching undetectable levels. Although the optimal value is controversial, a nadir of <0.5 ng/mL has been associated with a favorable outcome (Ray et al. 2006). The initial ASTRO definition of BCR after RT of three consecutive increases in PSA was not linked to clinical progression or survival. It was therefore newly defined in 2005 at the RTOG-ASTRO Phoenix Consensus Conference as a ≧2 ng/mL or more rise above the PSA nadir after external beam radiation therapy with or without hormone therapy (accuracy >80%) (Roach et al. 2006).

Various definitions have been offered for PSA recurrence after HIFU or cryotherapy, most setting a cutoff PSA level of <1 ng/mL combined with negative posttreatment biopsy. However, so far none of the endpoints have been validated against clinical features (Aus 2006).

Management of BCR

The natural history of biochemical failure and subsequent risk of PCa-specific mortality (PCSM) vary after RP versus RT. After diagnosis of PSA relapse, it is important to discriminate local from distant cancer recurrence. The risk of metastasis may be predicted by initial pathologic factors, PSA kinetics, and interval to BCR. After RP, slowly increasing PSA most likely indicates local recurrence, rapidly rising PSA distant metastases. Additionally, time to PSA recurrence and tumor differentiation are important predictive factors distinguishing local from systemic recurrence (Partin et al. 1994). After RT, PSA-DT is significantly correlated with site of recurrence: patients with local recurrence have a doubling time of 9–12 months compared to 3–6 months in patients with distant metastases (Riedinger et al. 2009). Local treatment failure with distant metastases and undetectable PSA levels is rare and mostly occurs in patients with undifferentiated tumors (Oefelein et al. 1995).

Imaging techniques for assessment of metastases should be used only when findings affect treatment decisions and should accord with previous local treatment, PSA values, and PSA kinetics. Table 1 summarizes current guidelines for imaging in patients with biochemical failure according to the Prostate Cancer Panel of the European Association of Urology (EAU). The standard workup for detecting metastases in PCa with bone scintigraphy and abdominopelvic CT has a very low probability of positive findings at initial diagnosis of BCR. Only 11–14% of CT scans of men with BCR after RP are positive and <5% of bone scintigraphies are positive at a PSA level of <7 ng/mL (Beresford et al. 2010). These common imaging modalities are therefore only recommended in patients with a high PSA baseline or adverse PSA kinetics (Table 1). Choline PET/CT has a higher sensitivity (55–96%) and specificity (57–100%) for detecting bone metastases (Calabria et al. 2014). The sensitivity also strongly correlates with PSA value and kinetics. At a PSA level of <1 ng/mL, metastasis is detected in only 5–24% of patients, but this increases to 67–100% at levels >5 ng/mL (Kitajima et al. 2014).

Prostate-specific membrane antigen PET/CT (PSMA-PET/CT) is a promising new imaging modality for recurrent PCa. A recent systematic review and meta-analysis showed an increasing PET positivity of 42%, 58%, 76%, and 95% for PSA categories 0–0.2 ng/mL, 0.2–1 ng/mL, 1–2 ng/mL, and >2 ng/mL with a specificity of 86%. Shorter PSA-DT was also associated with increased PET positivity (Perera et al. 2016). Little is known about the accuracy of whole-body or axial MRI in patients with BCR after local therapy. A recently published retrospective single-center study comprising 76 patients with suspected recurrent disease after RP with a median PSA of 0.36 ng/mL (range: <0.05–56.12) demonstrated a concordance

between combined whole-body/multiparametric MRI with other imaging modalities in 36/43 (84%) of patients, with four false-negative findings in bone scan and CT and one false-positive finding of 18-FDG-choline PET/CT when compared to MRI (Robertson et al. 2017).

Although these new imaging modalities promise very high diagnostic performance, their role in detecting local recurrence, lymph node, and bone metastases in BCR patients and their effect on clinical outcome and survival are still uncertain.

Biochemical Recurrence in Postradical Prostatectomy Patients

The natural course of BCR in men who undergo RP is variable. In an analysis performed on the John Hopkins PCa database to estimate metastasis-free survival in 304 men with PSA recurrence after RP, only 34% developed metastases, 43% of whom died of PCa. The median time from PSA recurrence to metastasis was 8 years and from metastasis to death 5.3 years (0.5–15 years) (Pound et al. 1999). In a follow-up study by Freedland et al. that included a slightly larger cohort, the median survival from PSA recurrence to PCa death was not reached after 16 years (Freedland et al. 2005). A further report on 2,426 patients confirmed these results, reporting clinically evident recurrence in 23% and cancer-specific death in only 5.6% (Boorjian et al. 2011). The results obtained in these studies are important because they demonstrate that even in the absence of additional therapy before metastasis, men with PSA recurrence may have very long metastasis-free and overall survival.

Several factors affecting outcome have been identified in men with BCR after RP, allowing the delimitation of a patient group at high and low-risk for metastasis and PCSM (Table 2). An interval from RP to PSA recurrence after RP >3 years, PSA-DT >9 months after RP, specimen Gleason score ≤7, pathological stage pT2, and negative margin status are associated with favorable outcome (10-year PCSM >75%) even without additional therapy after PSA recurrence following RP. These men might be suited for an observation protocol (Freedland et al. 2005; Brockman et al. 2015). High risk of metastases and mortality (10-year PCSM >50%) is characterized by adverse pathological tumor characteristics (Gleason score 8–10, seminal vesical infiltration), time from RP to PSA-recurrence <3 years and PSA-DT <3 months. Furthermore, there is a significant overlap of these parameters with those reported to be associated with local recurrence: A specimen Gleason score ≤7, PSA increases developing >2 years following RP, PSA-DT >12 months, or a PSA velocity <0.75 ng/mL/year are more often associated with local recurrence (American Society for Therapeutic Radiology and Oncology Consensus Panel 1997; Roach et al. 2006; Lange et al. 1989; Trapasso et al. 1994). These men might be good candidates for local salvage treatment. However, such substratification into different risk groups should be used carefully because in the past mainly low- and intermediate-risk PCa patients were analyzed. Comparable data for high-risk patients are lacking due to the high rate of early and delayed adjuvant and salvage treatments they often receive (Pound et al. 1999; Freedland et al. 2005, 2007).

In summary, the natural course of BCR after RP is heterogeneous. Men with a longer interval until PSA recurrence, a PSA-DT >9 months, specimen Gleason score ≤7, and favorable tumor stage are more likely to have local cancer recurrence. These patients are likely candidates for either observation or salvage RT. Men with

Table 2 Prostate **cancer-specific** mortality **in low-risk and high-risk** patients with biochemical progression after local treatment (Freedland et al. 2005; Brockman et al. 2015; Zumsteg et al. 2015; Denham et al. 2008)

	Low risk	High risk
After RP	GS ≤7 *and* organ-confined disease (pT2) *and* interval to BCR >3 years *and* PSA-DT >9 months	GS 8–10 *or* seminal vesicle invasion (pT3b) *and* interval to BCR ≤2 years *and* PSA-DT <3 months
After RT	GS ≤7 *and* organ-confined disease (pT2) *and* interval to BCR >3 years *and* PSA-DT >15 months	Any two risk factors: GS 8–10 *or* clinical stage cT3b–T4 *or* interval to BCR <3 years *or* PSA-DT <3 months

BCR **biochemical** recurrence, *GS* **Gleason** score, *PSA-DT* prostate-specific antigen doubling time, *RP* radical prostatectomy, *RT* radiotherapy

high-grade tumors, or early PSA recurrence, and a short PSA-DT have an exponentially higher risk for metastatic disease and therefore suited for systemic salvage therapy.

Biochemical Recurrence in Postradiotherapy Patients

Analogous to the natural history of the disease in men with PSA recurrence after RP, the natural history in patients after RT is highly variable. In two retrospective series on this issue, local recurrence-free and distant metastasis-free survival rates 5 years after RT were reported to be 74% and 53%, respectively (Freedland et al. 2007; Lee et al. 1997). Early BCR (<12 months after end of RT) and a PSA-DT <12 months significantly predicted the presence of distant metastasis. Overall and cancer-specific survival at 5 years ranged from 58% to 65% and 73% to 76%, respectively. Several other studies attempted to identify factors influencing metastasis and PCSM and to substratify risk categories for patients with BCR following RT (Table 2). Favorable outcome is reported for patients with a time to BCR of >3 years, PSA-DT >15 months, biopsy Gleason score <7, and tumor stage <cT3a (Zumsteg et al. 2015; Denham et al. 2008). Patients with any two high-risk factors (time to BCR <3 years, PSA-DT <3 months, biopsy Gleason score 8–10, and clinical stage cT3b–T4) have a significantly higher risk of developing metastases and PCSM than those without risk factors or those harboring only one risk factor (Zumsteg et al. 2015). These patients are likely candidates for early salvage treatment.

Management of Nonmetastatic Failure Following Radical Prostatectomy

Currently, no standard management of PSA-recurrent PCa following RP exists. Controversy surrounds the optimal time and modality of initiating salvage treatment. The therapeutic options are salvage radiation therapy (SRT; defined as radiotherapy to at least the prostatic bed), continuous or intermittent hormone therapy, and observation.

Determining the precise site of local recurrence following RP is not generally recommended because it seldom affects the plan of treatment. However, locating the site of recurrence may spare unnecessary treatment and treatment-related side effects. Before salvage treatment, determining the precise site of local recurrence by imaging modalities is only needed if histological proof of the recurrence is mandatory or if this localization could affect the plan of treatment. Transrectal ultrasound-guided biopsies have a low sensitivity for detecting local recurrence. The detection rate depends largely on the PSA level and ranges from 14% to 45% positive biopsies for PSA levels <1 ng/mL to 40–71% for PSA levels >1 ng/mL (Rouviere et al. 2010). Choline-PET/CT may detect local recurrences but its sensitivity is less than that of MRI. Dynamic contrast-enhanced MRI has shown the best detection rates for local recurrences, with a sensitivity of 84–95% and specificity of 89–100% (Cirillo et al. 2009). However, two studies evaluating endorectal multiparametric MRI for PSA levels <0.5 ng/mL, the commonly used threshold for salvage therapy, produced controversial results: the sensitivity was only 13% for men with PSA levels ≤0.3 ng/mL and 86% for men with PSA <0.4 ng/mL. Thus, further studies are required to determine the role of MRI in these patients (Liauw et al. 2013; Linder et al. 2014).

Due to the limitations of all imaging techniques to accurately detect the recurrence site in patients with low PSA, most patients undergo early-SRT as recommended for PSA <0.5 ng/mL. This may change in future with improved imaging techniques with greater sensitivity – especially, PSMA-PET-CT – for detecting the recurrence site.

Salvage Radiation Therapy

SRT is frequently used as salvage treatment in patients with PSA progression after RP. Until now, however, no prospective randomized trial has been conducted designed to demonstrate an overall survival benefit from SRT compared with observation in patients with BCR after RP.

Two randomized controlled trials (RCT) assessed the value of adjuvant RT in men at high risk for progression after RP. Although there were some differences in the inclusion criteria, the two studies demonstrated a benefit from immediate adjuvant RT in terms of BCR (Bolla et al. 2005; Thompson et al. 2009). But only the SWOG study could show a significant improvement in metastasis-free and overall survival of 1.8 and 1.9 years, respectively (Thompson et al. 2009). The numbers needed to treat to prevent metastasis and death in one patient at 12 years of follow-up were 12 and 9, respectively. The risk of overtreatment is obvious. Therefore, further studies have analyzed the outcome of patients after adjuvant RT versus early SRT. The larger study retrospectively analyzed 890 men with pT3 pN0, R0–R1 PCa and found that BCR-free survival was similarly improved by adjuvant RT and early SRT (Briganti et al. 2012). In this study, HT was excluded and the median pre-SRT PSA value was 0.2 ng/mL. The 2- and 5-year BCR-free survival rates were 91.4% and 78.4% for adjuvant RT versus 92.8% and 81.8% for initial observation with early SRT in case of relapse. No differences in the 2- and 5-year BCR-free survival rates were found. Three prospective randomized trials are currently comparing the efficacy of these two approaches (adjuvant RT vs. SRT) plus that of neoadjuvant HT: the "RADICALS" trial (Radiotherapy and Androgen Deprivation In Combination After Local Surgery) by the Medical Research Council, the RAVES trial (Radiotherapy Adjuvant Versus Early Salvage) by the Trans-Tasman Oncology Group (TROG), and the GETUG-AFU 17 trial by the Groupe d'Etude des Tumeurs Uro-Génitales.

Multiple studies have confirmed the relevance of pre-RT PSA levels for treatment results: the lower the pre-RT PSA levels, the better the results. Stephenson et al. identified a significant relationship between PSA serum concentrations at the time of RT and therapeutic outcome in a cohort of 1,603 men with PSA progression after RP who underwent surgery in 17 North American tertiary referral centers (Stephenson et al. 2007). The 6-year BCR-free survival rate was 48% in men with PSA <0.5 ng/mL, but only 40%, 28%, and 18% in men with PSA levels of 0.5–1 ng/mL, 1–1.5 ng/mL, and >1.5 ng/mL, respectively. Another more recent systematic review of identifying predictors of biochemical disease control and late toxicity in patients receiving early SRT also found that BCR-free survival rates decreased significantly with increasing PSA before SRT (-18.1% per 1 ng/mL increase) (Ohri et al. 2012). The 5-year BCR-free survival rate for patients with a PSA value ≤ 0.5 ng/mL was $>60\%$. Interestingly, the maximum achievable 5-year BCR-free survival rate appeared to be between 70% and 80%, suggesting that a portion of patients who receive SRT with curative intent already have occult extrapelvic disease.

However, it has not yet been shown in prospective randomized trials that SRT therapy improves overall survival. One retrospective comparative analysis of 635 patients showed a threefold increase in cancer-specific survival rates after SRT when compared to a "wait-and-see" strategy. Notably, the three groups analyzed (no salvage treatment, SRT, SRT + HT) differed significantly for all prognostic factors except surgical margin status, and men undergoing no salvage treatment had a much higher prevalence of positive lymph nodes than men receiving SRT or SRT + HT (30% vs. 3% and 4%; $P < 0.001$), thus limiting the value of this analysis (Deo et al. 2008). A positive response to SRT treatment was found for longer time intervals from RP to PSA recurrence (>2–3 years), lower pre-SRT PSA levels, PSA-velocity <2 ng/mL/year, PSA-DT after RP >12 months, Gleason score <7, pT2/3a tumors, positive surgical margins, and no lymph node invasion. These factors were used to determine whether PSA recurrence is caused by a local recurrence. Importantly, the increase in PCa cancer-specific survival associated with SRT was limited to men with a PSA-DT <6 months and remained so after adjustment for pathological stage and other established prognostic factors. SRT initiated more than 2 years after recurrence provided no significant increase in PCa cancer-specific survival.

The optimal dose of percutaneous SRT is still not well defined. Reported doses vary between 64 Gy and 70 Gy. According to the ASTRO/AUA guidelines, a dose of 64–65 Gy is regarded as the minimum that should be delivered post-RP (Valicenti et al. 2013). The current EAU guidelines recommend applying an even higher dose of at least 66 Gy to the prostatic fossa (Cornford et al. 2017). Furthermore, a systematic review demonstrated a positive correlation between escalating SRT-dose and a 2% increase in relapse-free survival for each additional Gy, suggesting the administration of a dose above 70 Gy (King 2012). However, even if the rate of severe complications is relatively low, SRT is an invasive approach and has several potential side effects whose incidence and severity increase with dose escalation >68 Gy even using new techniques (Ost et al. 2011).

Addition of HT to SRT was recently shown to improve PCa outcomes in two RCTs. The RTOG 9601 trial showed an improvement in overall survival from 78% to 82% after 10 years and a reduction in death from PCa from 7.5% to 2.3%, with a number needed to treat of 17 for the study group receiving bicalutamide (150 mg) for 24 months additionally to RT compared to the group receiving RT and placebo (Shipley et al. 2017). The GETUG-AFU 16 trial investigated the effect of short-term HT (goserelin for 6 months vs. placebo) additionally to SRT and found the HT group more likely to be free of biochemical progression or clinical progression at 5 years (80% vs. 62%; $P < 0.0001$) (Carrie et al. 2016). Survival in this trial remained unchanged.

In summary, men with a longer interval from RP to PSA recurrence, favorable PSA kinetics and histopathological parameters, and positive surgical margins are potential candidates for SRT. There is a significant overlap, however, with those parameters that identify men who have excellent outcome with observation alone. Patients at high risk need early and aggressive salvage treatment. Careful patient selection after multidisciplinary discussion of the individual case is mandatory to avoid overtreatment.

Management of Nonmetastatic Failure Following Radiation Therapy

The evidence supporting salvage treatment in patients with local recurrent PCa after radiotherapy is sparse and allows no general recommendation on standardized management. The therapeutic options are salvage radical prostatectomy (SRP), cryosurgical ablation of the prostate, brachytherapy, HIFU ablation, continuous or intermittent hormone therapy, and observation.

According to an ASTRO consensus recommendation, routine prostate biopsy should no longer be performed for evaluation of PSA-only recurrences following RT (Valicenti et al. 2013). However, biopsy is the cornerstone of the decision-making process for salvage therapy for local recurrence and histological proof of recurrence should be considered mandatory in light of the morbidity of local salvage treatments (Heidenreich et al. 2008). Local recurrences after RT are diagnosed with high accuracy by multiparametric MRI, which offers better spatial resolution than PET/CT (Rouviere et al. 2010). Furthermore, MRI can be used for targeted biopsies and local salvage treatment.

Salvage Radical Prostatectomy

Salvage radical prostatectomy (SRP) is the longest used salvage treatment option for localized recurrence after initial RT with curative intent. However, according to data of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) on 2336 patients with initially irradiated PCa, 92% of the patients were treated with HT for PSA progression (Grossfeld et al. 2002). Obviously, the main reason for the reluctant use of SRP is its greater risk of possible adverse events (due to impaired wound healing and fibrosis after RT) compared to primary surgery. Chade et al. reported on the oncologic and functional outcome of SRP for radiation-recurrent PCa in a systematic review of the literature comprising 40 studies (Chade et al. 2012). The BCR-free survival rate after SRP ranged from 47% to 82% at 5 years and from 28% to 53% at 10 years. Cancer-specific

survival and overall survival varied from 70% to 83% and 54% to 89% at 10 years. The strongest prognostic predictors for progression-free survival, organ-confined disease, and cancer-specific survival were pre-SRP PSA level and prostate biopsy Gleason score. Further significant pre-SRP variables for predicting clinical outcomes were pre-RT clinical stage, percentage of positive cores at biopsy, and a PSA-DT >12 months. In postoperative models, organ-confined disease, negative surgical margins, and the absence of seminal vesical invasion or lymph node metastases were favorable prognostic factors. In terms of complications, anastomotic stricture was the most frequent adverse event, occurring in 7–41% of patients followed by rectal injury in 0–28%. Major complications ranged from 0% to 25%, urinary continence from 21% to 90% after SRP.

In summary, SRP can be considered as a salvage treatment of recurrent PCa after primary RT in patients with low comorbidities and a life expectancy >10 years who have organ-confined tumor, no lymph node involvement pre-SRT, a Gleason score <7, pre-RT PSA-level <10 ng/mL, and favorable post-RT PSA kinetics. The benefits need to be balanced with the potential harms.

Salvage Brachytherapy

Due to the limited total dose that can be administered by RT, the chance of cure by additional external salvage radiation in patients who have undergone prior RT with curative intent is low; there is no indication for such an approach. Some relatively small studies, however, have shown salvage treatment with high-dose-rate or low-dose-rate brachytherapy to be effective with an acceptable toxicity profile in patients with local recurrent PCa following definitive RT. A retrospective analysis by Chen et al. comprised 52 patients treated with salvage HDR-brachytherapy. After a median follow-up of 59.6 months, the 5-year overall survival rate was 92%, the 5-year BCR-free survival 51%. Grade 3 genitourinary and grade 2 gastrointestinal toxicities each comprised 4% of cases (Chen et al. 2013). Another study with 37 patients undergoing LDR brachytherapy demonstrated a 10-year BCR-free survival rate of 54% (Burri et al. 2010). A phase-II trial comprising 42 patients from Memorial Sloan-Kettering Cancer Center in New York showed a 5-year BCR-free survival rate of 68.5%, a 5-year distant metastases-free survival of 81.5%, and cancer-specific survival of 90.3%. Late grade 2 genitourinary and gastrointestinal toxicities were found in 48% and 8%, respectively. Three patients (7%) developed grade 2 late urinary toxicity (urethral stricture), which were corrected with urethral dilatation, and one patient developed grade 3 urinary incontinence (Yamada et al. 2014).

In summary, salvage brachytherapy is a treatment option for carefully selected patients with local recurrence after RT. However, due to the small study populations and not yet conclusively studied long-term side effects, it is currently not recommended as a standardized option and should only be offered in experienced centers.

Salvage Cryosurgical Ablation of the Prostate

Salvage cryosurgical ablation of the prostate (SCAP) was proposed at the end of the 1990s as an alternative to SRP based on its potential for lower morbidity and equal efficacy. To date, however, the few studies published have presented mainly disappointing results. Spiess et al. report BCR-free survival rates of 39.6% after a median follow-up of 40.8 months in a series of 450 patients (Spiess et al. 2010). One case-matched control study comparing oncological outcomes of SRP and SCAP was performed in men with recurrent PCa after RT (Pisters et al. 2009). After a mean follow-up of 7.8 years (SRP group) and 5.5 years (SCAP group), the 5-year BCR-free survival and the overall survival rates were significantly better following SRP (61%) than after SCAP (61% vs. 21% and 95% vs. 85%, respectively).

Initial complication rates associated with cryoablation were significant. Urinary incontinence was reported in 28–73%, obstructive symptoms in 67%, impotence in 72–90%, and perineal/

rectal pain in 8–40% of patients. In addition, 4% of patients underwent surgical procedures for management of treatment-related complications (Pisters et al. 2008; Cespedes et al. 1997). Third-generation technology has produced a significant decrease in complications over the past decade (urinary incontinence in 12%, obstructive symptoms in 7%) (Ahmad et al. 2013).

In conclusion, SCAP for radiation failure needs further evaluation in prospective clinical trials and cannot be recommended at present.

Salvage HIFU Ablation

Only a few small retrospective studies, most of whose data was generated by one high-volume center with short follow-up and nonstandardized endpoints, have reported on the outcome of an alternative thermal ablation technique with salvage HIFU after RT. For this reason, the oncological outcome of this approach cannot be fully assessed. Urinary tract infections (35%), dysuria (26%), and urinary incontinence (6%) were among the most frequently reported side effects. Seven percent of the men developed recto-urethral fistula as a major complication that is difficult to handle after RT and HIFU therapy (Ahmed et al. 2012). BCR-free survival rates after 2 years were 43–59% (Ahmed et al. 2012; Uchida et al. 2011). Salvage thermal ablation with HIFU must be considered experimental at this time.

Salvage Lymph Node Dissection

Several retrospective studies have analyzed the benefit of salvage lymph node dissection (SLND) in patients with (recurrent) nodal metastases (Karnes et al. 2015; Winter et al. 2015; Tilki et al. 2015). Globally 50% of patients remained disease-free after short-term follow-up. However, the high rate of androgen deprivation therapy (ADT) use (almost 2/3s of patients) might lead to overestimation of BCR-free survival rates after salvage treatment. Moreover, heterogeneity among study populations, definitions of progression, types of adjuvant treatments, and study endpoints make it difficult to estimate the exact impact of SLND (Ploussard et al. 2015). Thus, SLND should currently be considered as experimental.

Hormone Therapy for Biochemical Recurrence

Although patients with PSA-recurrence after RP and RT often undergo hormonal treatment, the benefit of this approach is uncertain and the literature shows conflicting results. A recently published systematic review has summarized the data on this topic published from 2000 onwards including 27 studies (2 RCTs, 8 nonrandomized comparative studies, and 17 case series) (van den Bergh et al. 2016). The studied populations were highly heterogeneous regarding tumor biology. There is only one as yet unpublished, underpowered RCT that analyzed the effect of salvage ADT for a median follow-up of 5.0 years (Duchesne et al. 2016). This RCT, like several other studies, showed a survival benefit in the early HT group with an increase in the 6-year overall survival rate from 79% to 86%; other studies found no favorable effect of HT. No data is currently available on the effectiveness of different types of HT. The RCT of Crook et al. suggested noninferiority of intermittent to continuous HT in patients with rising PSA after local RT, showing some improvement in QOL for intermittent HT with respect to physical function, fatigue, urinary problems, hot flashes, libido, and erectile function (Crook et al. 2012). A high Gleason score, high PSA, short PSA-DT (<6 months), increased age, and comorbidities are associated with poor outcomes. High-risk patients with a long life expectancy seem to benefit most from HT. A retrospective cohort analysis by Pinover et al. comparing HT and watchful waiting in 248 men with BCR after RT showed no improvement in the 5-year metastasis-free survival rate with use of HT in patients with a PSA-DT of >12 months after RT (88% vs. 92%, $P = 0.74$) (Pinover et al. 2003).

In summary, due to its lack of efficacy and associated side effects, systemic salvage HT should only be initiated in carefully selected patients with BCR

after local treatment who are at high risk of developing metastases or PCSM and have a long life expectancy. Potential benefits of salvage HT must be balanced against its potential harms. In older patients, especially, if they have cardiovascular risk factors, HT may even decrease life expectancy (O'Farrell et al. 2015). In patients with a PSA-DT >12 months, HT does not seem to provide any benefit and is therefore currently not recommended. In case of a good response to HT, intermittent therapy should be considered to improve patient QOL.

Management of Oligometastatic PCa Recurrence

The literature on metastasis-directed therapy for oligometastatic PCa recurrence consists of small heterogeneous studies. A retrospective multi-institutional analysis pooled data from different institutions using stereotactic body radiotherapy (SBRT) to treat oligometastatic PCa recurrence in 119 patients with ≤3 metastases. The median distant progression-free survival (DPFS) was 21 months, the 3- and 5-year DPFS were 31% and 15%, respectively. The median 3-year local progression-free survival (LPFS) was 93%, but it was significantly lower in patients treated with a lower dose of ≦100 Gy (3-year LPFS 79%) (Ost et al. 2016). However, further prospective randomized studies are needed to allow clear recommendations on the diagnosis (i.e., modern imaging: MP-MRI, Choline-PET-CT, PSMA-PET-CT) and management of oligometastatic PCa recurrence. In the meantime, patients should be treated according to the principles for treatment of metastatic disease.

Summary

For nonmetastatic recurrent PCa after local therapy, selection of further treatment depends on many factors, including previous treatment, tumor-specific parameters, PSA kinetics, comorbidities, and individual patient considerations. Observation is a feasible option in patients with low-risk profiles, who are elderly or who have severe comorbidities with a life expectancy <10 years. It is also appropriate for men who do not wish to undergo second-line curative options due to the mostly benign natural course of the disease. SRT is the preferred curative treatment option for men with local recurrence after RP. Salvage prostatectomy is the preferred treatment option in patients after RT. However, these salvage treatments may be associated with severe side effects and may negatively impact patient QOL. Patients should therefore be carefully selected for salvage treatment for nonmetastatic recurrent PCa. A multidisciplinary discussion of the individual case is crucial before initiating salvage therapy.

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Systemic Treatment of Castration-Resistant Metastatic Prostate Cancer

14

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Contents

Abstract

Current treatments for men with castration-resistant prostate cancer (CRPC) include the next-generation androgen receptor-targeting agents abiraterone acetate and enzalutamide, cytotoxic drugs docetaxel and cabazitaxel, immunotherapy sipuleucel-T, and radionuclide radium-223 dichloride. For men with bone metastases, the supportive bone-targeting agents zoledronic acid or denosumab are also commonly administered, although these do not improve survival. Newer treatments that aim to target specific genomic aberrations are in late-stage clinical testing. In this chapter, current and emerging treatments across the spectrum of CRPC will be reviewed, including relevant

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limitations and future directions from late-phase trials.

Introduction

Prostate cancer that is no longer controlled by medical or surgical reduction of systemic androgens is referred to as castration-resistant prostate cancer (CRPC). While castration may provide ongoing control of some cancer clones, additional treatments are required to delay cancer-related morbidity and mortality.

Since 2004, six agents have showed survival advantages for men with metastatic CRPC (mCRPC). These "survival-prolonging" agents include the cytotoxic drugs docetaxel and cabazitaxel, "next-generation" androgen receptor (AR)-targeting agents abiraterone acetate (abiraterone) and enzalutamide, immunotherapy with sipuleucel-T, and the bone-targeting radionuclide radium-223 dichloride (^{223}Ra). Each of these agents has a unique treatment schedule and toxicity profile, and not all agents are available in every region globally.

The introduction of multiple effective agents for mCRPC has provided greater options for patients and clinicians. Men with contraindications to one treatment are able to access alternative agents, while the use of sequential active agents has compounded survival gains for the overall mCRPC population. Despite these advantages, there are many unanswered questions in mCRPC management. The concurrent development and specific protocol requirements of many of the therapies meant that most trial patients lacked prior exposure to any other survival-prolonging agent. It cannot be assumed that the effects of subsequent treatments are independent of those of prior treatments, and optimal treatment sequencing remains unclear. Most agents have been tested in isolation, and it is not yet known whether combination treatments will provide synergistic benefits. In this chapter, therapeutic options have been grouped according to their current use across the spectrum of mCRPC.

"Floating" Agents

Agents classed as "floating" have efficacy data supporting their use across the spectrum of mCRPC and perhaps even earlier. At present, floating agents comprise abiraterone and enzalutamide, along with similar agents in late-phase clinical trials. While efficacy has been shown before or after chemotherapy, there are few data to support the choice between these agents, and case series data suggest poor response to the second agent when they are used sequentially.

Abiraterone Acetate

Overview

Abiraterone (Zytiga®; Janssen Pharmaceuticals) is an androgen biosynthesis inhibitor used in the management of CRPC. Proven benefits include extending survival, improving response rates, and preserving quality of life (de Bono et al. 2011; Ryan et al. 2013). Further investigation is underway regarding sequencing or combining of abiraterone with other therapies, as well as the role of potentially useful biomarkers. More recently, the phase III LATITUDE and STAMPEDE trials demonstrated a substantial survival benefit from commencing abiraterone at the initiation of androgen deprivation therapy.

Mechanism of Action

The AR signaling pathway has an important role in the progression of CRPC. Residual androgens from adrenal precursors and intratumoral androgen synthesis can drive disease progression despite androgen deprivation therapy (ADT) (Attard et al. 2008).

Abiraterone is a high-affinity, selective, irreversible inhibitor of the cytochrome P450 CYP17 enzymes 17-alpha-hydroxylase and C17,20-lyase (Pezaro et al. 2012). In the steroid biosynthesis pathway, pregnenolone is converted by 17-alpha-hydroxylase to 17-hydroxypregnenolone, while C17,20-lyase facilitates the conversion of 17-hydroxypregnenolone to dehydroepiandrosterone (DHEA). Inhibition of CYP17 function

Table 1 Outcomes for abiraterone with prednisone in phase III COU-AA-302 (pre-chemotherapy) and COU-AA-301 (post-docetaxel) trials (de Bono et al. 2011; Ryan et al. 2013)

Endpoint	Abiraterone + prednisone pre-chemotherapy	Placebo + prednisone pre-chemotherapy	Abiraterone + prednisone post-docetaxel	Placebo + prednisone post-docetaxel
Overall survival	NR[a]	27.2 months	14.8 months	10.9 months
	HR 0.75		HR 0.66	
	$p = 0.01$		$p < 0.001$	
PSA response rate	62%	24%	38.0%	10.1%
Radiographic PFS	16.5 months	8.3 months	5.6 months	3.6 months
	HR 0.53		HR 0.67	
	$p < 0.001$		$p < 0.001$	
Time to PSA progression	11.1 months	5.6 months	10.2 months	6.6 months
	HR 0.49		HR 0.58	
	$p < 0.001$		$p < 0.001$	
Grade 3 or 4 toxicity	48%	42%	Overall figure not reported	Overall figure not reported

[a]The COU-AA-302 trial was terminated at interim analysis after reaching 43% of the expected overall survival events
NR not reached, *HR* hazard ratio

results in a significant decrease in DHEA, androstenedione, and testosterone levels (Attard et al. 2008). Abiraterone is administered in combination with ADT, to prevent a compensatory LH surge (Pezaro et al. 2012).

Activity in CRPC Settings

Abiraterone, given with prednisone, prednisolone, or dexamethasone, has shown clinical efficacy before and following docetaxel for men with mCRPC (see Table 1). The COU-AA-301 phase III trial enrolled 1195 men with mCRPC progressing after docetaxel chemotherapy, randomizing them to receive 5 mg prednisone twice daily with either 1000 mg abiraterone or placebo (de Bono et al. 2011). The COU-AA-302 trial randomized 1088 men with mCRPC between the same regimens, but in the pre-docetaxel setting (Ryan et al. 2013). In both trials, abiraterone with prednisone/prednisolone treatment resulted in improvements in overall survival, time to PSA progression, progression-free survival (PFS), and PSA response rates compared to prednisone alone.

Toxicity Management

The profound CYP17 inhibition from abiraterone also results in an excess of upstream biosynthetic pathway precursors and, when administered as monotherapy, can cause a syndrome of secondary mineralocorticoid excess. Relevant adverse events reported in the COU-AA-301 and COU-AA-302 trials were largely mild to moderate and included fluid retention, hypertension, and hypokalemia (de Bono et al. 2011; Ryan et al. 2013). Other effects included impaired liver function and cardiac side effects; the most frequent were tachycardia and atrial fibrillation (de Bono et al. 2011; Gillessen et al. 2015).

Co-administration of abiraterone with low-dose glucocorticoids such as prednisolone is well tolerated and blocks the compensatory increase in adrenocorticotropic hormone seen with abiraterone monotherapy (Pezaro et al. 2012). However, the use of these steroids may lead to the binding and activation of mutant AR, causing progression of prostate cancer (Richards et al. 2012). The mineralocorticoid antagonist eplerenone has also been used to counteract the effects of CYP17 inhibition (Richards et al. 2012). Translational and phase II data have suggested that dexamethasone may have greater anticancer activity in mCRPC (Venkitaraman et al. 2015), but prednisone/prednisolone continues to be widely used concomitantly with abiraterone.

Table 2 Outcomes of the phase III PREVAIL (pre-chemotherapy) and AFFIRM (post-docetaxel) enzalutamide trials (Scher et al. 2010; Beer et al. 2014)

Endpoint	Enzalutamide pre-chemo	Placebo pre-chemo	Enzalutamide post-chemo	Placebo post-chemo
Overall survival	32.4 months	30.2 months	18.4 months	13.6 months
	HR 0.71		HR 0.63	
	$p < 0.001$		$p < 0.001$	
PSA response rate	78%	3%	54%	2%
Radiographic PFS	NR	3.9 months	8.3 months	2.9 months
	HR 0.19		HR 0.4	
	$p < 0.001$		$p < 0.001$	
Time to PSA progression	11.2 months	2.8 months	8.3 months	3.0 months
	HR 0.17		HR 0.4	
	$p < 0.001$		$p < 0.001$	
Grade 3 or 4 toxicity	43%	37%	28%	34%

Research Activity

Several phase III trials are currently studying abiraterone in men with CRPC. Combination trials include testing of abiraterone with apalutamide (ARN-509, Janssen; clinicaltrials.gov trial identifier: NCT02257736), enzalutamide (NCT01949337), and ^{223}Ra (NCT02043678).

Other late-phase studies will investigate abiraterone in patients with mCRPC who responded poorly to first-line combined androgen blockade (CAB) (NCT02405858) and also the use of circulating tumor cells (CTC) as an efficacy-response measure (NCT01961843). Head-to-head drug comparisons are also planned, against cabazitaxel (NCT02485691) and, in men with germline DNA repair defects, against olaparib (NCT02987543).

Enzalutamide

Overview

Enzalutamide (MDV3100; Xtandi®; Medivation) is a second-generation AR antagonist. Administered orally on a continuous daily schedule, enzalutamide may be used in men with mCRPC either before or following docetaxel chemotherapy. Enzalutamide is well tolerated in the majority of men, with rare but unique challenges relating to penetration of the central nervous system. Ongoing trials are examining the use of enzalutamide for biochemical CRPC with occult metastases, or in combination with other anticancer agents.

Mechanism of Action

Enzalutamide is a potent antagonist of the AR. In addition to blocking ligand binding, enzalutamide also inhibits nuclear localization of AR and binding to DNA (Tran et al. 2009). Enzalutamide lacks the partial agonism activity of first-generation AR antagonists, but case reports of withdrawal responses following enzalutamide suggest that agonism is still possible in rare situations (Rodriguez-Vida et al. 2015).

Activity in CRPC Settings

Efficacy data in mCRPC are available from two large phase III trials (see Table 2). These trials were similar in design, comparing enzalutamide to placebo. Both trials demonstrated that enzalutamide treatment was associated with significant improvements in survival, disease control, and quality of life measures (Scher et al. 2010; Beer et al. 2014). In the post-chemotherapy AFFIRM trial, participants were allowed concurrent treatment with prednisone/prednisolone.

Toxicity Management

Enzalutamide is well tolerated in the majority of men. The most common all-grade toxicity in phase III testing included fatigue, gastrointestinal disturbances, arthralgias, and hot flushes (Scher et al. 2010; Beer et al. 2014). Seizures occurred in five men on the AFFIRM trial, each of whom had additional medication or disease factors that may have lowered the seizure threshold. In view of the

ability of enzalutamide to cross the blood-brain barrier and possible contribution to seizures, enzalutamide is not recommended for patients with a history of seizures or recent cerebrovascular events. Caution is required in men taking other medications that penetrate the blood-brain barrier and also in men with falls or preexisting cognitive impairment.

Research Activity

The PROSPER and SPARTAN trials (NCT02003924 and NCT01946204 respectively) are investigating the use of enzalutamide and the similar agent apalutamide in the treatment of occult metastatic disease with rising PSA. Awaited or ongoing phase III trials are evaluating the addition of enzalutamide to abiraterone (NCT01949337), ^{223}Ra (mCRPC-PEACE III; NCT02194842), and the anti-PD-L1 antibody atezolizumab (IMbassador250; NCT03016312). In a selected population of men with mCRPC and poor-risk features, the OZM-054 trial (NCT02254785) will evaluate sequencing of next-generation AR-targeting agents and cabazitaxel and may provide biological insights that can be extrapolated to the general mCRPC population.

"Semifixed" Agents

"Semifixed" agents include docetaxel chemotherapy, which was the first agent to improve survival for men with CRPC and became an artificial treatment divider in subsequent trials of anticancer therapies. ^{223}Ra has also been placed in this category, due to currently available efficacy data, as have the supportive bone-targeting agents zoledronic acid and denosumab.

Docetaxel

Overview

Docetaxel is one of the taxane chemotherapeutic agents. With the TAX-327 and SWOG 99–16 trials published in 2004, it became the first agent proven to improve survival in men with mCRPC. Docetaxel is administered in combination with continuous low-dose prednisone/prednisolone and continues to be a mainstay of treatment, providing palliative benefits with a manageable toxicity profile. While the optimal timing of docetaxel has been challenged by recent data demonstrating marked benefit in men prior to the emergence of castration-resistant disease, exposure to docetaxel continues to be a marker in judging activity of some therapies and in some countries is linked to reimbursement criteria or subsequent drug access.

Mechanism of Action

Docetaxel is a semisynthetic taxane, originally derived from needles of the European Yew tree. Taxane chemotherapies are mitotic inhibitors that act by interrupting microtubule function. Preclinical data suggest that this action may indirectly impair shuttling of AR into the nucleus, contributing to its activity in prostate cancer (Darshan et al. 2011). Docetaxel resistance mechanisms to docetaxel include tumor hypoxia and impaired drug delivery, drug efflux pumps, altered microtubule structure or function, and disordered apoptosis pathways (Antonarakis and Armstrong 2011).

Activity in CRPC Settings

The TAX-327 trial enrolled 1006 men with CRPC and randomized them equally between three treatment arms of 3-weekly mitoxantrone, 30 mg/m^2 docetaxel weekly for 5 of 6 weeks, or 75 mg/m^2 docetaxel administered 3-weekly. Participants in all arms received prednisone. Compared to mitoxantrone, 3-weekly docetaxel treatment resulted in improved survival (median OS 18.9 vs. 16.5 months, HR 0.76, $p = 0.009$) (Tannock et al. 2004). Secondary measures of activity also favored docetaxel treatment, including $\geq$50% PSA declines (45% vs. 32%), significant pain reduction (35% vs. 22%), and improved quality of life (22% vs. 13%). At least half of men randomized to 3-weekly docetaxel received 9 or more cycles of treatment, with treatment delay and dose reduction required by 24% and 12%, respectively.

The preponderance of bone metastases in trial participants contributed to a relatively

low rate of radiographic responses. Patients were treated until progression or unacceptable toxicity, or completion of the planned ten cycles of treatment. This treatment course was selected due to concerns about cumulative mitoxantrone toxicity, and extended courses of docetaxel can be delivered safely, with prolonged disease control reported in selected cases.

The benefit of three-weekly docetaxel was confirmed by the SWOG 99–16 trial, a phase III trial of docetaxel in combination with estramustine, which confirmed superiority over the comparator of mitoxantrone with estramustine (Petrylak et al. 2004).

Toxicity Management

The toxicity profile of docetaxel is familiar to most oncology clinicians. The most common toxicities associated with three-weekly docetaxel in the TAX-327 trial were fatigue, nausea, alopecia, diarrhea, nail changes, sensory neuropathy, and anorexia. Grade 3–4 neutropenia occurred in 32%, with 3% experiencing febrile neutropenia. The incidence of clinically significant peripheral neuropathy increased with cumulative dose and may be treatment-limiting in some men. Ethnic variation in toxicity has also been described, with some data suggesting that 60 mg/m^2 may be a more appropriate starting dose in Asian men (Kenmotsu and Tanigawara 2015).

Research Activity

Multiple phase III trials have attempted to improve on the single-agent activity of docetaxel, adding agents with complementary, additive, or alternative mechanisms of activity. Unfortunately, no combination has yet provided a meaningful advantage over the standard protocol. A small phase III trial suggested that an alternative two-weekly dosing schedule may lessen treatment morbidity (Kellokumpu-Lehtinen et al. 2013).

Renewed enthusiasm for docetaxel was provided by the recent CHAARTED and STAMPEDE trials that demonstrated significant survival advantages by moving chemotherapy earlier, for men commencing ADT for advanced prostate cancer (Sweeney et al. 2015; James et al. 2016). The implications of these data for the treatment of mCRPC, and whether docetaxel should still be used in the same way, are still being explored.

Radium^{223} Dichloride

Bone-targeting radionuclides have been used in advanced prostate cancer for many years. Treatment with the beta-emitters strontium-89 and samarium-153 resulted in valuable palliation in some men with widespread bone-predominant CRPC, but these agents failed to improve survival in small phase III trials and were associated with myelosuppression (Sartor 2004).

^{223}Ra (Xofigo®, Bayer) is an alpha-emitter, delivering radiation across a very short path length. Following infusion, ^{223}Ra acts as a calcium mimetic and is taken up into newly formed bone stroma, such as occurs in bone metastases.

^{223}Ra showed encouraging activity in early-phase studies, leading to the phase III ALSYMPCA trial. This was a placebo-controlled randomized trial in 921 men with mCRPC, multiple bone metastases, and no significant non-bone disease, who had either progressed following docetaxel or had not received docetaxel due to frailty or patient wishes. A total of 395 men (43%) on the trial were docetaxel-naïve (Parker et al. 2013).

^{223}Ra was administered as a 50 kBq/kg infusion on a monthly basis. A maximum of six treatments (median number of cycles = 6) were delivered on trial. The trial was halted early, after meeting the interim efficacy threshold. Treatment resulted in a median 3.6-month survival advantage over placebo (14.9 vs. 11.3 months, hazard ratio (HR) = 0.7, $p < 0.001$). The time to symptomatic SRE, reduction in alkaline phosphatase, and quality of life were all improved with ^{223}Ra treatment. The toxicity profile was mild, including all-grade anemia in 31%, along with mild nausea, other gastrointestinal toxicities, and fatigue.

Further clinical trial data regarding activity in other patient populations are still awaited.

Bone-Targeting Agents

Prostate cancer shows a marked preponderance to spread to the bone, resulting in a significant burden of the disease morbidity. Malignant spinal cord compression is one of the most severe complications resulting from bone metastases and requires urgent recognition and treatment. Malignant hypercalcemia is another complication associated with bone metastases and can become life-threatening if neglected. Fractures can be pathological at the site of metastases or osteopenic as a result of prolonged ADT.

The predominance of skeletal-related events (SREs) in advanced prostate led to testing of a number of different bone-targeting agents. Use of the bisphosphonate zoledronic acid, then the RANK-ligand inhibitor denosumab, showed stepwise improvements in the rate of SREs for men with CRPC, but neither agent impacted on the overall survival of these populations.

The head-to-head trial of these agents was a phase III double-blind non-inferiority study, randomizing 1904 patients to monthly treatment with denosumab 120 mg subcutaneously or zoledronic acid 4 mg intravenously. The primary endpoint was time to SRE, defined as a composite of pathological fracture, radiotherapy to the bone, surgery to the bone, or spinal cord compression. Denosumab proved to be superior for prevention of SRE (median time to SRE 20.7 months versus 17.1 months; HR 0.82, $p = 0.008$) (Fizazi et al. 2011).

Because zoledronic acid and denosumab were tested prior to the introduction of survival-prolonging therapies for CRPC, the relative benefit of these agents in combination with other anticancer therapies is not known. Adding to the complexity, no fixed treatment duration is recommended, but toxicities are cumulative and with improvements in survival; open-ended treatment durations may be much longer than tested in trials, without proof of additional benefit.

"Fixed" Agents

"Fixed" agents have been classed as those with clear evidence as to the population of patients most likely to benefit from treatment. Cabazitaxel chemotherapy has proven efficacy after docetaxel and has been categorized as a "fixed" agent. The strongest data supporting the use of sipuleucel-T was in men with low-volume and treatment-naïve disease; thus it has also been categorized as "fixed." Also in this category are the emerging agents that target specific genomic aberrations. While these treatments are still investigational, there is a strong biological rationale and promising preliminary clinical data, and it is hoped that they will add important new options for subsets of patients.

Cabazitaxel

Overview

Cabazitaxel (XRP6258; Jevtana®; Sanofi) is a semisynthetic taxane. It was initially identified by screening for effects against taxane-resistant cell lines in vivo and in an animal tumor model of docetaxel resistance (Yap et al. 2012). Cabazitaxel has clear evidence for efficacy in men with progressive CRPC after docetaxel; however troublesome myelosuppression led to additional phase III testing of potential starting doses.

Mechanism of Action

As a member of the taxane family, cabazitaxel mediates its activity through the promotion of tubulin assembly and stabilization of microtubules but appears to be less dependent on the AR than docetaxel (van Soest et al. 2015). Cabazitaxel has low affinity for the drug efflux molecule P-glycoprotein and appears to have favorable penetration of the blood-brain barrier (Calcagno et al. 2013).

Activity in CRPC Settings

Initial phase I and II clinical trials identified an optimal schedule of 3-weekly intravenous infusions and suggested dose-limited toxicity at 20 or 25 mg/m^2 (Yap et al. 2012). Phase 1 testing included two patients with CRPC who had radiological partial remissions and substantial reductions in PSA (Yap et al. 2012), leading to further testing in the CRPC setting. The pivotal phase III TROPIC trial (de Bono et al. 2010) involved 755 men with metastatic CRPC who had

Table 3 Outcomes of the TROPIC trial (de Bono et al. 2010)

Endpoint	Cabazitaxel	Mitoxantrone
Overall survival	15.1 months	12.7 months
	HR 0.7	
	$p < 0.0001$	
Overall response rate[a]	14.4%	4.4%
PSA response rate	39.2%	17.8%
PFS	2.8 months	1.4 months
	HR 0.74	
	$p < 0.0001$	
Time to progression	8.8 months	5.4 months
	HR 0.61	
	$p < 0.0001$	
Time to PSA progression	6.4 months	3.1 months
	HR 0.75	
	$p = 0.001$	
Pain response	9.3%	7.7%
	$p = 0.63$	
Time to pain progression	Not reached	11.1 months
	$p = 0.52$	
Grade 3 or 4 toxicity	82%	58%

[a]For patients with measurable disease by RECIST (Response Evaluation Criteria In Solid Tumors)

progressed during or after docetaxel. Visceral metastases were present in 25%, 45% had pain on baseline, and about 30% had two or more previous chemotherapy regimens. Additionally, 29% had progressed on docetaxel, suggesting primary refractory disease, and an additional 45% had progressed within 3 months of docetaxel, portending a poor outcome. The primary endpoint of the study was overall survival. Secondary endpoints included a composite of tumor progression, pain progression, and death, as well as a number of response and progression measurements.

Men were randomized between three-weekly cabazitaxel 25 mg/m^2 or standard mitoxantrone, with all men receiving continuous oral prednisone 10 mg daily. Granulocyte colony-stimulating factor was permitted for patients experiencing prolonged neutropenia or complications.

The key findings of the TROPIC trial are summarized in Table 3. A total of ten cycles of treatment was planned and was completed by 28% of those on cabazitaxel (median six cycles) and 12% on mitoxantrone (median four cycles). The trial met its primary endpoint of improved overall survival for participants receiving cabazitaxel. Tumor response rate and PSA response rate also favored of cabazitaxel, although there was no significant difference in pain responses or time to pain progression.

Both the timing and dosing of cabazitaxel have subsequently been tested in phase III trials. Limited data are yet available on these outcomes. The PROSELICA trial (NCT01308580) has been reported so far only in abstract form (Eisenberger et al. 2017). PROSELICA was a non-inferiority study comparing cabazitaxel at starting doses of 20 mg/m^2 or 25 mg/m^2. The trial met its primary endpoint of non-inferiority of the lower dose for overall survival, with HR of 1.024 (upper boundary of the one-sided 98.89% confidence interval was 1.184, less than the prespecified non-inferiority boundary of 1.214). PSA responses occurred more commonly with the higher dose (42.9% versus 29.5%, $p < 0.0001$), but toxicity was more common. The study concluded that 20 mg/m^2 was non-inferior in terms of overall survival and had a better safety profile.

The FIRSTANA trial (NCT01308567) has also to date only been reported in abstract form (Oudard et al. 2017). This trial involved chemo-naïve

participants with metastatic CRPC, randomized to receive cabazitaxel at either 20 mg/m^2 or 25 mg/m^2, or standard docetaxel chemotherapy. The primary endpoint was overall survival. The trial was reported with 24 months of median follow-up and showed no statistically significant difference in overall survival. Very few participants had received prior enzalutamide or abiraterone.

Toxicity Management

Toxicity was a key issue in the TROPIC study. Grade 3 or 4 adverse events occurred in 82% of participants receiving cabazitaxel, compared to 58% receiving mitoxantrone. The commonest toxicity was myelosuppression, with 8% febrile neutropenia and 2% deaths due to neutropenia with cabazitaxel. Significant diarrhea was also more common with cabazitaxel (6% versus <1%). Peripheral neuropathy was uncommon (<1% in each group). Later studies subsequently suggested that toxicity in the "real-world" treatment setting was more manageable than the TROPIC data suggested (Moriceau et al. 2015).

Sipuleucel-T

Sipuleucel-T (PROVENGE®) is an active cellular immunotherapy, comprising autologous peripheral blood mononuclear cells collected by leukapheresis and activated using a recombinant fusion protein combining prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor. Two small trials were initially performed, with progression-free survival as the primary endpoint and overall survival as a secondary endpoint (Higano et al. 2009). Both trials failed to meet their primary endpoint but showed consistent and similar benefits in overall survival. This was counterintuitive and unexpected, so the IMPACT trial (NCT00065442) was conducted with overall survival as the primary endpoint (Kantoff et al. 2010). IMPACT involved 512 participants randomized 2:1 to sipuleucel-T versus a placebo intervention (cultured autologous peripheral blood mononuclear cells without exposure to the fusion protein). Eligible participants had metastatic CRPC and were asymptomatic or minimally symptomatic. Participants had generally good prognosis features: only 15% of participants had previously received docetaxel; 82% were ECOG performance status 0; and the median time from diagnosis was 7 years.

The analysis was performed with a median follow-up of 34 months. Sipuleucel-T treatment was very well tolerated. Sipuleucel-T was associated with improved overall survival relative to placebo: median survival was 25.8 months in the sipuleucel-T group and 21.7 months in the placebo (HR 0.78; $p = 0.03$). Objective responses on the study were rare. There was no difference in time to progression, an observation that remains unexplained, although it has been a consistent feature in other types of immunotherapy studies.

These outcomes led to the approval of sipuleucel-T by the US FDA, the first approved cellular immunotherapy for any type of solid cancer. However, uptake of this treatment has occurred almost exclusively within the United States. The reasons for this relate to the logistics of production and the very high cost of the treatment (Simpson et al. 2015). Sipuleucel-T remains controversial, with some clinicians concerned that outcomes for the placebo group appeared to be inferior to those of comparable trials, raising questions as to whether the use of the placebo compromised outcomes as opposed to sipuleucel-T improving them (Huber et al. 2012). Sipuleucel-T continues to be studied in the context of other immunotherapeutic approaches or drug combinations.

Novel Technologies and Targeted Treatments

Gene sequencing technologies have allowed detailed analyses of the genomic landscape of primary (The Cancer Genome Atlas Research Network 2015) and metastatic prostate cancer (Robinson et al. 2015), demonstrating frequent and characteristic aberrations. Common mutational events in primary prostate cancer (The Cancer Genome Atlas Research Network 2015) fall into various subtypes involving gene fusions (such as ERG, ETV1/4, and FLI1) or mutations (such as SPOP, FOXA1, and IDH1), as well as epigenetic events. Genomic events affecting AR

function are also very common particularly in tumors carrying SPOP and FOXA1 mutations. Lesions in PI3K or MAPK pathways, and defects in DNA repair genes, are also commonly observed and may indicate potential therapeutic targets. Advanced prostate cancer is also characterized by similar events, as well as mutations in PIK3CA/B, R-spondin, BRAF/RAF1, APC, beta-catenin, and ZBTB16/PLZF (Robinson et al. 2015).

CTC are cancer cells that are detectable in peripheral blood. These cells are heterogeneous, but there is evidence that important information about cancer biology can be derived from their study. The simplest evaluation is to enumerate CTC, and this has been shown in CRPC to correlate with survival (de Bono et al. 2008). Similarly, patients whose CTC counts move from "unfavorable" to "favorable" have better outcomes than those whose CTC counts remain or become unfavorable; these findings correlate better than changes in serum PSA levels (de Bono et al. 2008). The value of CTC enumeration has also been shown with newer therapies such as abiraterone, where CTC counts and serum LDH were shown to correlate with 2-year survival in the COU-AA-301 trial (Scher et al. 2015).

More detailed understanding of the cancer's biology is also possible. For example, the detection in CTC of the AR mRNA splice variant ARv7, which lacks the ligand-binding domain of the receptor, was associated with the lack of response to therapies targeting the AR axis (Antonarakis et al. 2014). Nuclear-specific localization of the truncated ARv7 splice variant predicts for better outcomes with taxane-based therapies, compared to tests that are unable to distinguish the subcellular localization of the splice variant protein product (Scher et al. 2017). However, despite high specificity, these methods are insensitive and cannot yet be used to determine treatment choices and sequencing.

Detection and evaluation of fragmented cell-free DNA (cfDNA) is another promising biomarker for profiling the tumor genome. AR alterations in cfDNA have been linked to deleterious outcomes on AR-targeted agents such as abiraterone (Ritch and Cookson 2016) and enzalutamide (Azad et al. 2015; Wyatt et al. 2016), illustrating the potential utility of cfDNA for noninvasive molecular profiling of mCRPC. Genomic aberrations in cfDNA have also been linked to therapeutic outcomes. AR aberrations including amplification and mutations have been shown to be linked to the development of treatment failure with both enzalutamide (AR amplification, AR F877 L mutation) and abiraterone (AR H874Y and T877A mutations) (Azad et al. 2015). More recently, several cfDNA biomarkers have been shown to correlate with inferior outcomes with enzalutamide therapy, including AR amplification, heavily mutated AR ($\geq$2 mutations), and RB1 loss (Wyatt et al. 2016). At the time of progression on enzalutamide, cfDNA sequencing revealed mutations or copy number changes in all patients tested, including clinically actionable alterations in DNA damage repair genes and PI3K pathway genes. Therefore, analysis of cfDNA in mCRPC patients not only identifies key biomarkers of treatment resistance but may also help to deliver personalized medicine through the identification of actionable molecular targets.

Many of these new technologies may point to novel treatment targets or to newly defined subgroups of prostate cancers that require different treatments. Examples include prostate cancers carrying somatic defects in DNA repair pathways, which may benefit from PARP inhibition or platinum compounds (Mateo et al. 2015; Hager et al. 2016), N-terminal AR-targeted therapies for cancers with mutations or splice variants affecting the ligand-binding domain (Myung et al. 2013); inhibition of Aurora A kinase in neuroendocrine differentiation driven through *N-MYC* (Lee et al. 2016); and perhaps even predictors of response to immune checkpoint inhibitors (Topalian et al. 2016).

Response and Progression Assessment

The clinical impacts of prostate cancer vary immensely, making thorough response assessments a challenging task. In addition, the use of PSA to monitor progression can be an inaccurate

Table 4 Response assessment recommendations during treatment for mCRPC

Assessment	Recommended frequency[a]
Radiographic	
Bone scintigraphy	Regularly
Computed tomography	Regularly[b]
Biochemical	
PSA	Regularly
Blood count, ALP, LDH	At initial workup, as prognostic factors
Clinical (for new symptoms, e.g., pain)	Regularly

[a]These recommendations have been adapted from the St Gallen Advanced Prostate Cancer Consensus Conference (2015). Consensus opinions (≥70% of experts agreeing) were not reached for the recommended frequency of assessments (Gillessen et al. 2015)
[b]Regular CT scans were recommended by consensus, even in the absence of clinical indicators

reflection of the status of disease. In phase III trials, early clinical assessments focused on toxicity identification and management. The first biochemical and radiographic response assessments were often conducted after 3 months of treatment. Standard progression assessments were conducted, including PSA and bone scintigraphy interpretation, based on adaptations of the criteria proposed by the prostate cancer working group (Scher et al. 2008) and using the original or revised RECIST (Eisenhauer et al. 2009) for interpretation of soft tissue lesions. In order to avoid premature termination of treatment, a complex of clinical, biochemical, and radiographic progression was recommended (see Table 4) (Gillessen et al. 2015).

Treatment Sequencing

Perhaps the most contentious issue remains the sequencing of therapy. Small retrospective studies investigating the use of docetaxel or enzalutamide after first-line abiraterone, or for enzalutamide followed by abiraterone, have shown limited activity for the second therapy, suggesting significant cross-resistance. So far, small studies investigating sequential therapies have shown increasingly poor activity in populations not selected using any kind of predictive biomarker (Mukherji et al. 2014).

Pretreatment of animals with enzalutamide blocks AR-related mechanisms of action of docetaxel; however cabazitaxel retains its activity (van Soest et al. 2015). The same observation has been made in patients receiving this sequence of therapy (Mukherji et al. 2014). This suggests that cabazitaxel might be a better choice for patients with CRPC progressing after docetaxel and one of the newer AR-targeted therapies such as abiraterone or enzalutamide, rather than moving to the alternative AR-targeted therapy. This hypothesis requires confirmation in carefully designed prospective clinical trials.

Conclusion

A number of therapies are currently available for men with mCRPC, providing options to delay symptoms, preserve quality of life, and extend survival. The optimal use of these agents continues to be tested in ongoing trials, and additional therapies are in late-stage testing, offering a promise of further improvements in the near future. While the biological action of some agents suggests that they are likely to be active across the spectrum of CRPC, other agents have more limited or fixed indications for use. There are currently limited data regarding the impact of each treatment on the activity of subsequent agents, and optimal treatment sequences remain uncertain. The use of agents prior to the development of castration-resistant disease will add further complexity to these decisions. It is highly unlikely that most patients will benefit from random sequential use of all therapies, and the cost and toxicity of such an approach will be substantial and possibly unjustifiable. It is hoped that

the development of companion biomarkers and early markers of response or progression may improve the selection and rationalize the use of available agents while better selecting populations for further research.

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Androgen Deprivation Therapy for Advanced Prostate Cancer

15

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Abstract

The current treatment for patients with hormone-sensitive metastatic disease is either medical castration with a luteinizing hormone-releasing hormone (LHRH) agonists, gonadotropin-releasing hormone (GNRH) antagonists, or surgical castration by orchiectomy, either alone or in combination with an anti-androgen. Treatment with a combination of chemotherapy with docetaxel and ADT or abiraterone and ADT demonstrated a significant survival benefit, and this combination is now considered standard of care. For men with castrate-resistant prostate cancer (CRPC), new treatment options with overall survival benefit are available including combined treatment with abiraterone and enzalutamide, nonhormonal therapies like chemotherapy with docetaxel and cabazitaxel, vaccine, and radium-223. According to the recent guidelines, androgen deprivation therapy should be continued.

Introduction

Prostate cancer (PCa) is the most prevalent cancer in men; median survival of patients with newly diagnosed metastases is 4 years (EAU Guidelines 2017; James et al. 2015).

In the 1940s, Huggins and Hodges showed the responsiveness of prostate cancer to androgen deprivation therapy (ADT); since this time, androgen-suppressing strategies are the basis of any management of advanced and metastatic prostate cancer (Huggins and Hodges 1972; EAU Guidelines 2017).

Testosterone suppression can be achieved by orchidectomy, estrogens, luteinizing hormone-releasing hormone (LHRH) agonists, and gonadotropin-releasing hormone (GNRH)

antagonists. Anti-androgens inhibit the action of circulating androgens at the level of their receptor. The normal testosterone concentration in man is age-dependent and is subject to daily fluctuations, with medical or surgical castration serum testosterone levels fall to <50 ng/dL (<1.73 nmol/l).

ADT is increasingly used in earlier disease stages. Multiple phase III randomized trials demonstrated a significant survival benefit for men with locally advanced or high-risk localized prostate cancer when treated with a combination of Radiotherapy (RT) with ADT compared to RT alone (Bolla et al. 2010; Pilepich et al. 2005).

For men treated for advanced prostate cancer, initial response to androgen withdrawal is high; however, this response is only temporary and almost all patients will develop a castrate resistant disease.

Prognostic factors for survival include parameters like number and location of bone metastases, presence of visceral metastases, Gleason score, performance status, and serum parameters like initial PSA, alkaline phosphates, and hemoglobin as well as PSA-response after ADT (Glass et al. 2003; Gravis et al. 2015).

For men with metastatic hormone naive prostate cancer, combined treatment with a combination of chemotherapy with docetaxel and ADT has demonstrated a significant survival benefit, and this combination is now considered standard of care (Sweeney et al. 2015; EAU Guidelines 2017; NCCN Guideline 2017).

For men with castrate-resistant prostate cancer (CRPC), new treatment options with overall survival benefit are available including Abiraterone and Enzalutamide, nonhormonal therapies like chemotherapy with docetaxel and Cabazitaxel, Vaccine, and Radium-223. According to the recent guidelines, androgen deprivation therapy should be continued; this recommendation applies to metastatic CRPC and nonmetastatic CRPC (Merseburger et al. 2015).

Androgen Deprivation Treatment (ADT)

The current treatment for localized, early stage prostate cancer involves either surgery, radiation, active surveillance, or watchful waiting, while the standard treatment for patients with hormone-sensitive metastatic disease is either medical castration with a luteinizing hormone-releasing hormone (LHRH) agonists, gonadotropin-releasing hormone (GNRH) antagonists, or surgical castration by orchiectomy, either alone or in combination with an anti-androgen.

In 1941, Huggins et al. demonstrated the favorable impact of androgen deprivation therapy (ADT) on metastatic prostate cancer (mPCa) (Huggins and Hodges 1972). However, hormone ablation represents a palliative treatment for advanced prostate cancer.

Mechanism of Hormonal Treatment

Growth of prostate cells is androgen-dependent. Testosterone, dehydroepiandrosterone, and androstenedione provide their growth-promoting influence on the prostate cell via the androgen receptor. Ninety percent of androgens are produced in the Leydig cells of the testes, 10% are additionally released by the adrenal cortex (Harris et al. 2009; Chang et al. 2014).

Androgen synthesis is regulated through hypothalamic and pituitary influence. Luteinizing releasing hormone (LHRH) is formed in the hypothalamus and causes the formation and release of the gonadotropins LH (luteinizing hormone) and FSH (follicular-stimulating hormone) from the pituitary anterior lobe. LH stimulates the Leydig intermediate cells to grow and produce androgens. FSH promotes spermiogenesis in man and increases formation of testosterone in the Sertoli cells (Luu-The et al. 2008).

All these mechanisms result in an androgenic release, which in turn controls the hypothalamus-pituitary axis through feedback mechanisms.

Only approximately 10% of the circulating testosterone is unbound (FT), the majority of released testosterone is bound to SHBG (sex hormone binding globulin) or albumin.

In the prostate, testosterone is converted into dihydrotestosterone, which has a significantly higher affinity for the intracellular androgen receptor than testosterone (Chang et al. 2014).

Testosterone-Lowering Therapy (Castration)

Bilateral Orchiectomy

Surgical castration is a primary treatment modality for ADT. It leads to a rapid decline in testosterone levels <50 ng/dL (1.7 nmol/L).

Current analytical methods have shown that the mean testosterone levels after surgical castration is 15 ng/dL (Oefelein et al. 2000). Therefore, a lower level of testosterone <20 ng/dL as definition for castrate level may be more appropriate than the historical <50 ng/dL (1.7 mmol/L).

Bilateral orchiectomy can be performed under local anesthesia (Desmond et al. 1988) and results in castrate levels of testosterone within 12 h; however studies have demonstrated that it leads to more psychological stress compared to medical castration (Nicholson 1986). The majority of patients with advanced or metastatic prostate cancer shows a drug-induced hormonal ablation.

Medical Androgen Depletion

Medical androgen depletion can be achieved by inhibiting testosterone production or by blocking the androgen receptors while maintaining testosterone production. The inhibition of androgen production is achieved by the use of LHRH agonists, LHRH antagonists, and estrogens.

Luteinizing-Hormone-Releasing Hormone (LHRH) Agonists

The luteinizing-releasing hormone (LHRH) is a synthetic decapeptide, which was discovered in 1971. It is secreted in a pulsatile manner by the hypothalamus and has a half-life of 2–5 min (Seidenfeld et al. 2000).

LHRH analogues bind to the LHRH receptor with high affinity resulting in increased secretion of FSH and LH and increased testosterone production.

The constant receptor stimulation results in a down-regulation of the pituitary receptor with a paradoxical and sustained drop in gonadotropin secretion. This downregulation occurs after 7–10 days. While this phase is reversible, it can be maintained when GnRH agonists treatment is continued (Seidenfeld et al. 2000).

Since 1980, LHRH analogues have been used for clinical purposes. Synthetic long-acting LHRH agonists are the most commonly used forms of ADT.

These analogues of LHRH were initially administered by daily subcutaneous injections or nasal inhalations. Today long-acting depot formulations with 1-, 2-, 3-, 6-monthly or yearly basis are used and have significantly improved the compliance of treatment.

The different products have practical differences that need to be considered in daily practice, including optimal storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection (EAU Guidelines 2017).

It is important to carefully follow the directions for using a particular drug to avoid any misuse.

No direct comparison exists between the different agonists; however, they are considered equally effective and sufficient testosterone suppression is usually obtained after 2–4 weeks (Klotz et al. 2008).

The "flare-up" at the beginning of the treatment with increased testosterone production may lead to a clinical "flare phenomenon" in advanced disease which may include increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and fatal cardiovascular events due to hypercoagulation status and delays the therapeutic benefit. Patients at risk are patients with high-volume, symptomatic bony disease, which account for 4–10% of metastatic patients. To prevent "flare-up," antiandrogens should be started one week before administration of the LHRH analogue and should be continued for a 2-week period (EAU guideline 2017).

Gonadotropin-Releasing Hormone (GnRH) Antagonists

These receptor blockers antagonize the gonadotropin-releasing hormone receptor (GnRHR) in the pituitary and thus the action of

GnRH. GnRH antagonists compete with natural GnRH for binding to GnRH receptors; thus decreasing or blocking GnRH action leading to a rapid decrease in LH, FSH, and testosterone levels.

Unlike the LHRH agonists, which cause an initial stimulation of the hypothalamic-pituitary-gonadal axis, leading to a surge in testosterone levels, GnRH antagonists have an immediate onset of action, rapidly reducing sex hormone levels without an initial surge (Van Poppel and Nilsson 2008; EAU Guidelines 2017).

Currently approved GnRH antagonists include the following four drugs:

Degarelix, Abarelix, Cetrorelix, and Ganirelix; these are administered either by intramuscular injection or by subcutaneous injection. Elagolix, a non-peptide, orally-active GnRH antagonist which is still in development, is administered orally.

The practical shortcoming of these compounds is the lack of a long-acting depot formulation with only monthly formulations being available.

Degarelix, which is the most commonly used component, is an LHRH antagonist with a monthly subcutaneous formulation. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at day 3 (Crawford et al. 2011). Data suggest a lower cardiotoxicity compared to orchiectomy or LHRH analoga (Albertsen et al. 2014).

Estrogens

Estrogens were the first substances used as an alternative to orchiectomy for the hormonal treatment of metastatic prostate cancer.

They resulted in a drop of LH serum level and consequently of testosterone level within several weeks. However, increased cardiovascular complications, which were dose-dependent, were observed in the therapy with estrogens. Due to the cardiotoxicity, estrogens are not considered as standard treatment (EAU Guidelines 2017).

Antiandrogens

These compounds are classified according to their chemical structure as.

Steroidal antiandrogens, e.g., cyproterone acetate (CPA), megestrol acetate, and medroxyprogesterone acetate and nonsteroidal, e.g., bicalutamide, flutamide, and nilutamide, which lead to an unchanged or slightly elevated testosterone level. Younger patients may benefit from such treatment, as side effects like libido and erectile dysfunction are less often observed. Side effects of the nonsteroidal antiandrogens include gynecomastia and mastodynia; liver function disorders may also occur with potential severe liver toxicity (EAU Guidelines 2017).

Steroidal Antiandrogens

Steroidal antiandrogens influence LH release due to the additional progesterone-like effect, thus inhibiting testosterone production. Both compounds compete with endogenous androgens for binding on the androgen receptor (Cornford et al. 2017).

Cyproterone Acetate

Cyproterone acetate is an antiandrogen and progestogen; it is available orally and i.m. with a half-life of 40 h. It was first marketed in 1973 and was the first antiandrogen to be introduced for medical use. The drug is available widely throughout the world, but is not approved for use in the United States (Index Nominum 2000).

It blocks the effect of testosterone as well as testosterone production. Side effects include gynecomastia and feminization in general, sexual dysfunction, mental symptoms like depression, fatigue, liver toxicity, and adrenal insufficiency.

Nonsteroidal Antiandrogens

Nonsteroidal antiandrogens do not suppress testosterone secretion, and this may preserve libido, overall physical performance, and bone mineral density (Smith et al. 2004).

Bicalutamide

Bicalutamide is the most widely used antiandrogen in the treatment of prostate cancer. It is well-absorbed, the half-life is 6 days. It is approved at a dosage of 50 mg/day as combination therapy with a LHRH analogue or orchiectomy and as monotherapy at a dosage of 150 mg/day for the treatment of stage C or D1 locally advanced prostate cancer. Bicalutamide is not indicated for the treatment of localized prostate cancer due to negative findings in the Early Prostate Cancer (EPC) trial (Wellington and Keam 2006; Wirth et al. 2004).

Common side effects include breast enlargement, breast tenderness, hot flashes, and constipation as well as feminization and changes in mood and liver as well as lung toxicity; monitoring of liver enzymes is recommended during treatment (Schellhammer and Davis 2004).

Flutamide

Flutamide is a synthetic, nonsteroidal antiandrogen (NSAA), which has been largely replaced by newer NSAAs, namely, bicalutamide due to better safety, tolerability, and pharmacokinetic profiles. Flutamide has been studied as monotherapy. Flutamide is a pro-drug, and the half-life of the active metabolite is 5–6 h, leading to a three times daily use. The recommended daily dosage is 750 mg. The non-androgen pharmacological side-effect of flutamide is diarrhea and hepatotoxicity; it does not appear to have a risk of cardiovascular side effects (Goldspiel and Kohler 1990).

Extragonadal ablation of androgen synthesis from precursors through inhibition of cytochrome P450 17α-hydroxy/17,20-lyase (CYP17) enzymes like Abiraterone have already been approved for men with mCRPC. Newer CYP17 inhibitors like orteronel and galeterone continue to be developed which are either more selective or have concomitant inhibitory actions on AR signaling (Cornford et al. 2017).

Abiraterone Acetate

Abiraterone acetate (AA) is a CYP17 inhibitor (a combination of 17 hydrolase and 17–20 lyase inhibition). By blocking CYP17, AA significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone (2 × 5 mg) to prevent drug-induced hyperaldosteronism.

Based on the results of the COU-AA-301 trial, the FDA approved the use of Abiraterone for the treatment of mCRPC in the post-chemotherapy setting in April 2011 (De Bono et al. 2011). The COU-AA 301 trial observed an overall survival (OS) benefit, increase in time to prostate-specific antigen (PSA) progression and progression-free survival (PFS) (median OS, 15.8 versus 11.2 months; median time to PSA progression, 8.5 versus 6.6 months; median radiologic PFS, 5.6 versus 3.6 months). Later studies have demonstrated its efficacy in chemotherapy-naïve patients with mCRPC. In a phase III randomized trial with a median follow up of more than 4 years, treatment with AA prolonged OS compared with prednisone alone (34.7 versus 30.3 months; hazard ratio (HR), 0.81), suggesting its favorable efficacy and safety profile in CRPCa chemotherapy-naive patients as well (Ryan et al. 2015).

Orteronel

Orteronel (TAK-700) is an oral, nonsteroidal CYP17A1 inhibitor. It completed two phase III clinical trials for metastatic, hormone-refractory prostate cancer but failed to extend overall survival rates, and development was voluntarily terminated as a result (Alex et al. 2016).

However, when men were stratified by regions, a significant improvement in OS was seen in men in the non-Europe/North American regions (15.3 versus 10.1 months, $p = 0.019$), despite having similar baseline clinical and disease characteristics. This discrepancy in OS by region may have been related to the decreased exposure to post-trial

treatment with AA and enzalutamide, as these agents were available earlier in North American and European regions (Alex et al. 2016; Poorthuis et al. 2017).

Galeterone

Galeterone is a CYP17 inhibitor with multiple mechanisms of action, including CYP17 inhibition, AR antagonism, and decrease in intratumoral AR levels. Preclinical results indicate that treatment with Galeterone caused marked downregulation of AR protein expression, in contrast to treatments with bicalutamide or androgen deprivation therapy (ADT), which may induce upregulation of AR protein expression. It also caused a significant reduction in tumor growth compared with AA (Alex et al. 2016; Poorthuis et al. 2017).

Ketoconazole

Ketoconazole is a synthetic imidazole antifungal drug used primarily to treat fungal infections.

Ketoconazole inhibits the activity of several enzymes necessary for the conversion of cholesterol to steroid hormones through inhibition of 17α-hydroxylase and 17,20-lyase. Based on these antiandrogen and antiglucocorticoid effects, ketoconazole has been used with some success as a second-line treatment for certain forms of advanced prostate cancer (Zelefsky et al. 2008). Ketoconazole is an androgen receptor antagonist, competing with androgens such as testosterone and dihydrotestosterone (DHT) for binding to the androgen receptor.

However, in the treatment of prostate cancer, concomitant glucocorticoid administration is needed to prevent adrenal insufficiency (Mahler et al. 1993).

In 2013, the European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) recommended not to use oral ketoconazole for systemic use in humans throughout the European Union, after concluding that the risk of serious liver injury from systemic ketoconazole outweighs its benefits.

The recent NCCN guideline still recommends its use as an option for men with metastatic CRPCA (NCCN guideline 2017).

Enzalutamide

Enzalutamide is a synthetic nonsteroidal antiandrogen with a half-life of 8–9 days and a higher affinity than bicalutamide for the AR receptor. In 2012, the FDA approved enzalutamide for the treatment of castration-resistant prostate cancer based on the results of the AFFIRM trial (Scher et al. 2012). Enzalutamide induces enzyme activity of CYP3A4, CYP2C9, and CYP2C19.

Side effects of enzalutamide include gynecomastia, breast pain, fatigue, diarrhea, hot flashes, headache, sexual dysfunction, and seizures. Other side effects include neutropenia, anxiety, cognitive disorder, memory impairment, hypertension, dry skin, and pruritus (Tombal et al. 2015).

Apalutamid

Apalutamide (ARN-509, JNJ-56021927) is a nonsteroidal antiandrogen and selective competitive antagonist of the androgen receptor. It has a 5- to ten-fold greater affinity for the AR compared to bicalutamide. Apalutamide is currently tested in phase III clinical trials in men with castration-resistant prostate cancer. Based on the positive findings in the PHASE III Trial SPARTAN in men with M0 CRPCA, this drug is approved for treatment in men with short PSA-doubing time and no evidence for metastatic disease (N Engl J Med. 2018 Apr 12;378(15):1408-1418).

Apalutamide may also be effective in a subset of prostate cancer patients with acquired resistance to abiraterone acetate. Apalutamide shows potent induction potential of CYP3A4 similarly to enzalutamide (Fizazi et al. 2015).

Complete Androgen Blockade (CAB)

The CAB (also known as Maximum Androgen Blockade (MAB)) includes the additional administration of an antiandrogens for hormonal ablation followed by orchiectomy or administration of an LH-RH analogue. A clinical benefit in the primary therapy of metastatic hormonal prostate carcinoma has been studied in numerous studies.

Antiandrogens produce an inhibition of ligand binding of the androgen receptor and an inhibition of androgen-independent activation of the receptor. Over the last 25 years, more than 30 clinical trials of CAB versus monotherapy have been published.

The largest randomized controlled trial in 1286 M1b patients found no difference between surgical castration with or without flutamide (Eisenberger et al. 1998).

The Prostate Cancer Trialists' Collaboration Group meta-analysis on the MAB demonstrated a nonsignificant 2% benefit in 5-year survival in patients with a maximum androgen blockade (Schmitt et al. 2000). While the subgroup analysis of MAB with nilutamide or flutamide resulted in a significant 5-year survival benefit in favor of the complete blockade of 3%; this advantage in a small subset of patients must be balanced against the increased side effects associated with long-term use of NSAAs.

Intermittent Androgen Deprivation Therapy (IAD)

The intermittent androgen blockade includes an induction phase with ADT over a period of 6–9 months. If a response to therapy is seen, treatment is stopped to allow testicular function to recover.

This may result in a potential decrease in specific side effects like, e.g., hot flushes and an improvement in erectile function, bone health, and quality of life.

When tumor progression is observed under normalized testosterone values, a new treatment with ADT is started. Multiple reviews (Niraula et al. 2013; Sciarra and Salciccia 2014; Botrel et al. 2014) and a meta-analysis (Brungs et al. 2014) analyzed the clinical efficacy of IAD.

So far, the SWOG 9346 (Hussain et al. 2013) is the largest trial conducted in M1b patients. Out of 3040 selected patients in the SWOG 9346 trial, 1535 were randomized based on the inclusion criteria set. This non-inferiority trial led to inconclusive results, the pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, inferior survival with IAD cannot be completely ruled out based on this study.

Other trials did not show any survival difference. These reviews and the meta-analysis concluded that there was no difference in OS or CSS between IAD and continuous androgen deprivation but a trend favoring IAD in terms of QoL, especially regarding treatment-related side effects (Verhagen et al. Verhagen et al. 2014).

According to the EAU, guidelines following recommendations can be made: The induction cycle should be 6–9 months; ADT should be stopped only if patients is well-informed and compliant, and no clinical progression and clear PSA response is seen, empirically defined as a PSA < 4 ng/mL in metastatic disease. Treatment with ADT is restarted when the patient progresses clinically or has a PSA rising above a predetermined threshold (Sciarra and Salciccia 2014).

Side Effects of Androgen Deprivation

By lowering testosterone serum level to the level of the castration, specific side effects like physical weakness, fatigue, hot flashes, loss of libido, erectile dysfunction, gynecomastia, mood swings, anemia, and osteoporosis may occur.

A systematic review of side-effects of long-term ADT has recently been published by Ahmadi and Daneshmand (2013).

Hot flushes are one of the most common side-effect of ADT and will significantly influence QoL. Other systemic side-effects of androgen-deprivation therapy include nonmetastatic bone fractures with an increased risk of up to 45% with long-term ADT (Smith et al. 2006).

An evaluation of Bone Mineral Density (BMD) should be performed in patients at risk by dual emission X-ray absorptiometry (DEXA) scan before initiating long-term ADT. An initial low BMD indicates a high risk of subsequent nonmetastatic fracture. For evaluating individual risk, WHO FRAX tool (http://www.shef.ac.uk/FRAX) should be used (EAU Guidelines 2017).

Metabolic effects include lipid alterations as well as also decreased insulin sensitivity and increases fasting plasma insulin levels and increased risk for the metabolic syndrome (Saylor and Smith 2009; Grundy et al. 2005).

Metabolic syndrome is an association of cardiovascular disease risk factors. The definition requires at least three of the following criteria like waist circumference >102 cm; serum triglyceride >1.7 mmol/L; blood pressure >130/80 mmHg or use of medication for hypertension; High-density lipoprotein (HDL) cholesterol <1 mmol/L; glycemia >5.6 mmol/L or the use of medication for hyperglycemia.

The published data regarding cardiovascular morbidity are inconclusive.

ADT is associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction (Keating et al. 2010). However, the RTOG 92-02 trial demonstrated no increase in cardiovascular mortality in men with locally advanced prostate cancer with longer duration of adjuvant LHRH therapy (Efstathiou et al. 2008).

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists (Albertsen et al. 2014).

However, to reduce the cardiovascular risk, patients should be encouraged to adopt lifestyle changes with increased physical activity, cessation of smoking, decreased alcohol consumption, and normalization of BMI (EAU Guidelines 2017).

Primary ADT for Nonmetastatic Prostate Cancer

Treatment with curative intent includes surgery and radiation therapy as well as delayed treatment with active surveillance.

If a patient decides against a therapy with curative intent, he should be informed about the concept of watchful waiting with symptom-dependent palliative intervention and an immediate ADT. Patients should understand that both options are palliative and that the immediate ADT is associated with adverse effects (EAU Guidleine 2017).

Immediate ADT is associated with improved progression-free survival but the effect on overall survival for men with nonmetastatic prostate cancer is unclear (Studer et al. 2006).

Neoadjuvant ADT of Localized Prostate Cancer Prior to Surgical Therapy

The goal of neoadjuvant as well as adjuvant therapy is to improve long-term survival for patients with high-risk disease. Neoadjuvant therapy may also provide a down-staging of locally advanced prostate cancer and improve surgical resection.

To assess the effect of neoadjuvant combination, ADT administered for 3 months before radical prostatectomy; Labrie et al. performed a prospective trial using leuprolide and flutamide for 3 months prior to RP compared to RP alone (Labrie et al. 1997).

The study showed that neoadjuvant combination ADT decreased positive surgical margins from 33.8% to 7.8% and resulted in down-staging in 54% in the neoadjuvant arm. In addition, pCRs were found in six RP specimens (6.7%). The authors concluded that the influence of neoadjuvant combination therapy on the stage of the disease suggests a major improvement in the morbidity and mortality from prostate cancer and that longer duration of neoadjuvant ADT could potentially increase the degree of benefit (Labrie et al. 1997).

A systematic review and meta-analysis of randomized trials of neo-adjuvant hormone therapy (NHT) in localized and locally advanced prostate cancer showed that neoadjuvant therapy had a beneficial and statistically significant impact in lowering the pathologic T stage, increasing the organ-confined rate, lowering the positive

surgical margin rate, and decreasing the number of pathologic N1 cases (Shelley et al. 2009).

The effect on positive surgical margins and organ-confined rates was significantly better with 8 months of neoadjuvant treatment as compared to only 3 months of treatment.

However, NHT prior to prostatectomy did not improve overall or disease-free survival. The beneficial effects on pathologic outcomes did not translate to improved DFS or OS. The DFS at 5 years, defined either as biochemical or clinical progression, remained unchanged between the treatment and control groups. The authors concluded that NHT is associated with significant clinical benefit when given with radiotherapy and improves pathological outcome prior to prostatectomy but is of minimal value prior to radical prostatectomy. The decision to use hormone therapy should be discussed between the patient, the clinician, and policy maker based on the benefits, toxicity, and cost.

Based on these findings, the recent guidelines do not recommend the use of neoadjuavant ADT before surgery. Approval of neoadjuvant therapy prior to RP in patients with high-risk prostate cancer will depend on positive results from well-designed phase III trials (McKay et al. 2013).

Adjuvant Androgen Ablation in Men with Localized Prostate Carcinoma After Surgical Therapy

Whether adjuvant treatment options improve overall survival for men treated with radical prostatectomy has been studied in various prospective randomized trials. One of the largest prospective studies was the Early Prostate Cancer (EPC) study, which examined the effect of adjuvant administration of bicalutamide (150 mg per day) versus standard care in different patient groups (Wirth et al. 2004).

For locally advanced tumors, after an average follow-up period of 7.4 years, an advantage could be shown in the clinical progression-free survival; no significant difference was found in overall survival.

A similar result was demonstrated by the trial with the antiandrogen flutamide in the dosage 3 × 250 mg; even after a median follow-up of 6.1 years, no difference in overall survival was seen; however, an improved progression-free survival was found.

The prospective randomized study by Messing et al. investigated the effect of immediate adjuvant hormonal therapy versus a delayed hormonal therapy at the time of clinical progression in patients with lymph node metastases who had received a radical prostatectomy with lymphadenectomy (Messing et al. 2006).

This study demonstrated a clear survival benefit for patients with lymph node metastases for immediate adjuvant hormone therapy.

However, this study was criticized for several reasons; on the one hand, the number of patients being 98 was low and patients included in this trial had high-volume N+ disease and adverse tumor parameters, and, on the other hand, patients in the control arm did not receive hormone therapy at the time of PSA progression but only at clinical progression.

According to the recent guidelines, should the possible benefits be judged against the potential side effects of long-term HT. Delaying the initiation of HT until PSA progression is an acceptable option in selected cases with <2 microscopically involved lymph nodes in an extended nodal dissection EAU Guidelines (2017).

Neoadjuvant/Adjuvant ADT for Localized and Locally Advanced Prostate Cancer in Men Treated with Radiation Therapy

Whether neoadjuvant and/or adjuvant ADT improves the results of radiation therapy in prostate cancer has also been investigated in numerous prospective randomized studies. These trials included high-risk PCa patients, mostly locally advanced prostate cancer (T3-T4 N0-X), as well as high-risk localized, T1-2, N0-X prostate cancer. The most powerful conclusion from these studies comes from the EORTC 22863 trial, which is the basis for the combination of RT and ADT in patients with locally advanced PCa as standard of care (Bolla et al. 2009).

For men with medium- or high-risk prostate cancer, these trial have demonstrated a clear survival advantage for additional ADT.

The current guidelines therefore recommend neoadjuvant and adjuvant hormonal therapy before and after radiotherapy in patients with localized prostate carcinoma and high risk according to the D'Amico classification as well as in patients with locally limited prostate carcinoma and intermediate risk (Hernandez et al. 2007).

However, the optimal duration of adjuvant hormone therapy after radiotherapy has not yet been conclusively clarified.

The data of Bolla et al. show that adjuvant therapy for 3 years significantly improves survival, but there are open questions about the hormone withdrawal with regard to the type of hormone therapy (LHRH-agonists alone versus maximum androgen blockade or testosterone receptor blockade alone or GNRH-antagonists).

According to the recent guidelines, ADT is started either at the onset of RT (for adjuvant ADT) or 2 or 3 months before (for neoadjuvant) long-term ADT, ranging from 2 to 3 years, is recommended for locally advanced disease rather than short term (6-months) (Bolla et al. 2009; Denham et al. 2011).

If a long-term ADT is necessary in patients with intermediate- or high-risk localized PCa is unclear. The use of short-term ADT for 4 months before and during radiotherapy was associated with significantly decreased disease-specific mortality and increased overall survival (RTOG 94-08). According to post hoc risk analysis, the benefit was mainly seen in intermediate-risk, but not low-risk, men (Jones et al. 2011) (Tables 1 and 2).

ADT for Biochemical Recurrence After Treatment with Curative Intent (Surgery/Radiation)

Cure rates for surgery or radiation for localized prostate cancer are depending on primary risk classification; biochemical failure can be observed in up to 30–50% (EAU Guidelines 2017).

The timing as well as the mode of treatment for PSA-only recurrences after RP or RT are still controversial.

Following RP, biochemical recurrence may be defined by two consecutive PSA values of >0.2 ng/mL (Moul 2000).

Following RT, according to the RTOG-ASTRO Phoenix Consensus Conference definition, biochemical recurrence may be defined by any PSA increase >2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir (Roach 3rd et al. 2006).

Therapeutic options for biochemical recurrence after rad. Prostatectomy include radiotherapy at least to the prostatic bed; androgen deprivation therapy, intermittent androgen deprivation (IAD), as well as observation. Therapeutic options for patients with biochemical progression post radiation include ADT or local procedures such as Salvage Radical Prostatectomy (SRP), cryotherapy, interstitial brachytherapy, and HIFU (Heidenreich et al. 2008; Ahlering et al. 1992; Zincke 1992; Lerner et al. 1995). Patients in the low-risk subgroup typically respond very well to salvage RT with a high probability of PSA being undetectable (Briganti et al. 2014).

Adding ADT to salvage RT has shown benefit in terms of biochemical PFS in retrospective series (Goenka et al. 2012; Choo et al. 2009) and in PFS for "high-risk" tumors (Soto et al. 2012); however, data from prospective randomized trials are missing.

Ongoing trials include the Radiation Therapy Oncology Group RTOG 96-01 comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting and the French GETUG 16 trial, comparing salvage EBRT with or without 6 months of ADT (EAU Guidelines 2017).

Recent data from RTOG 9601 suggested both CSS and OS benefits for adding 2 years of bicalutamide to SRT. According to GETUG-AFU 16, also 6 months treatment with gonadotropin-releasing hormone (GnRH) analogue can improve 5-year PFS significantly.

Clinical effectiveness of ADT after curative therapy is still unclear and the published data are inconsistent; a favorable effect was reported for high-risk patients with a short PSA-DT by Boorjian et al. (2011).

Because of the unproven benefit of early ADT for biochemical recurrence, the treatment

Table 1 Neoadjuvant or adjuvant hormone therapy plus radiotherapy (EAU Guidelines 2017). For men with locally advanced disease or high-risk patients, the combination of RT with ADT is superior to RT alone followed by deferred ADT on relapse, as shown by phase III RCTs. For intermediate risk, 6 months of ADT is recommended, for high-risk patients, up to 3 years of ADT is recommended. Studies of ADT in combination with RT for PCa

Trial	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65–70 Gy RT	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with GS 7–10
RTOG 94-13	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65–70 Gy RT	No significant difference at 10 yr
D'Amico AV, et	T2 N0 M0 (localized unfavorable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	Significant benefit (HR: 0·55, 95% CI: 0.34-0.90, p = 0.01) that may pertain only to men with no or minimal comorbidity
RTOG 92-02 [	T2c-4 N0-1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 yr. as adjuvant after 4 mo. as neoadjuvant	65–70 Gy RT	p = 0.73, p = 0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with GS 8–10
EORTC 22961	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr	70 Gy 3D-CRT	Better result with 3 yr. treatment than with 6 mo. (3.8% improvement in survival at 5 yr)
EORTC 22863	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist For 3 yr. (adjuvant)	70 Gy RT	Significant benefit at 10 yr. for combined treatment (HR: 0.60, 95% CI: 0.45–0.80, p = 0.0004).
TROG 96-01	T2b-4 N0 M0	802	Neoadjuvant ADT duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in OS reported; benefit in PCa-specific survival (HR: 0.56, 95% CI: 0.32–0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65–1.08; p = 0.18)
RTOG 99-10	intermediate risk (94% T1-T2, 6% T3-4)	1579	Short vs. prolonged ADT	LHRH agonist 8 + 8 vs. 8 + 28 wk	70.2 Gy 2D/3D	67 vs. 68% p = 0.62, confirms 8 + 8 wk. LHRH as a standard

ADT androgen deprivation therapy, *CI* confidence interval, *EBRT* external beam radiotherapy in standard fractionation, *GS* gleason score, *HR* hazard ratio, *LHRH* luteinizing hormone-releasing hormone, *mo* months, *n* number of patients, *OS* overall survival, *RP* radical prostatectomy, *RT* radiotherapy, *wk* week, *yr* year

Table 2 Studies of ADT in combination with or without RT for PCa (EAU Guidelines 2017)

Trial	Year	TNM stage	n	Trial	ADT	RT	Effect on OS
SPCG-7/ SFUO-3	2014	T1b-2 Grade 2–3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo. plus continuous flutamide	70 Gy 3D-CRT vs. no RT	18.9% (30.7%) vs. 8.3% (12.4%) CSM at 10 (15) yr. favouring combined treatment (HR: 0.35; $p < 0.0001$ for 15-yr results) NCIC CTG PR.3/MRC
PRO7/ SWOG	2015	T3-4 (88%), PSA > 20 ng/ mL (64%), GS 8-10 (36%) N0 M0	1205	ADT ± EBRT	Continuous LHRH agonist	65–70 Gy 3D-CRT vs. no RT	10-yr OS = 49% vs. 55% favoring combined treatment HR: 0.7, $p < 0.001$)
Mottet 2012	2012	T3-4 N0 M0	273 264	ADT ± EBRT	LHRH agonist for 3 yr	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr OS 71.4% vs. 71.5%

ADT androgen deprivation therapy, *CSM* cancer-spefic mortality, *EBRT* external beam radiotherapy, *GS* gleason score, *HR* hazard ratio, *LHRH* luteinizing hormone-releasing hormone, *mo* months, *n* number of patients, *OS* overall survival, *RT* radiotherapy

approach should be individualized based on a risk stratification with patient-specific factors like age, comorbidity, patient preferences, as well as disease-specific factors like Gleason score and PSA-DT (Zumsteg et al. 2015).

According to the recent EAU guideline, early HT should be recommended for patients with a high risk of disease progression with short PSA-DT at relapse (<6–12 months) and/or a high initial Gleason score (>7), and a long life expectancy.

For all other patients, the potential benefits of salvage HT should be balanced against its potential harms EAU Guidelines (2017); this is comparable to the German S3 guideline, which considers ADT for biochemical recurrence for men with a PSA doubling time <3 months and or symptomatic local progression.

First-Line Hormonal Treatment for Metastatic Prostate Cancer

For patients with symptomatic metastatic prostate cancer, ADT is standard of care for the past decades and should be recommended (Pagliarulo et al. 2012; EAU Guidelines 2017).

For symptomatic treatment, ADT is the preferred causal treatment option due to the good response rates in hormone naive prostate carcinomas and the demonstrated prolongation of progression-free survival.

Androgen deprivation therapy in addition has a significant effect on skeletal related events (SRE) and other complications, e.g., obstruction and hematuria.

However, the treatment of hormone-naive PCa noma has changed in the last 5 years based on the presented data from large randomized controlled trials, demonstrating a significant survival benefit for patients with metastasis when a combination of ADT with chemotherapy with docetaxel is given (Gravis et al. 2013; Sweeney et al. 2015; James et al. 2015).

Three trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks). Chemotherapy was given within 3 months of ADT initiation. The primary objective in all 3 studies was overall survival.

In the CHAARTED trial, all patients with newly diagnosed M1 Pca disease were included and patients were stratified according to disease volume; high volume being defined as either presence of visceral metastases or four or more bone metastases, with at least one outside the spine and pelvis (Sweeney et al. 2015). In the french

Table 3 Hormonal treatment combined with chemotherapy (EAU Guidelines 2017)

Study	Population	n	Med FU (mo)	Median OS (mo)		HR	p-value
				ADT + D	ADT		
Gravis, et al	M1	385	50	58.9	54.2	1.01 (0.75–1.36)	0.955
ASCO GU 2015	HV: 47%		82.9	60.9	46.5	0.9 (0.7–1.2)	0.44
Sweeney et al.	M1 HV: 65%	790	28.9	57.6	44	0.61 (0.47–0.8)	< 0.001
STAMPEDE	M1 [61%]/N+ [15%]/relapse	1184 /593 (D) 593 (D + ZA)		81 76	71 n.r.	0.78 (0.66–0.93) 0.82 (0.69–0.97)	0.006 0.022
	M1 only	725 + 362 (D)		60	45	0.76 (0.62–0.92)	0.005

D docetaxel, *FU* follow-up, *HR* hazard ratio, *HV* high volume: either visceral metastases or more than four bone metastases, with at least one outside the spine and pelvis, *n* number of patients, *n.r.* not reported, *ZA* zoledronic acid

GETUG 15 trial, the same inclusion criteria applied (Gravis et al. 2013).

The STAMPEDE is a multi-arm, multi-stage trial in which the reference arm standard of care ADT monotherapy included 1184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593 patients) (James et al. 2015).

Based on these data, upfront docetaxel combined with ADT should be considered as a new standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug (Vale et al. 2016) (Table 3).

Men with newly diagnosed metastases represent an inhomogeneous group of patients with a median survival of at least 42 months (James et al. 2015).

Different prognostic factors for survival have been suggested like number and location of bone metastases, presence of visceral metastases, Gleason score, Performance status, and initial PSA alkaline phosphatase but none of these parameters have been validated in a direct comparison (Gravis et al. 2015).

In the Charted trials, the number and location of bone metastases and the presence of visceral lesion were used as prognostic factors (Sweeney et al. 2015).

Prognostic groups can also be separated according to PSA response after ADT. In the SWOG 9346 trial, PSA level 7 months after ADT differentiated 3 prognostic groups, group 1 with a PSA < 0.2 ng/mL had a median survival of 75 months, group 2 with a PSA < 4 ng/mL had a median survival of 44 months, and group 3 with a PSA > 4 ng/mL had a median survival of only 13 months (Hussain et al. 2006).

Androgen Deprivation Combined with Other Agents

Combination with Abiraterone Acetate

A paradigm shift in the treatment of patients with mPCa has also been initiated by the results of 2 major phase-3 clinical trials (STAMPEDE Arm G, LATITUDE): They demonstrated also a significant advantage of ADT in combination with abiraterone/prednisone over ADT alone.

In the two large RCTs STAMPEDE and LATITUDE the addition of abiraterone acetate (1000 mg daily) plus Prednisone (5 mg daily) (AA plus P) to ADT in men with hormone-sensitive metastatic prostate cancer (mHSPC) was studied (Fizazi et al. 2017; James et al. 2017). Primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit of 38% at 3 years (HR: 0.62).

All secondary objectives such as progression-free survival, time to radiographic progression, time to pain, or time to chemotherapy were in favor of the combination.

Based on these data, upfront docetaxel or abiraterone combined with ADT should be

Table 4 Results from the STAMPEDE arm G and LATITUDE studies (EAU Guidelines 2017)

	STAMPEDE [James]		LATITUDE [Fizazi]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
n	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT – newly diagnosed M1 or N+ situations – locally advanced (at least two of cT3 cT4, GS $\geq$ 8, PSA $\geq$ 40 ng/mL) – relapsing locally treated disease with a PSA $>$ 4 ng/mL and a PSA-DT $<$ 6 mo. OR PSA $>$ 20 ng/mL, OR nodal OR metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: GS $\geq$ 8, $\geq$ 3 bone lesions, measurable visceral metastasis	
Primary objective	Overall survival		Overall survival Radiographic progression-free survival	
Median follow up (mo)	40		30.4	
3 years overall survival	83% (ADT + AA + P) 76% (ADT)		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.63 (0.52–0.76)		0.62 (0.51–0.76)	
M1 only				
n=	1002		1199	
3 years overall survival	NA		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.61 (0.49–0.75)		0.62 (0.51–0.76)	
HR	Failure-free survival (biological, radiological, clinical or death): 0.29 (0.25–0.34)		Radiographic progression-free survival: 0.49 (0.39–0.53)	

AA abiraterone acetate, *ADT* androgen deprivation therapy, *CI* confidence interval, *GS* gleason score, *HR* hazard ratio, *mo* month, *n* number of patients, *NA* not available, *P* prednisone

considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive these drugs (Table 4).

Castration Resistent Prostate Cancer (CRPCa)

According to the recent guidelines, CRPCa is defined as serum levels of testosterone $<$50 ng/dL or 1.7 nmol/L plus either biochemical progression with three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA $>$ 2 ng/mL or radiological progression according to the RECIST (Response Evaluation Criteria in Solid Tumors) (EAU guideline 2017).

All clinical trials in mCRPC include patients who maintain castrate levels of testosterone, and so clinical practice should adhere to this principle of continuing ADT when initiating abiraterone, enzalutamide, or chemotherapy (Merseburger et al. 2015).

The European Association of Urology (EAU) guideline clearly states that when castrate-resistant prostate cancer (CRPC) develops, androgen deprivation therapy (ADT) should be continued indefinitely; this recommendation applies to metastatic CRPC (mCRPC) and nonmetastatic CRPC (nmCRPC) EAU Guidelines (2017). Other guidance, such as that from the American Urological Association (AUA) (Cookson et al. 2013) and the National Comprehensive Cancer Network (NCCN) (NCCN 2017), likewise mention the need to maintain ADT when CRPC develops.

Treatment options with proven survival benefit in CRPCa to target the endocrine pathways include Abiraterone and Enzalutamide, nonhormonal therapies like chemotherapy with docetaxel and Cabazitaxel, Vaccine, and Radium-223.

Table 5 Randomized phase III controlled trials – first-line treatment of metastatic castration-resistant PCa (EAU Guidelines 2017)

ABIRATERONE				
COU-AA-302 Ryan CJ et al. 2013	abiraterone + prednisone	placebo + prednisone	No previous docetaxel ECOG 0–1 PSA or radiographic progression No or mild symptoms No visceral metastases	OS: 34.7 vs. 30.3 mo. (HR: 0.81 p = 0.0033) FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo. p < 0.0001)
ENZALUTAMIDE				
PREVAIL Beer TM et al.	enzalutamide	placebo	No previous docetaxel ECOG 0–1 PSA or radiographic progression No or mild symptoms 10% had visceral mets	OS: 32.4 vs. 30.2 mo. (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60–0.84) rPFS: 20.0 mo. vs. 5.4 mo. HR: 0.186 (95% CI: 0.15–0.23) p < 0.0001)

Abiraterone selectively inhibits the enzyme 17 α-hydroxylaze/C17, 20-lyase (CYP17) and thus inhibits androgen biosynthesis (Attard et al. 2005). Abiraterone also has direct activity on reducing the expression of the androgen receptor gene (Soifer et al. 2012).

Therefore, the need to eliminate as many parts of the androgen receptor signaling pathway as possible provides a rationale for combining abiraterone with ADT. Crucially, experimental evidence suggests that the testosterone suppression achieved by abiraterone monotherapy is not sustained in noncastrated men and is overcome by a subsequent 2- to three-fold surge in luteinizing hormone (LH) levels (O'Donnell et al. 2004). Conversely, the addition of abiraterone to backbone ADT results in sustained decreases in testosterone and adrenal steroid concentrations (Ryan et al. 2014). Although the pharmacokinetic study of O'Donnell et al. (2004) assessed a small number of men, it does suggest a need to maintain castrate levels of testosterone with ADT when initiating abiraterone therapy.

This rationale of combining ADT with abiraterone has been used in phase III trials. The efficacy of abiraterone (plus prednisolone) was demonstrated in two pivotal trials in patients with mCRPC; in one study, abiraterone was used before chemotherapy, and in another study, it was used after chemotherapy (Ryan et al. 2010; Fizazi et al. 2012). Importantly, castration levels of testosterone were maintained in both these studies with the continuation of ADT.

Clinical trials of enzalutamide in men with CRPC included the need for castration maintenance with ADT, and these studies have shown that this combination improved OS when used before chemotherapy and after chemotherapy (Scher et al. 2012).

Androgen receptor signaling persists during castration, and several mechanisms may be responsible for this persistence (Merseburger et al. 2015). Addition of androgen receptor blockers to ADT may achieve a more complete androgen blockade (Tables 5 and 6).

Since quality of life aspects are important, patients on ADT should be counceled regarding the management of side effects.

The british NICE guideline gives recommendation for managing possible adverse effects of hormone therapy (Graham et al. 2014).

Hot Flushes

Offer medroxyprogesterone (20 mg per day), initially for 10 weeks, to manage troublesome hot flushes caused by long-term androgen suppression and evaluate the effect at the end of the treatment period.

Consider cyproterone acetate (50 mg twice a day for 4 weeks) to treat troublesome hot flushes if

Table 6 Randomized controlled phase III – second-line trials in metastatic castration-resistant PCa*

Author	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
Fizazi et al. 2012	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel ECOG 0–2 PSA or radiographic progression	OS: 15.8 vs. 11.2 mo ($p < 0.0001$) FU: 20.2 mo. Radiologic PFS: no change
de Bono et al. 2011				OS: 14.8 vs. 10.9 mo. ($p < 0.001$ HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. Radiologic PFS: 5.6 vs. 3.6 mo.
ENZALUTAMIDE				
Scher et al. 2012	enzalutamide	Placebo	Previous docetaxel ECOG 0-2	OS: 18.4 vs. 13.6 mo. ($p < 0.001$ HR: 0.63; 95% CI: 0.53–0.75) FU: 14.4 mo. Radiologic PFS: 8.3 vs. 2.9 mo. HR: 0.40; 95% CI: 0.35–0.47 ($p < 0.0001$)

CI confidence interval, *ECOG* Eastern Cooperative Oncology Group, *FU* follow-up, *HR* hazard ratio, *mo* months, *OS* overall survival, *PFS* progression-free survival

*Median overall survival for the abiraterone group was longer than in the placebo group (15·8 months [95% CI 14·8–17·0] vs 11·2 months [10·4–13·1]; hazard ratio [HR] 0·74, 95% CI 0·64–0·86; p<0·0001).

medroxyprogesterone is not effective or not tolerated.

Tell men that there is no good-quality evidence for the use of complementary therapies to treat troublesome hot flushes.

Sexual Dysfunction

Before starting androgen deprivation therapy, tell men and, if they wish, their partner that long-term androgen deprivation will cause a reduction in libido and possible loss of sexual function.

Advise men, and if they wish, their partner, about the potential loss of ejaculation and fertility associated with long-term androgen deprivation and offer sperm storage.

Ensure that men starting androgen deprivation therapy have access to specialist erectile dysfunction services.

Consider referring men who are having long-term androgen deprivation therapy, and their partners, for psychosexual counseling.

Offer PDE5 inhibitors to men having long-term androgen deprivation therapy who experience loss of erectile function.

If PDE5 inhibitors fail to restore erectile function or are contraindicated, offer a choice of:

- Intraurethral inserts
- Penile injections
- Penile prostheses
- Vacuum devices
- Osteoporosis

Do not routinely offer bisphosphonates to prevent osteoporosis in men with prostate cancer having androgen deprivation therapy.

Consider assessing fracture risk in men with prostate cancer who are having androgen deprivation therapy, in line with Osteoporosis

Offer bisphosphonates to men who are having androgen deprivation therapy and have osteoporosis.

Consider denosumab for men who are having androgen deprivation therapy and have osteoporosis if bisphosphonates are contraindicated or not tolerated.

Gynecomastia

For men starting long-term bicalutamide monotherapy (longer than 6 months), offer prophylactic radiotherapy to both breast buds within the first month of treatment. Choose a single fraction of

8 Gy using orthovoltage or electron beam radiotherapy.

If radiotherapy is unsuccessful in preventing gynecomastia, weekly tamoxifen should be considered.

Fatigue

Tell men who are starting androgen deprivation therapy that fatigue is a recognized side effect of this therapy and not necessarily a result of prostate cancer.

Offer men who are starting or having androgen deprivation therapy supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve quality of life.

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Management of Metastatic Castration-Naïve Prostate Cancer

16

Axel Heidenreich, Maximilian Schmautz, Konstantin Richter, and David Pfister

Contents

Abstract

About 10% of newly diagnosed prostate cancer patients harbor systemic metastases requiring local and systemic therapy. In well-selected patients, cytoreductive radical prostatectomy or local radiation therapy to the primary exerts a beneficial effect on failure-free and overall survival. Systemic therapy might consist of ADT alone, ADT in combination with docetaxel, and ADT in combination with abiraterone and prednisone. CHAARTED and STAMPEDE have demonstrated a significant survival benefit for the combination of ADT plus docetaxel. This survival benefit was only demonstrated for patients with high-risk disease in the CHAARTED trials, whereas no stratification was performed in STAMPEDE. PSA nadir $\leq$0.2 ng/ml achieved 7 months after ADT is a significant prognostic marker associated with a significant survival benefit as compared to a PSA nadir >0.2 ng/ml. Also, a significant survival benefit was observed for the combination of ADT plus abiraterone acetate and prednisone in the LATITUDE trial for high-risk patients and in the STAMPEDE trial for the total cohort of patients. For daily routine, both combination therapies exert a significant and clinically relevant survival benefit. It is unclear which sequence is to be used, and it appears to be

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most appropriate to select the treatment option based on the comorbidities of the patient.

Keywords
Prostate cancer · Bone metastases · Androgen deprivation · LHRH analogues · LHRH antagonists · Docetaxel · Abiraterone acetate

Introduction

Prostate cancer is the most reported male cancer as well as the second leading cause of cancer-related deaths in Western men, excluding non-melanoma skin diseases (Heidenreich et al. 2014).

Even nowadays, about 10–15% of all men with newly diagnosed prostate cancer harbor systemic metastases with or without symptoms. Metastatic hormone-naive prostate cancer (mhPCA) might be part of a de novo diagnosis of men with newly diagnosed PCA or as progression following local therapies for initially organ confined or locally advanced prostate cancer (Heidenreich et al. 2014). Androgen deprivation therapy by subcapsular orchiectomy has been introduced more than 70 years ago, but median survival time of around 42 months has not changed significantly despite the development of new formulations of testosterone-lowering agents such as LHRH analogues and LHRH antagonists (Hussain et al. 2006). In the STAMPEDE trial, 917 men with mPCA and a median serum PSA concentration of 112 ng/ml were recruited in the control arm and received androgen deprivation therapy (James et al. 2015). After a median follow-up of 20 months, the median failure-free survival was 11 months, and the median overall survival was 42 months with 2-year survival rate of 72%. In multivariate analysis, presence of bone metastases independent on visceral metastases, high Gleason sum score, poor performance status, and younger age strongly correlated with overall survival. In men with high-volume disease median overall survival might be even reduced to 32–35 months (Sweeney et al. 2015; Fizazi et al. 2017).

Continuous ADT by means of orchiectomy, GnRH analogues or antagonists represented the treatment of choice for the last decades. Continuous ADT has been shown to be associated with a longer median overall survival of 5.8 compared to 5.1 years in the intermittent arm of the SWOG 9346 trial (Hussain et al. 2006). The SWOG trial did demonstrate that the PSA nadir at 7 months following initiation of ADT has a major prognostic impact with a median overall survival of 78 months and 17 months if a PSA $\leq$0.2 ng/ml and a PSA $>$ 4.0 ng/ml were achieved (Fizazi et al. 2017). Therefore, the PSA nadir might serve as an indicator to discuss intermittent ADT in men with good response characteristics as 94% of panelists of the APCCC would do (Gillessen et al. 2015).

As indicated in the STAMPEDE trial, the group of PCA patients with systemic metastases represents a very heterogeneous cohort of men with significantly different survival times depending on the location of metastases, the extent of metastases, the serum concentrations of alkaline phosphatase and PSA as well as the performance status of the patient. Gravis et al. (2015) evaluated the impact of age, performance status, Gleason score, hemoglobin level, PSA, alkaline phosphatase, LDH, metastatic localization, body mass index, and pain on oncological outcome. Visceral metastases, bone metastases, PS (0 vs. 1–2), Hb, ALP, LDH, PSA ($\leq$65 vs. $>$65 ng/ml), metastases (at diagnosis vs. onset after local treatment failure), and pain intensity ($\leq$16.7 vs. 16.7 or continuous) were significant univariate predictors of OS ($p < 0.05$). Statistical analysis identified alkaline phosphatase as the strongest predictor of overall survival with a median overall survival of 69.1 months and 33.6 months for patients with normal and with abnormal serum concentrations of alkaline phosphatase, respectively.

Recently, a number of prospective randomized clinical phase-III trials combining ADT with either docetaxel or abiraterone have challenged the traditional therapeutic approach. In addition, few retrospective studies have evaluated the role of local therapy of the primary in order to improving the therapeutic outcome of men with mhPCA.

It is the purpose of this chapter to critically review the current treatment options in patients with mhPCA.

Local Treatment of the Primary

The role of treating the primary tumor in the clinical scenario of metastatic disease is usually ignored in the decision-making process concerning the most appropriate therapy due to the common believe that the biology of the disease is attributed to the metastatic spread and that it cannot be positively influenced by local treatment of the prostate. Quite recently, however, it could be demonstrated that lethal PCA clones persist intraprostatically despite extensive pretreatment with ADT and docetaxel-based chemotherapy (Tzelepi et al. 2011). Furthermore, preclinical studies demonstrated that prostatectomy results in a significant reduction of newly developed metastases in animals subjected to prostatectomy as compared to ADT alone (Cifuentes et al. 2015). A few retrospective and case-control studies demonstrated the feasibility of cytoreductive radical prostatectomy (cRP) and demonstrated a benefit of cRP in terms of time to development of castration-resistant PCA, overall survival, and frequency of locally progressing PCA with lower and upper urinary tract obstruction (Heidenreich et al. 2015; Culp et al. 2014; Sooriakumaran et al. 2015; Gratzke et al. 2014; Fossati et al. 2015; Steuber et al. 2017; Leyh-Bannurah et al. 2017).

There are only very few retrospective studies reporting on the survival outcome following cRP which might serve as hypothesis-generating studies (Heidenreich et al. 2015; Culp et al. 2014; Sooriakumaran et al. 2015; Gratzke et al. 2014; Fossati et al. 2015; Steuber et al. 2017; Leyh-Bannurah et al. 2017). The Cologne study group reported a median CSS and clinical PFS of 47 months and 38.6 months, respectively, after cRP as compared to 40 months and 26.5 months, respectively, in men with ADT alone (Heidenreich et al. 2015). In their retrospective study on a cohort 8185 patients with mPCA, Culp et al. (2014) demonstrated that the 5-yr OS and predicted DSS were each significantly higher in patients undergoing cRP (67.4% and 75.8%, respectively) or brachytherapy (52.6% and 61.3%, respectively) compared with antihormonal therapy alone (22.5% and 48.7%, respectively) ($p < 0.001$). Sooriakumaran et al. (2015) report on a 2-year survival rate of 89% in a retrospective cohort of 106 patients. Gratzke et al. (2014) retrospectively studied 1538 patients from the Munich Cancer Registry with few bone metastases, of which 74 had cRP and 1464 had no surgery. Those who had surgery showed a 55% survival in contrast to 21% of those who had no surgery. In another retrospective analysis, 8197 mPCA patients were identified from the SEER database 2004–2011 in order to explore the potential benefit of local therapy as compared to nonlocal therapy (Fossati et al. 2015). The authors demonstrated a significant CSS benefit for local therapy ($p < 0.0001$), especially in patients with a cancer-specific mortality risk <40%. In the most recently published study, Steuber et al. (2017) analyzed the outcome of 43 patients who underwent cRP with 40 patients who underwent nonsurgical therapy only. Although the authors could not identify a survival benefit, they identified a significant benefit for cRP in terms of the prevention of local complications (7% vs. 35%, $p < 0.01$) despite a median follow-up of only 32.7 months. In another retrospective of 13.692 mPCA patients of whom 474 received local therapy, Leyh-Bannurah et al. (2017) observed a significantly improved cancer-specific survival rate following cRP especially for patients with M1a disease.

Recently, Heidenreich et al. (2018) reported on oncological and functional outcome of the largest series of 121 well-selected men with hormone-naive mPCA who were treated with systemic therapy and cRP with the rationale to improve oncological outcome and to prevent local complications from a progressing primary. Both, the mean OS time and the mean clinical relapse-free survival were high with 86.5 months and 72.3 months, respectively (Figs. 1 and 2). Additionally, they showed a 1-, 3-, and 5-year survival rate of 98%, 87.8%, and 79%, respectively. These data underline the potential role of cRP in the individual management of men with newly diagnosed mPCA if included in clinical protocols.

Although the group was not able to identify preoperative parameters associated with OS, they identified preoperative PSA and the extent of metastatic disease as indicators for an improved biochemical PFS. Patients who achieved a PSA nadir

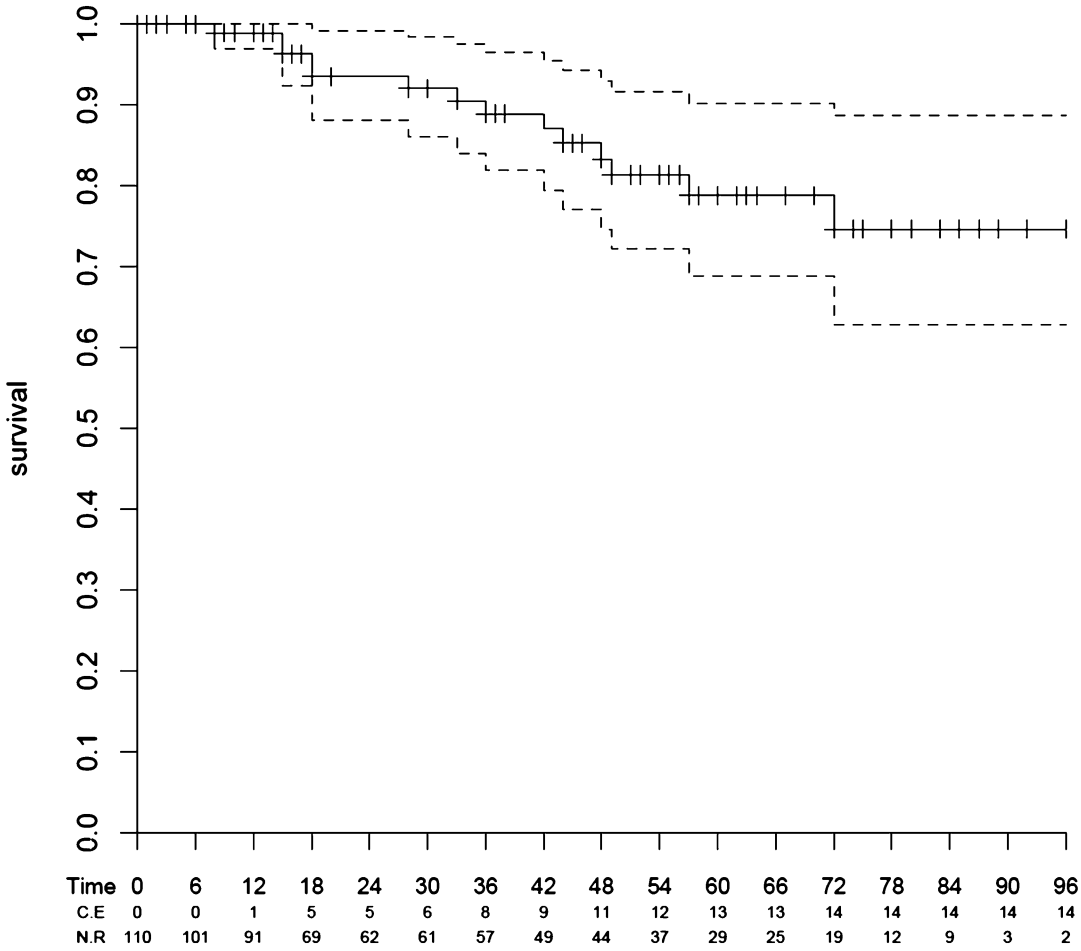

Fig. 1 Overall survival of the cohort of 113 patients. *CE* cumulative number of events, *NR* numbers at risk

<1.0 ng/ml following neoadjuvant ADT, patients with a PSA below the median preoperative PSA of 8 ng/ml, and men with low-volume metastatic disease exhibited a significantly better outcome. These patients might be the most appropriate candidates for CRP as the prognosis seems to be excellent.

With regard to surgery-associated complications, perioperative and 90-day mortality rate were 0%. These data underline that cRP represents a technically feasible and safe procedure if performed by experienced surgeons. In addition, we could demonstrate that patients with low-volume metastatic disease, a preoperative PSA < 4 ng/ml, and neoadjuvant ADT experienced significantly less serious complications.

Functional outcome in terms of urinary continence also was in line with data of RP for locally advanced PCA: 68% and 18% of patients achieved complete or minimal incontinence. Following RP for clinical T3 disease, continence rates vary between 70% and 80% considering patients with total continence or the use of one safety pad.

When considering surgery-related complications of cRP, one also has to consider the local and systemic complications if ADT is performed as monotherapy. In their two retrospective studies, local complications were observed in 29% of patients of the ADT group after a mean follow-up of 44 months, whereas none of the patients in the cRP group experienced such complications

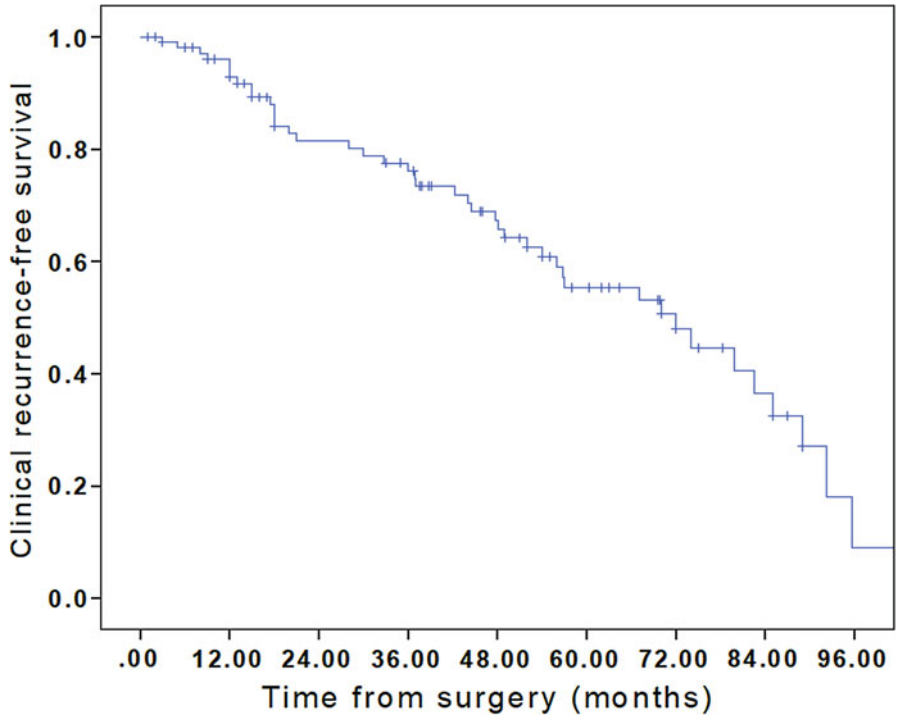

Fig. 2 Clinical relapse-free survival. *CE* cumulative number of events, *NR* numbers at risk

(Heidenreich et al. 2015, 2018). Similarly, Poelaert et al. (2017) demonstrated significant differences in local complications between cRP and ADT alone. At 3 months of follow-up, five (29.4%) patients undergoing cRP reported stress urinary incontinence without any further local symptoms, whereas 6.8%, 37.9%, and 6.8% of patients suffered urge incontinence, obstructive voiding, and ureteric obstruction following ADT alone.

In addition, the study of Rusthoven et al. (2016) underlines the importance of effective local therapy of the primary. The authors demonstrated a superior median (55 vs. 37 months) and 5-year OS (49% vs. 33%) with prostate RT plus ADT compared with ADT alone ($p < 0.001$). In a similar approach, Joensuu et al. (Heidenreich et al. 2018) demonstrated a 5-year overall survival of 81.3% and a median OS time of 8.35 years in a super-selected group of 46 men with mPCA who underwent ADT plus IMRT.

Despite the favorable results of local treatment in mPCA, we have to be aware of the limitations concerning the current data. All studies are retrospective in nature, and only selected patients have been treated so that cytoreductive local therapy in mPCA is still an individual and experimental therapy and it does represent the standard of care. Currently a number of prospective randomized trials of ADT ± surgery or ADT ± radiotherapy are ongoing, and we have to await the final results.

Systemic Treatment in mPCA

ADT Plus Docetaxel-Based Chemotherapy

The *CHAARTED* trial was the first prospective randomized clinical phase-III trial comparing the therapeutic efficacy of androgen deprivation therapy versus the combination of ADT plus docetaxel (Sweeney et al. 2015). 790 patients were randomized to receiving either continuous ADT with LHRH analogues or surgical castration ($n = 393$) or a combination of continuous ADT with six cycles of docetaxel at a dose of

75 mg/m2 delivered at 3-week intervals (n = 397). A time interval of up to 120 days was allowed between initiation of ADT and systemic chemotherapy. The primary endpoint of the trial was improvement of overall survival. Secondary endpoints were progression-free survival, PSA response, etc.

Patients were stratified according to age, extent of disease (low risk vs. high risk), ECOG performance status, medical prevention of skeletal-related events, and previous adjuvant ADT. High-risk disease was defined by the presence of visceral metastases or the presence of at least four skeletal metastases with one being located outside the axial skeleton.

After a median follow-up of 28.9 months, a significant survival benefit of 13.6 months (57.6 months vs. 44 months) with a hazard ratio of 0.61 (95% CI, 0.47–0.80, $p < 0.001$) was observed resulting in a 39% relative risk reduction of prostate cancer death. The only stratification with significant impact on survival was the presence of low-risk versus high-risk disease. Patients in the high-risk disease group achieved a survival benefit of 17 months (49.2 vs. 32.2 months) with the combination of ADT plus docetaxel resulting in a 40% relative risk reduction of death (HR = 0.60, 95% CI 0.45–0.91, $p < 0.001$). No survival benefit was observed in the low-risk PCA cohort where the median overall survival has not been reached in both arms (HR = 0.60, 95% CI 0.32–1.13, $p = 0.11$). Even at long-term follow-up, no survival benefit was observed for the low-risk group, whereas the survival advantage was validated for the high-risk group. Forest plot analysis did demonstrate a survival benefit for all subgroups even for the groups of elderly men, patients with poor performance status, and visceral metastases with or without bone metastases.

Quite recently, the authors performed a landmark survival analysis 7 months after initiation of therapy using the SWOG9346 PSA cut points of ≤0.2 ng/ml, >0.2–4.0 ng/ml, and > 4.0 ng/ml (Harshman et al. 2018). The median follow-up which started after 7 months of ADT was 23.1 months. The median overall survival was significantly longer in the total cohort of patients when comparing a PSA serum concentration ≤ 0.2 ng/ml versus >4.0 ng/ml (Table 1). Patients with visceral metastases had a higher likelihood of not achieving a PSA ≤ 0.2 ng/ml, and in fact the percentage of patients with visceral metastases and a 7-month PSA > 4.0 ng/ml was 20.9% as compared to only 12% in the group of men with a 7-month PSA ≤0.2 ng/ml (Fig. 3).

The *STAMPEDE* trial is another adaptive, multiarm, multistage, randomized controlled trial in which the addition of docetaxel, zoledronic acid, or both to first-line continuous ADT was evaluated (James et al. 2016). In this trial, a total of 1184, 993, 992, and 993 men received standard hormonal therapy, ADT plus ZA, ADT plus docetaxel, or ADT plus ZA and docetaxel, respectively, with the primary endpoint to improving overall survival. It has to be noted that a total of 2962 patients were included in the trial but that 1145 (42.5%) patients did not exhibit metastases, whereas 1817 (56.5%) men were newly diagnosed with metastatic disease.

After a median follow-up of 43 months, the median overall survival time in men with mPCA was 45 months in the ADT-alone group with a 5-year survival rate of 39%. There was no benefit in the median overall survival time in the ADT plus ZA group with 46 months and a 5-year survival rate of 43% (HR = 0.93, 95% CI 0.77–1.11, p = 0.416).

Table 1 Median overall survival dependent on PSA nadir after 7 months of ADT therapy

Median overall survival (months)						
	ADT alone			ADT + docetaxel		
PSA, ng/ml	≤0.2	>0.2–4.0	>4.0	≤0.2	>0.2–4.0	>4.0
Total cohort	72.8	NR	21.6	60.4	45.5	25.2
Low risk	NR	NR[a]		NR	29.4[a]	
High risk	40.1	25.4[a]		60.4	45.4[a]	

[a]Median overall survival for patients who did not achieve a PSA ≤0.2 ng/ml at 7 months of ADT

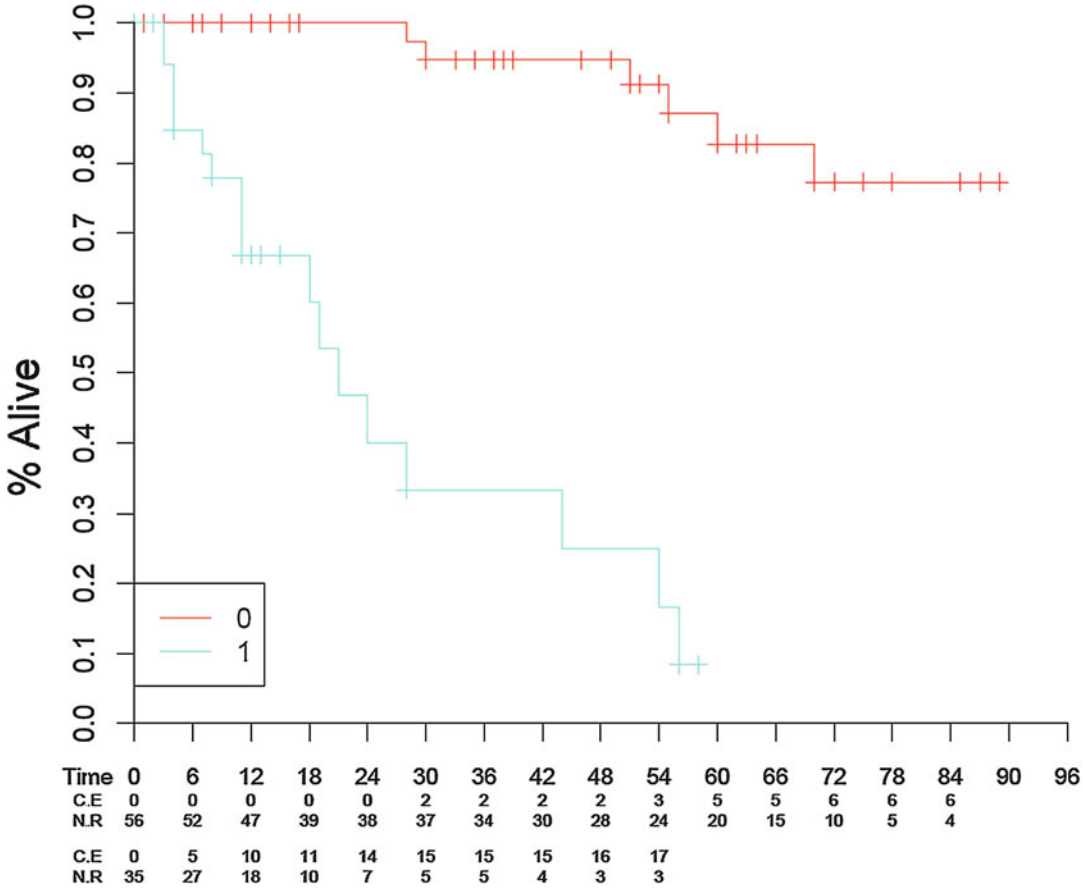

Fig. 3 Overall survival depending on a PSA serum level < 0.1 ng/ml (red) or > 0.1 ng/ml (blue) 6 weeks postoperatively, p = 0.0003. *CE* cumulative number of events, *NR* numbers at risk

A significant survival benefit, however, could be observed for the ADT plus docetaxel arm with a median overall survival time of 60 months and a 24% relative risk reduction of death (HR = 0.76, 95% CI 0.62–0.92, p = 0.005). The 5-year survival rate was 50%. A similar survival benefit was observed for the combination of ADT plus ZA and docetaxel with a median survival time of 55 months and a 21% relative risk reduction of death (HR = 0.79, 95% CI 0.66–0.96, p = 0.015). Comparing the groups of ADT plus docetaxel and ADT and ZA plus docetaxel, no survival benefit was observed for the addition of ZA (HR 1.06, 95% CI 0.86–1.30, p = 0.592). A similar benefit was observed for ADT plus docetaxel and ADT and ZA plus docetaxel concerning prostate cancer-specific survival.

In addition, the potentially positive impact of ZA on the development of skeletal-related events (SRE) was evaluated. 328/1184 (xx%) patients randomized to ADT alone developed SREs. The time to first SRE was improved with ADT plus docetaxel (HR 0.60, 95% CI 0.48–0.74, p = 0.0000127) and with ADT and ZA plus docetaxel (HR 0.55, 95% CI 0.44–0.69, $p = 0.277x10^{-7}$), but it was not improved with ADT plus ZA (HR 0.89, 95% CI 0.73–1.07, p = 0.221). Concentrating on the patients with skeletal metastases, there was also no benefit of ADT plus ZA on the time to first SRE and frequency of SRE (HR 0.94, 95% CI 0.76–1.16; p = 0.564). Taking into consideration the whole cohort of patients, the median to the development of SREs was 61.4 months, 68.0 months, and

68.3 months, for ADT alone, ADT plus docetaxel ($p = 0.177 < 10^{-4}$), and ADT and ZA plus docetaxel ($p = 0.249x10^{-5}$), respectively.

Finally, the GETUG-15 trial (Gravis et al. 2013) did not identify a survival benefit between the ADT alone and the ADT plus docetaxel group after a median follow-up of 83.3 months with a median survival of 48.6 and 62.1 months (HR 0.88, 95% CI 0.68–1–14, p = 0.3). Subgroup analysis trended to be in favor of a survival advantage for the combination therapy in men with high-volume disease. However, the subgroups were too small for a conclusive data analysis.

Based on these data, all international guidelines recommend the combination of chemohormonal therapy for men with high-volume disease, whereas ADT alone should be the preferred treatment in men with low-volume, metastatic hormone-naive prostate cancer (Morris et al. 2018; Gillessen et al. 2018). The addition of ZA is not recommended in addition to ADT alone or to combination of ADT plus docetaxel.

ADT Plus Abiraterone and prednisone

Following the life-prolonging impact of AA/P in patients with metastatic castration-resistant PCA prior to and following docetaxel chemotherapy, two trials evaluated the therapeutic efficacy of AA/P plus ADT versus ADT alone in men with newly diagnosed, hormone-naive mPCA (Fizazi et al. 2017; James et al. 2017).

The LATITUDE trial recruited a total of 1199 patients with mhPCA who exhibited at least two of the three high-risk criteria which were a Gleason score $\geq$ 8, $\geq$3 lesions on bone scan, and visceral metastases (Fizazi et al. 2017). Patients were randomized in a 1:1 fashion so that 597 men were randomized in the combination arm (abiraterone acetate at a dose of 1000 mg/day, prednisone 2 × 5 mg/day, and continuous LHRH analogues) and 602 men were randomized in the standard arm. The co-primary endpoints were overall survival and progression-free survival. The secondary endpoints were time to pain progression, time to PSA progression, time to symptomatic SREs, and time to chemotherapy and safety.

After a median follow-up of 30.4 months, there was a statistically survival benefit in the ADT plus AA/P group in which the median overall survival was not reached versus 34.7 months in the ADT alone (HR 0.62, 95% CI 0.51–0.76, p < 0.0001). Also, the second primary endpoint was met with a statistically significant benefit of 18.2 (33.0 vs. 14.8 months) concerning radiographic progression-free survival (HR 0.47, 95% CI 0.39–0.55, p < 0.0001). In addition, all secondary endpoints were met and demonstrated a statistically significant benefit for the ADT plus AA/P group (Table 2).

Table 2 Secondary endpoints in LATITUDE for the treatment and the placebo group

Endpoint	ADT + AA/P (n = 597)	ADT + placebo (n = 602)	HR (95% CI)	p
Median time to pain progression	NR	16.6 months	0.70 (0.58–0.83)	<0.001
Median time to PSA progression	33.2 months	7.4 months	0.30 (0.26–0.35)	<0.001
Median time to symptomatic SRE	NR	NR	0.70 (0.54–0.92)	0.009
Median time to chemotherapy	NR	38.9 months	0.44 (0.35–0.56)	<0.001
Median time to next PCA-specific therapy	NR	21.8 months	0.42 (0.35–0.50)	<0.001
Patients with PSA response[a]	91%	67%	1.36 (1.28–1.45)	<0.001

[a]PSA response = PSA decrease ≥50% from baseline

Treatment-associated side effects did not occur at higher frequency or severity in the treatment arm as compared to the placebo arm. The profile of side effects did resemble the well-known scenario of AA/P in the COUGAR-301 and COUGAR-302 trials.

With regard to the treatment sequence at time of progression, it became evident that only 53% of the patients in the AA/P arm were thought to be fit enough to receiving a second-line therapy as compared to 78% in the placebo arm. Furthermore, only 38% as compared to 46% of patients in the AA/P and the placebo arm received some type of systemic chemotherapy, respectively.

In a similar approach, 1917 patients with hormone-naive PCA were randomized in a 1:1 fashion to receive AA/P plus ADT versus ADT alone in the STAMPEDE trial (James et al. 2017). Different to the LATITUDE trial, no regulation with regard to the inclusion of only high-risk patients was given. Patients with newly diagnosed and node-negative PCA and newly diagnosed node-positive and newly diagnosed metastatic PCA could be recruited for the trail. A total of 941 patients belonged to the group of newly diagnosed metastatic, hormone-sensitive PCA of whom 476 and 465 patients were randomized to receiving ADT and ADT plus AA/P, respectively. Those patients form the basis of the current chapter.

After a median follow-up of 40 months, a statistically significant survival advantage was observed for the group of patients receiving the combination therapy versus the ADT alone group. 218 versus 150 deaths were observed in the ADT group and the ADT plus AA/P group, respectively, resulting in a 39% relative risk reduction of death (HR 0.61, 95% CI 0.49–0.75). Forest plot analysis reported a statistically significant survival benefit of AA/P plus ADT for all subgroups except for elderly patients $\geq$70 years. Similar data were achieved with regard to failure-free survival where a 69% relative risk reduction (HR 0.31, 95% CI 0.26–0.37) was observed for the combination group.

In STAMPEDE, a higher frequency of grade 3–5 adverse events was observed in the combination group with 47% as compared to the ADT group with 33%. Especially cardiovascular disorders (10% vs. 4%), hepatic disorders (7% vs. 1%), and respiratory disorders (5% vs. 2%) developed much more often in the combination group. There was, however, no difference with regard to adverse events of grade 5 only (1% in both groups).

With regard to treatment at time of progression, the absolute number of patients receiving life-prolonging agents was higher in the ADT-alone group as compared to the combination group (310 vs. 131 patients).

Based on these two prospective randomized trials, the combination of ADT and AA/P exerts a statistically significant and clinically relevant advantage in terms of overall survival and failure-free survival as compared to ADT alone in men with newly diagnosed metastatic and hormone-naive prostate cancer (Morris et al. 2018; Gillessen et al. 2018; James et al. 2017; Mottet et al. 2017; Rydzewska et al. 2017). The increased frequency of grade 3–5 adverse cardiovascular, hepatic, and respiratory events has to be taken into consideration when counseling patients.

Sequencing Strategies

No data on the best sequencing strategy exist so that no reliable and valid recommendations can be given with regard to best sequence (Morris et al. 2018; Gillessen et al. 2018; James et al. 2017; Mottet et al. 2017; Rydzewska et al. 2017).

Comparing CHAARTED and LATITUDE with regard to their oncological efficacy, various findings need to be taken into consideration. The LATITUE trial only allowed high-risk patients to be recruited so that outcome data of high-risk and high-volume disease (CHAARTED) should only be compared.

The median overall survival in the ADT alone was nearly identical in both high-risk and high-volume groups with 34.7 months and 34.4 months in LATITUDE and CHAARTED, respectively. Radiographic progression-free survival was 14.8 months and 13.0 months for the ADT-alone group in LATITUDE and CHAARTED, respectively, whereas PFS was 33.0 and 27.3 months in the treatment group resulting in a relative risk

reduction of 53% and 47% in LATITUDE and CHAARTED, respectively. Concerning overall survival, both trials achieved a similar benefit with a relative risk reduction of death of 38% and 37% in LATITUDE and CHAARTED, respectively.

Concerning the treatment-associated adverse events, one has to consider the significantly increased frequency of cardiovascular, hepatic, and respiratory events in the combination arm as compared to the ADT-alone arm in the LATITUDE trial (22% vs. 7%, respectively). The median treatment duration of 33 months with side effects such as fatigue, cognitive dysfunction, etc. also needs to be taken into account. With regard to ADT and docetaxel, the risk of neutropenia was 32%, 3.1%, and 12% in the GETUG-15, CHAARTED, and STAMPEDE trial. The risk of neutropenic fever was 7%, 3.8%, and 15% in GETUG-15, CHAARTED, and STAMPEDE. Considering these adverse events, it needs to be taken into consideration that the median treatment duration of docetaxel was 4.5 months and that basically all patients recovered rapidly after discontinuation of chemotherapy. Comparing both treatment options, one needs to take into consideration the pre-existing chronic comorbidities which might interfere with abiraterone or docetaxel.

With regard to the sequence, one also has to consider the different rates of follow-up therapies in men who have received AA/P or docetaxel. Whereas 88% and 83% of patients in the ADT-alone group and in the docetaxel group received a life-prolonging second-line therapy, only 53% as compared to 78% of patients in the ADT alone and in the AA/P group were thought to be fit enough to receiving a follow-up treatment with life-prolonging agents. One might consider first-line chemotherapy especially in elderly patients with relevant comorbidities who might not be fit enough to receiving chemotherapy after long-term ADT therapy.

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Part III

Bladder Cancer

Epidemiology and Sociocultural Differences for Bladder Cancer

17

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Abstract

Bladder cancer (BCa) is the second most common genitourinary cancer in men and the most common in women. Every year, worldwide, more than 400,000 patients receive a BCa diagnosis and 145,000 succumb to it. The epidemiology is influenced by several factors such as age, gender, race, geography, sociocultural status, and exposure to risk factors. Women have a lower risk of developing BCa compared to their male counterpart but present with more aggressive features and suffer from worse outcomes. Black patients seem to have a higher risk of advanced disease and worse survival. BCa is typically a disease of the elderly with a higher preponderance in developed countries. However, the change in the geography of smoking from developed to developing countries together with the improvement of life expectancy will lead to an increase in the incidence in these regions. Moreover, in Western countries, mainly due population aging, BCa will become even more frequent, resulting in an even bigger public health challenge. Indeed, BCa is the most cost-intensive cancer per person mainly because of the excessive costs related to the high recurrence rate and ongoing invasive monitoring required in the surveillance of non-muscle invasive BCa (NMIBC) patients. The new revolution in awareness and innovation in BCa will certainly change this disease in the near future.

Introduction

Bladder cancer (BCa) is the second most common genitourinary cancer in men and the most common in women. Due to its high incidence and its relatively low mortality rates, especially regarding low-risk non-muscle invasive BCa (NMIBC), it represents a challenge for the urologist.

Understanding BCa epidemiology and its variations among age, gender, ethnicity, geographical location, and socioeconomic status is of fundamental importance for the medical community, not only to improve diagnosis and treatment, but also to plan specific primary prevention measures and public health policies. Moreover, it is estimated that BCa prevalence will increase worldwide in the next decades as the result of population aging, population growth, as well as the absolute increase in smoking, but likely with a shift from the USA, Europe, and Australia to the rest of the world. Therefore, understanding BCa epidemiology, its economic burden, and its trends is of particular interest to patients, healthcare providers, and policymakers to improve the cost and management of BCa in order to allow affordable care for all patients.

Epidemiology of Bladder Cancer

Incidence, Prevalence, and Mortality

BCa is the 9th most common cancer worldwide, representing the 7th most common cancer in men and the 17th most common cancer in women (Babjuk et al. 2013; Babjuk 2017). It is responsible for 4.7% of all new diagnoses of cancer in the USA. According to GLOBOCAN estimates, 430,000 new BCa cases occurred in 2012 (Fig. 1), with an age-standardized incidence of 10.1 per 100,000 for men and 2.5 per 100,000 for women (Ploeg et al. 2009). Based on data from the Surveillance, Epidemiology, and End Results (SEER) program, in Western countries, approximately 2.4% of men and women will receive a diagnosis of BCa at some point in their life (4% and 1.2% of lifetime probability for white males and females, respectively), and it is estimated that in 2017, there will be 79,000 new BCa diagnoses only in the USA.

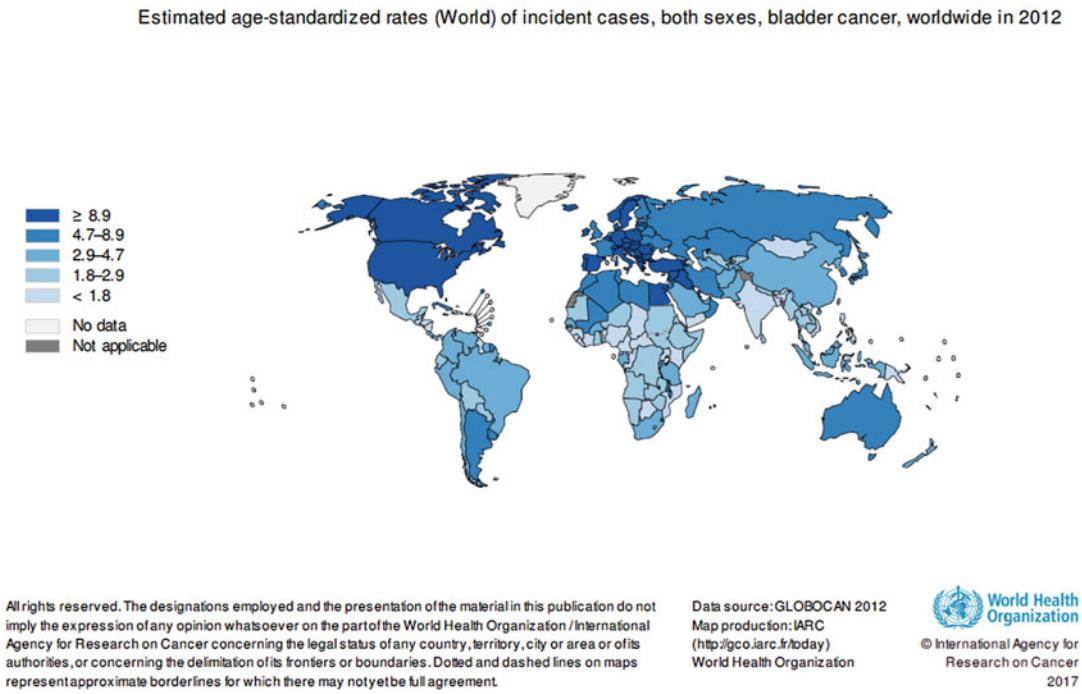

Fig. 1 Estimated age-standardized rates (World) of incident cases, both sexes, bladder cancer, worldwide in 2012

BCa incidence and prevalence vary according to several factors such as exposure to risk factors, age- and gender-related risk, and sociocultural and geographical differences (Babjuk et al. 2017). However, part of this variability can be explained by differences in methodology and reporting. Actually, several national registries do not include patients with Ta stage disease (the largest group of BCa patients) and/or with carcinoma in situ (CIS) in BCa statistics (Crow and Ritchie 2003). If one would only consider registries which also include Ta patients into BCa estimates, the incidence of BCa would increase, thus becoming the fourth most common cancer worldwide (Burger et al. 2013). Moreover, differences exist in the report of metachronous tumors, as in cases of muscle-invasive tumors (MIBC) following NMIBC (Ploeg et al. 2009). Therefore, due to the relatively high risk of bias, epidemiologic data obtained from national registries should be interpreted with caution, mostly underestimating the incidence and prevalence of BCa.

BCa prevalence and mortality are mainly affected by age at diagnosis, stage at presentation, and efficacy of treatment, together with all the other competing mortality causes. Actually, the prevalence corresponds to the number of patients alive with BCa at a specific time point and is a direct function of incidence and the duration of the disease. While the incidence of the disease is relatively easier to assess, the duration is object of debate. This is related not only to the survival but also to the question of how long from the initial diagnosis a patient without recurrence should be considered a BCa patient (usually 5 or 10 years) (Babjuk et al. 2017). Therefore, the worldwide prevalence of the disease remains difficult to assess. In 2012, the worldwide 5-year estimated prevalence was 1,319,749 (1,018,415 males and 301,334 females) (Fig. 2) (GLOBOCAN n.d.). However, based on US data, Ploeg et al., ignoring global survival differences, estimated an overall prevalence of 2,677,500 (Ploeg et al. 2009). Even if the accuracy of these estimations is limited (Rink et al. 2012), they can help to provide a representative image of BCa burden.

BCa is the 13th leading cause of cancer death worldwide and the 9th in the USA, with a number of

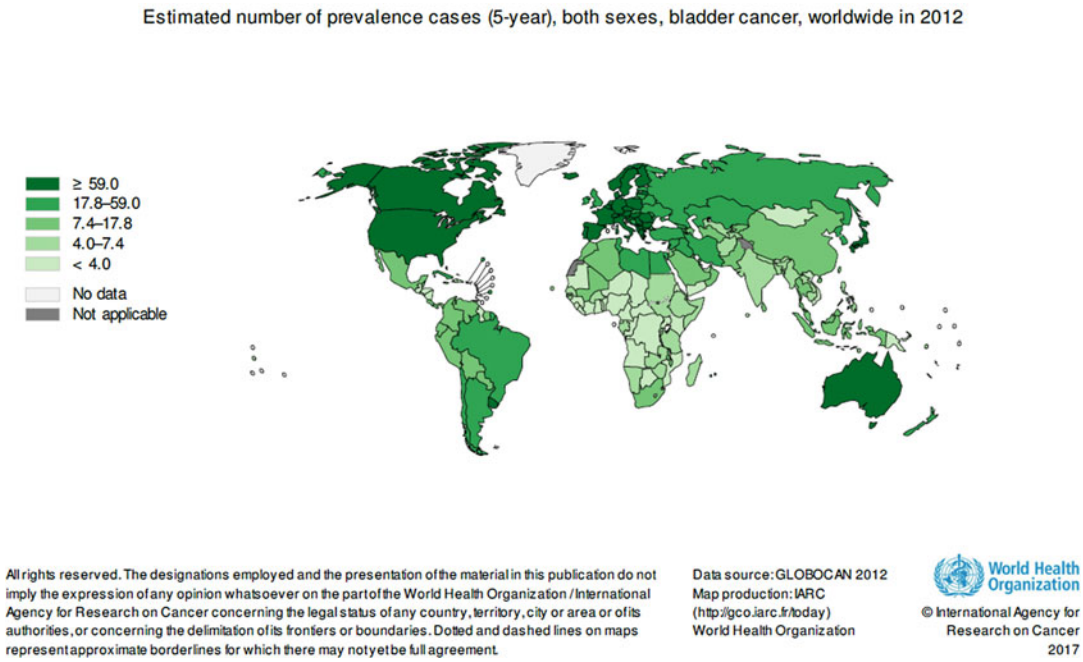

Fig. 2 Estimated number of prevalence cases (5-year), both sexes, bladder cancer, worldwide in 2012

deaths of 4.4 per 100,000 men and women per year, based on 2010–2014 deaths (GLOBOCAN n.d.; Siegel et al. 2015). Overall, approximately 145,000 patients die yearly from BCa. Mortality is mainly related to the progression rates of NMIBC to muscle-invasive disease and to the disappointing curative rates of MIBC. Therefore, due to the fact that the differences in registration reports among invasive disease are lower, the variability in mortality rate between countries is lower too (Fig. 3). However, geographical differences in systemic treatments availability (i.e., systemic chemo- and immunotherapy) should be taken into account as they will increase the geographic discrepancies.

Age Influence

BCa is mainly a disease of the elderly with a median age at diagnosis of 73 years and the majority of new diagnoses occurring in the decade between 75 and 84 years. The risk of developing BCa directly increases with age, being for men and women 0.45% and 0.14% before the age of 60 and 2.81% and 0.82% before the age of 80, respectively (Ries et al. 2008). Both sexes have the highest risk of developing BCa after the age of 75. As a consequence, also the mortality rates are higher in the elderly (Nielsen et al. 2007), with the highest amount of cancer deaths occurring among people aged 75–84 with a median age at death of 79 years (US data) (Siegel et al. 2015). Age is therefore considered the greatest risk factor for developing and dying from BCa (Chromecki et al. 2012), and several hypotheses concur to explain the relationship between carcinogenesis and aging (Fajkovic et al. 2011). First, the cumulative exposure to carcinogens and the lag time between the initial cellular transformative events and the clinical expression of the disease could account for the appearance of BCa in the old population. Second, genetic mechanisms such as an increased oncogene activity and a decreased capacity to repair DNA mutations seem to be age-related (Shariat et al. 2010). Management of BCa in the elderly is also a challenge due to decreased reserves and multispeciality approach (Grubmueller et al. 2016; Soria et al. 2016).

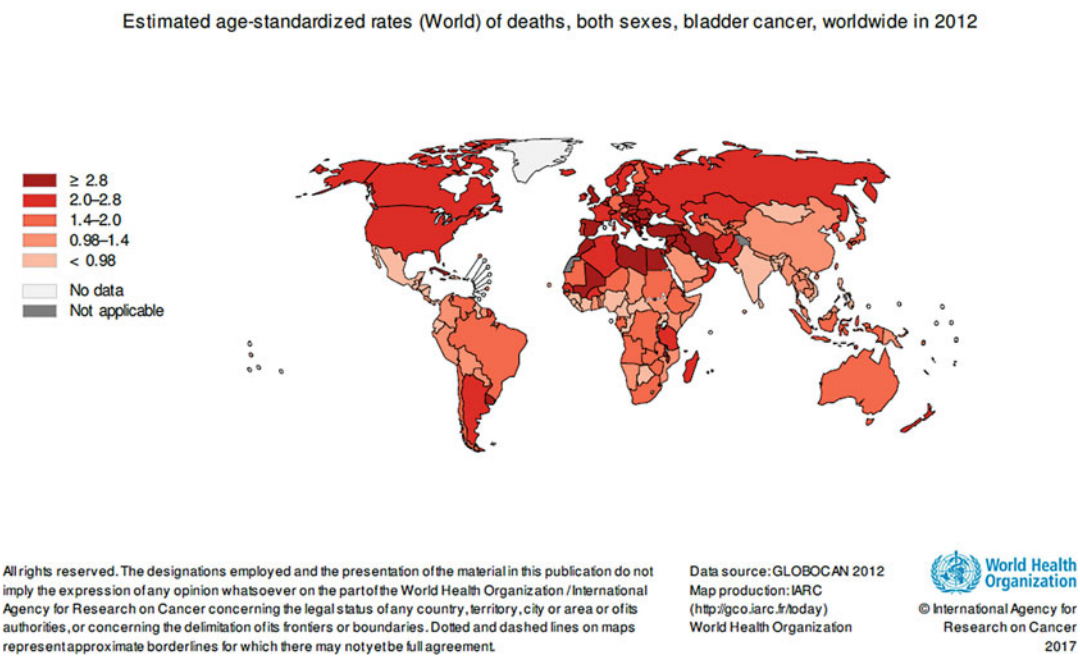

Fig. 3 Estimated age-standardized rates (World) of deaths, both sexes, bladder cancer, worldwide in 2012

Gender Influence

Together with esophagus and larynx cancers, BCa is one of the tumors with the largest sex disparities reflected in the fourfold male preponderance in incidence and mortality rates (Siegel et al. 2015). According to epidemiological data, men have a three- to fourfold greater risk of developing BCa in their life and are usually diagnosed at a younger mean age compared to their female counterparts (Fajkovic et al. 2011). In addition, BCa incidence increased 25% faster in men that in women during the last decade likely due to the differentially increasing male exposure to smoking and occupational carcinogens (Siegel et al. 2015). Despite these findings, women usually present with more advanced tumors at the time of diagnosis (Dobruch et al. 2016). Actually, from the top 10 most frequent cancers, only BCa shows worse outcomes in women (Najari et al. 2013). As reported in a retrospective study of the Netherlands Cancer Registry, men are more likely diagnosed with NMIBC (71% vs. 63%) even if the occurrence of metastatic disease at the time of presentation is similar among genders (Mungan et al. 2000). Moreover, women are more likely to harbor high-grade, multifocal, and larger lesions. In addition, female sex seems to carry out a greater risk of unfavorable oncologic outcomes: although men are 3 times more likely to receive a diagnosis of BCa, they are only twice as likely to die from the disease (Shariat et al. 2010; Messer et al. 2014; Kluth et al. 2014). More in details, women have an increased risk of intravesical recurrence and progression in NMIBC and an increased cancer-specific mortality after radical cystectomy. As a consequence of these disparities, gender was included as prognosticator for BCa outcomes in various prediction tools (Fernandez-Gomez et al. 2009; Aziz et al. 2016). Conversely, gender seems not to be a predictor of poor outcomes in locally advanced and metastatic BCa.

These gender disparities could be explained with the delay in diagnosis experienced by women. Even BCa symptoms do not differ between genders, women presenting with hematuria are less likely to be referred to the urologist and to undergo abdominal or pelvic image, thus being frequently misdiagnosed as urinary tract infection. In a retrospective population-based

study of 5,416 men and 2,233 women examining the timing from presentation with hematuria to BCa diagnosis, a significant higher proportion of delayed diagnosis (>6 months) was reported in the female group (Cohn et al. 2014). However, the delay in diagnosis could not alone explain the different behavior of the disease among genders. Several factors such as different smoking habits, occupational exposure, genetic factors, tumor biology, bladder anatomy, and the influence of sex steroids could play a role in determining the gender-related differences in BCa (Lucca et al. 2015).

Geographical Differences

BCa epidemiology differs between countries with 55% of all cases and 43% of disease-related deaths occurring in the 20% of population living in countries with a very high Human Development Index (HDI). On the other hand, only 5% of all BCa diagnoses occur in low HDI countries (Antoni et al. 2017). Europe is the continent with the highest incidence rate (especially in Southern countries such as Spain and Italy, with an age-standardized incidence of 33 to 37 per 100,000 men), followed by Western Asia (Israel, Turkey, and Saudi Arabia) and North America. On the contrary, people living in Central and South America and Africa have the lowest probability to develop the disease during their life (age-standardized incidence of 4 per 100,000). An exception is Egypt, where BCa is still the most common malignancy, with an age-standardized incidence rates varying between 10 and 30 per 100,000 men (Fedeli et al. 2011). This has been historically related to the endemic presence of *Schistosoma haematobium*, a trematode that, after the penetration of the bladder wall, induces a chronic bladder inflammation and eventually leads to the development of squamous cell carcinoma (SCC) (Mostafa et al. 1999). However, recently, SCC incidence has been declining while urothelial cell carcinoma increased, probably as a consequence of the increased exposure to other risk factors such as smoking and environmental pollution (Salem and Mahfouz 2012).

These geographical differences and the related incidence and prevalence trends mostly reflect the exposure rates to well-known risk factors, in particular to cigarette smoking. Smoking is associated with a higher risk of not only developing BCa but also failing to respond to therapy as well as to experience disease recurrence and progression and death after therapy (Rink et al. 2013a, b, 2015; Crivelli et al. 2014). Moreover, the natural BCa history should be considered, since current epidemiologic data reflect tobacco exposure rates of previous 20–40 years. This could explain the high rates observed in Western countries, where the smoking prevalence in the 1970s and 1980s was very high (42% of US men in 1965 and 63% of Spanish men in 1978) (Antoni et al. 2017; Regidor et al. 2010). In high HDI countries, smoking prevalence in men started to decrease over the past decades, but, due to the long lag time between exposure and disease development, the effect of this change is probably still awaited or masked by other factors such as the aging of population, leaving the population more susceptible to develop BCa by lowering rate of the weight of competing causes of death. Conversely, among growing economies, smoking prevalence just started to decrease or is still increasing, suggesting that BCa prevalence and mortality will probably not decrease or will even increase in the next decades. Moreover, while the proportion of smokers decreases, the absolute number of people is increasing, leading to a net increase in the absolute number of smokers.

When diagnosed with BCa, the mortality rates vary worldwide geographically. The age-standardized mortality rates are higher in Western Asia and Northern Africa (4.6 and 4.4 per 100,000, respectively) compared to those in more developed countries (Greiman et al. 2017).

The different patterns of exposure to cigarette smoking or to other risk factors such as the presence of arsenic in drinkable water or the working exposure to aromatic amines cannot alone fully explain the observed geographical differences. Disparity in terms of healthcare systems could limit the access to diagnosis and treatment in some countries. Actually, the mortality-to-incidence ratio (MRI), which can be considered as an indirect measure of biological difference in

disease behavior or health system-related attributes (Hébert et al. 2009), is higher in less developed countries (0.40–0.68 vs. 0.20 for Western and Eastern African regions vs. European and North American ones, respectively). A strong inverse relationship between HDI and MIR has been shown.

Finally, since the highest probability of developing BCa occurs in the decade between 75 and 85 years, the much lower life expectancy in many developing countries could play a non-negligible role in lowering incidence rates in these regions. As the life expectancy disproportionally increases in these countries, this is likely to lead to a differentially faster increase in BCa incidence, prevalence, and mortality in these countries.

Ethnicity Differences

Race also has a significant influence on BCa epidemiology. BCa is twice as common among American Caucasian compared to African-American men. Moreover, the incidence in Hispanic and Native Americans is one half and one sixth, respectively, of that of White Americans (Madeb and Messing 2004). Data from SEER program collected between 1995 and 1997 showed that the lifetime probability to receive a BCa diagnosis was 3.7% among White male and 1.2% among their female counterpart compared to 1.3% and 0.8% among African male and female, respectively (Schairer et al. 1988).

Despite the lower incidence rates, African Americans have a younger age at diagnosis and may often harbor more aggressive disease at the time of presentation. This could be related to the higher proportions of variant and rare histologies such as SCC and adenocarcinoma among black patients contributing to the tendency toward advanced stage at diagnosis and worse survival (Madeb and Messing 2004; Rogers et al. 2006). However, independently from histology, black race was found to be associated with a higher rate of high grade and MIBC as well as with a higher proportion of metastatic disease at diagnosis (Klaassen et al. 2016; Mallin et al. 2011; Lee et al. 2006).

As a partial consequence of these disparities, racial differences also lead to different survival patterns. African Americans have a significantly higher risk of dying from BCa during the first 3–4 years from diagnosis compared to White Americans (Scosyrev et al. 2009). Blacks have the worst 5-year cancer-specific survival among all ethnic groups (82.8%, 81.9%, 80.7%, and 70.2% in whites, Asian/Pacific Islanders, Hispanic, and blacks, respectively) (Yee et al. 2011).

Differences in mortality rates between races also remain after accounting for the effect of standard clinicopathologic characteristics, suggesting that host-related features such as racial biological variation and individual differences in carcinogens' detoxification and in DNA repair mechanisms could play a role in various phases of carcinogenesis and contribute to differential susceptibility's patterns between races. However, access to care surely plays a part in the differentially worse outcomes of black BCa patients.

Racial disparities have also been observed in regard to diagnostic evaluation and treatment administration. It has been found that, among US population, African Americans with an incident diagnosis of hematuria had a lower chance to undergo a complete hematuria evaluation compared to Caucasian patients, even after adjusting the analyses for the effects of socioeconomic factors, availability of medical care, and risk factors for BCa (Ark et al. 2017). Moreover, black patients with MIBC were less likely to undergo radical cystectomy as well as pelvic lymph node dissection (Williams et al. 2017). More generally, blacks undergoing radical cystectomy experienced lower quality of care, as evidenced by the use of lower-volume surgeons and hospitals, the lower use of evidence-based process of care, and the higher incidence of adverse events (Barocas et al. 2014). This is likely due to limitations in healthcare access, which can be influenced by several factors including socioeconomic status, insurance, distance to care facilities, transportation, and social support. Finally, social factors such as smoking habit and occupational exposure vary among races, are difficult to account for in retrospective cohorts, and should always be taken into consideration.

Socioeconomic Aspects

For many malignancies, patients belonging to lower socioeconomic groups experience worse oncological outcomes secondary to multifactorial causes such as a delay in diagnosis and treatment. This seems to be also true for BCa. A study on 90,000 patients diagnosed with breast, lung, colon, rectal, ovarian, endometrial, renal, bladder, and prostate cancer showed that advanced stage at diagnosis was independently associated with an increasing level of socioeconomic deprivation (Lyratzopoulos et al. 2013). A single-center study conducted in the UK found that women coming from more deprived areas were more likely to present with advanced stage and had a significant worse survival compared to those coming from richer areas. Possible explanations are that patients with hematuria from poorer areas are more likely to delay visiting their general practitioner and that BCa symptoms are more often misattributed to urinary tract infections in these patients, leading to a delay in referral to the urologist (Moran et al. 2004). Moreover, since smoking not only represents the main risk factor for BCa development but also influences the prognosis of BCa patients, the higher proportion of smokers among lower socioeconomic status groups could play an undeniable role in supporting these disparities. Indeed, men and women from lower socioeconomic background are more likely to be exposed to heavy long-term tobacco and occupational hazards and carcinogens.

The Current and Future Burden of Bladder Cancer

The costs of BCa were estimated to be €4.9 billion per year in 2012 across Europe, with the 5 most populous countries (Germany, France, Spain, Italy, and UK) accounting for 3 quarters of the total. In the USA, the cost of BCa was estimated at €3.2 billion per year in 2010 (Leal et al. 2016; Mariotto et al. 2011). BCa contributed to 3% of the total cancer costs, compared to the 15% of lung, 12% of breast, 10% of colorectal, and 7% of prostate cancers. However, after accounting for the effect of the different prevalence rates of the diseases, the healthcare cost per patient of BCa is the highest of all cancers reaching €5621 per patient, making BCa the most cost-intensive cancer over the lifetime. This is the consequence of the excessive costs related to the very high recurrence rate and ongoing invasive monitoring required for the surveillance of NMIBC patients and of those related to the treatment of metastatic disease and to the end-of-life care (Svatek et al. 2014).

With the aging of population, BCa will become even more frequent and develop in an even bigger public health challenge (Soria et al. 2016). Actually, in the next 40 years, in developed countries, the population over 60 years is expected to double. As a consequence of these expected trend, by 2030, the annual BCa incidence in Europe is projected to increase from the current 124,000 to 219,000 cases, with two fifth of this increase due to the aging of population (Leal et al. 2016). However, at least in developed countries, it is possible that the increase of BCa incidence due to the aging of population will be mitigated or even neutralized by a decreased exposure to risk factors such as tobacco exposure and occupational carcinogens. In support of this argument, the incidence of BCa is recently decreased in some registries, mainly reflecting a decreased smoking habit and better occupational regulations. However, the trend seems to be ununiform also between equal-developed countries. Actually, and surprisingly, while the age-standardized incidence in the UK is decreasing, BCa rates remained stable in white Americans in the same period (Burger et al. 2013).

The burden of BCa will instead strongly increase in developing countries, as the result of several factors. First, the world population is expected to increase by 2.5 billion in the next 40 years, and this increase will be almost completely absorbed by the less developed regions (GLOBOCAN n.d.). Second, we are witnessing a change in the geography of smoking, with a shift from the developed to the developing world, that will result in a serious increase in BCa incidence in the next decades. Third, the slow but continuous improvement in life expectancy among developing regions will result in an increased proportion of patients at risk of developing, suffering, and dying from BCa. While the

proportions will increase slowly but steadily, the absolute numbers will explode.

While, worldwide, the incidence of BCa will probably increase in the next future, a positive trend with decreasing mortality could be observed in most regions, especially in Western countries. Actually, mortality rates tended to increase in men in most European countries between 1960 and 1990, with a subsequent decline, even if no clear pattern of trends could be observed in women. The decrease in BCa-specific mortality seems to be mostly related to the changes in risk factors exposure and more effective and safer care. Actually, smoking impacts on NMIBC and, probably, also on MIBC outcomes, being associated with recurrence and cancer-specific mortality. Moreover, smoking cessation and time since cessation have been associated with reduced recurrence rates and improved oncological outcomes, even if the magnitude of this association remains controversial (Rink et al. 2013a, b; Soria et al. 2017).

It has to be underlined that the decrease in mortality seems to be only moderate and inconstant (in the USA, mortality has essentially not varied in the last 25 years), mainly due to the treatment options available for more advanced and metastatic disease, which remained mostly the same for 40 years. However, the recent advent of immunotherapeutic agents, in combination with better systemic chemotherapy and surgical management, promises to radically change the future of advanced disease patients, leading to a critical improvement of oncological outcomes while preserving safety and an acceptable quality of life over long periods of cancer cycle. The advent of novel technologies in cancer diagnostics and care delivery together with processes such as centralization of care and precision medicine strategies will lead to transformative improvement for BCa patients.

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Symptoms and Diagnostic Tools for Bladder Cancer

18

Tobias Grimm, Jan-Friedrich Jokisch, and Alexander Karl

Contents

Abstract

The **symptoms of bladder cancer** (BC) can vary widely; sometimes only unspecific dysuria with irritative or obstructive symptoms can be present. **Painless gross hematuria** represents the most common symptom of BC. Ostial or urethral tumor obstruction might lead to impaired renal urine outflow, leading to **flank pain**. Advanced localized BC can display in **abdominal distention, pelvic pain, and even palpable masses** whereas metastases can be associated with multiple symptoms. **Urine tests** often represent the initial diagnostic marker. The ***urinary cytology*** **(UC),** in which exfoliated cells of the urothelium are extracted and microscopically examined, **promotes a high sensitivity in high grade (G3) tumors and carcinoma in situ.** UC should be utilized as an adjunct to cystoscopy, since positive UC can indicate urothelial tumors in the entire urinary tract. In order to improve sensitivity of UC, numerous different ***urinary marker tests*** were developed; however, a use for regular screening is not recommended, yet. In patients with suspected BC the ***white light cystoscopy*** **(WLC)** represents the diagnostic gold standard. The ***fluorescence cystoscopy*** **(photodynamic diagnosis (PDD))** shows diagnostic advantages compared to WLC, outlined in improved detection rates and improved recurrence free survival. ***Narrow-band imaging (NBI)*** represents another promising visualization tool. ***Computed tomography*** **urography and MRI** can help to identify tumorous lesions in both the bladder and the upper urinary tract.

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Introduction

Bladder cancer is the ninth most common cancer worldwide, while 430,000 new cases were diagnosed in 2012. Male patients have a strong predominance of these tumors; tobacco smoking is considered to be the main risk factor for the development of urothelial cancer. In general, survival from bladder cancer differs by region; while bladder cancer mortality slightly declines in high-income countries, less developed regions of the world have a much higher burden with more than 60% of all bladder cancer cases and half of all cancer deaths.

New treatment approaches as well as new technologies for an optimized diagnosis of bladder tumors have been established over the recent years. These current developments could help to reduce morbidity and also increase survival rates in the future.

Symptoms

At initial diagnosis bladder cancer (BC) patients may present with different symptoms. Many of these symptoms are even completely unspecific and resemble those of other diseases of the urinary tract. In early stages, many patients even do not describe any complaints at all. Bladder tumors tend to bleed with increasing size since angiogenesis plays an important role in tumor growth (Wallace et al. 2002).

As consequence the leading and also the most common symptom in BC patients is painless gross hematuria. In this case, patients often notice a brownish-reddish discoloration of their urine, but usually there are no symptoms of pain during urination. The presence of blood in the urine is quite often self-limiting. Some studies report about gross hematuria as a symptom in BC patients in up to 97.5% of all cases with an allover positive predictive value up to 10.3% (Fus and Gornicka 2016; Carson et al. 1979). Regarding this, male patients over 60 years present with the highest positive predictive value with 22.1%. The positive predictive value decreases considerable with patient's age in the same study (Kiragu and Cifu 2015).

Above this asymptomatic microhematuria may indicate BC or malignancies of the urinary tract too. However, asymptomatic microhematuria shows a lower sensitivity compared to gross hematuria and shows tumor of the urinary tract in up to 15% of all cases. With asymptomatic microhematuria one should even think of carcinoma in situ of the bladder (Bruyninckx et al. 2003; Massey et al. 1965).

Bladder tumor in general and particularly carcinoma in situ of the bladder might additionally come along with dysuria symptoms. These symptoms obviously do not just concern to men but simulate lower urinary tract symptoms with all its usual complaints. On the one hand, there are irritative symptoms like high micturition frequency, the sensation of incomplete voiding, nocturnal polyuria, urinary urgency, or even vesical tenesm. Irritative symptoms occur in up to 25% of all BC patients. A frequent cause could here be attendant urinary tract infection, which is described in up to 40% of all cases (Cox et al. 1969; Turner et al. 1977). Even more causes could be decreased bladder capacity, pain, or tumor necrosis with accompanying inflammation. As recently shown this might even be reflected in changes regarding patient's laboratory values like elevated CRP levels or leukocytosis (Ozcan et al. 2015; Grimm et al. 2015). On the other hand, there are obstructive symptoms like low urine flow rate with persistent storage symptoms that may be caused by bladder neck obstruction of local tumor growth.

Depending on the localization and the spread of the tumor, various complaints may occur. As already described bladder neck obstruction may lead to lower urinary tract symptoms as tumor growth close to the bladder ostium might effect ostial and ureteral obstruction. As a result, a sufficient urine flow from the renal pelvis to the bladder is no longer ensured, which could lead to flank pain.

In patients with locally advanced BC, you could find complaints of abdominal distention, pelvic pain, and even palpable mass at initial diagnosis. In patients with metastatic BC, afflictions dependent on the localization of metastases arise. For instance, pain caused by osseous

metastases or disrupted lymph drain of the lower limb could emerge caused by lymph node metastases.

In principle, however very unspecific, the presence of B symptoms can also be indicative for BC.

Diagnostic Tools

An adequate diagnosis for malignant lesions of the bladder is essential for an effective treatment of both: non-muscle-invasive (NMIBC) and muscle-invasive bladder cancer (MIBC). Since there is no sufficient marker for general screening and systemic early detection, numerous diagnostic tools are required to ensure effective diagnosis.

Urine tests ("dipsticks") often represent the initial diagnostic marker for symptomatic or asymptomatic patients. Urine test stripes detect even minor microhematuria quickly and effectively and have a high availability. Dipsticks should be completed by a light microscopy of urine samples. This allows further qualification as size and structure of erythrocytes can help to clarify origin of bleeding.

The ***urinary cytology*** **(UC)** in which exfoliated cells of the urothelium are extracted and microscopically examined shows a high diagnostic specificity for BC cells (90–100%). In G3 tumors, UC promotes a high sensitivity whereas only low sensitivity in G1 lesions is shown (Turco et al. 2011). For the detection of CIS the sensitivity rises up to 21–100% (Têtu 2009). Therefore, UC should be utilized as an adjunct to cystoscopy in high-risk tumors of the bladder, since positive UC can indicate urothelial tumors anywhere in the urinary tract. Nevertheless, negative UC does not exclude the presence of malignancy of the bladder. Accuracy of UC is limited by examiner's experience and can be impeded by local urinary infections, nephrolithiasis, and intravesical instillation therapy (Lokeshwar et al. 2005; van Rhijn et al. 2005).

In order to improve sensitivity of UC, numerous different ***urinary marker tests*** were developed. Different marker systems such as *NMP22, ImmunoCyt, BTA stat, BTA TRAK, cytokeratins, and FISH (UroVysion)* have been admitted by the US Food and Drug Administration (FDA) (Tritschler and Scharf 2007).

Protein-based marker systems: Nuclear matrix protein number 22 (NMP22) reflects the cell proliferation by quantifying mitotic activity. The marker system utilizes an immunoassay using monoclonal antibodies detecting the NMP22 (Tritschler and Scharf 2007). Bladder tumor antigen (BTA: BTA stat and BTA TRAK) detects complement factor H-related protein, which is typically elevated in bladder tumor patient's urine. Presence of hematuria and infection can also influence the results; therefore, BTA is not recommended as a regular screening procedure (Goodison et al. 2013). Cytokeratins (CK) are stromal proteins that can be found in BC patient's urine. Elevation of molecules such as CK-18, CK-20, and CYFRA 21-1 can be utilized as a urinary tumor marker.

Cellular-based marker systems: ImmunoCyt uses three monoclonal antibodies in patient's urine in order to detect urothelial cells. Whereas fluorescence in situ hybridization (FISH/UroVysion) detects cell alterations, indicating genetic instability as a sign of malignancy (Tritschler et al. 2013) (Table 1).

Although usually sensitivity for high-grade tumors in urinary marker tests was shown to be higher, specificity normally appears to be inferior

Table 1 Summary of urinary marker systems (Adapted by EAU Guidelines) (Babjuk et al. 2015)

Markers	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumors (%)
FISH (UroVysion)	30–86	63–95	66–70
Immuncyt/uCyt+	52–100	63–79	62–92
NMP22	47–100	55–98	75–92
BTA stat	29–83	56–86	62–91
BTA TRAK	53–91	28–83	74–77
Cytokeratins	12–88	73–95	33–100

to UC. Therefore, current guidelines (AUA and EAU guidelines) do not recommend urine marker tests for screening, diagnosis, or follow-up of patients with BC (Babjuk et al. 2015). An additional utilization of FISH can be considered in the presence of uncertain UC results in order to enhance the specificity (Schlomer et al. 2010).

In patients with a suspected malignancy, the rigid or flexible ***white light cystoscopy*** **(WLC)** presents the diagnostic gold standard for NMIBC and MIBC. Sensitivity and specificity in WLC in terms of detection rate varies between 6–84% (sensitivity) and 43–98% (specificity) (Jocham et al. 2008). WLC efficiency depends strongly on the performing physician (Babjuk et al. 2015). If the presence of a BC is evident, a transurethral resection of the tumor (TURB) is mandatory. The procedure of TURB is the basis for both: histopathological diagnosis and the complete resection of the lesion. TURB should therefore be performed systematically and in individual steps (Babjuk et al. 2015). It is essential for the further treatment and patient's prognosis that detrusor muscle is included in resection in order to perform an adequate histological staging and in order to reduce risk of recurrence (Herr and Machele Donat 2008; Mariappan et al. 2010). Especially for CIS and micropapillary lesions, WCL and white light TURB show diagnostic limitations.

The ***fluorescence cystoscopy*** **(photodynamic diagnosis (PDD))** shows diagnostic advantages compared to WLC (Filbeck et al. 2002). Fluorescence cystoscopy utilizes violet light after an intravesical instillation of a photosensitizer like hexaminolevulinic acid (HAL). Data indicate that PDD has a significant higher detection rate compared to white light in terms of patients-levels (92% vs. 71%) and biopsies-levels (93% vs. 65%) (Mariappan et al. 2010; Mowatt et al. 2011; Kausch et al. 2010). The detection rate for CIS lesions is considered to be up to 40% higher using PDD (Kausch et al. 2010; O'Brien et al. 2013). Therefore, PDD in the initial TURB is highly recommended by different studies (Babjuk et al. 2015). Additionally PDD should be performed in patients with: multifocal tumors, high-grade tumors in patient's history, and suspected CIS (Babjuk et al. 2015; Onkologie 2016). Although the utilization of PDD significantly improves recurrence free survival and increases time to recurrence, there is no evidence for a reduction of progression rate for PDD in TURB (Mowatt et al. 2011; Yang 2014).

Narrow-band Imaging (NBI) represents another visualization tool in which different light spectra lead to a contrast enhancement between urothelium and BC. Data indicate that NBI improves tumor detection rate (Cauberg et al. 2010; Zheng et al. 2012). So far there is no evidence concerning a reduction of progression compared to WLC or PDD.

Imaging in Bladder Cancer

If there is clinical evidence for a BC, *abdominal ultrasound* of the bladder represents a noninvasive imaging of the bladder and can therefore help to identify intravesical lesions. Renal ultrasound can also help to identify hydronephrosis caused by obstructive tumor infiltration.

Computed tomography (CT) urography can help to identify tumorous lesions in both the bladder and the upper urinary tract. If CT urography is not available, MRT urography or intravenous urography (IVU) can be recommended. At the moment CT urography is the state-of-the-art imaging for the urinary tract. After diagnosis of high-risk lesions of the bladder, multifocal tumors, or tumors localized near the trigonum or ostia, CT urography is recommended (Onkologie 2016). If MIBC is evident, abdominal and thoracic CT scan is mandatory in order to complete staging. Bone scintigraphy or CT scan of the caput is only recommended if clinic indicates such imaging. MRT is only recommended for evaluation of soft tissue infiltration of tumor. So far PET-CT/MRT is not commonly recommended for staging or follow-up for BC.

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Transurethral Resection of Bladder Cancer and Its Applications

19

Stefania Zamboni, Marco Moschini, and Atiqullah Aziz

Contents

Abstract

Transurethral resection of bladder tumors (TURBT) is a procedure performed to diagnose and stage bladder cancer (BCa) and to resect all visible tumors. This chapter is focused on TURBT surgical technique, possible complications, and available tools which can improve the quality of resection to correctly stage the neoplasm and to reduce recurrences and progressions of non-muscle-invasive BCa.

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Introduction

Transurethral resection of bladder tumors (TURBT) is a procedure which represents the initial treatment to diagnose, stage, and resect all visible tumors if technically possible and to perform biopsies of suspicious areas. TURBT is not only a diagnostic procedure but also a therapeutic procedure. In case of a suspicious bladder tumor, TURBT remains crucial in order to obtain a histopathological confirmed diagnosis of a bladder. Furthermore, TURBT is the essential procedure to decide whether an organ sparing approach in case of non-muscle-invasive disease is sufficient or a radical cystectomy is required in case of a muscle-invasive disease or high-risk non-muscle-invasive disease. Taking this all into consideration, TURBT is a key step in the treatment of bladder cancer.

Preoperative Diagnostics

The indication for a TURBT is a suspicious finding of bladder tumor via cystoscopy or imagings. Preoperative laboratory evaluation of coagulation and kidney parameters, respectively, should be performed. A preoperative ultrasound examination of the kidneys should be done in order to exclude hydronephrosis and if necessary to perform a urinary diversion via nephrostomy before TURBT. Further imagings via CT/MRI of the abdomen and chest should be performed after histopathological evaluation in case of a locally advanced disease to exclude an extraorgan extension and metastases, respectively.

Anesthesia

The aim of the anesthesia is to enable a safe resection with appropriate analgesia and relaxation of the pelvic floor, the abdominal wall, and the bladder. A general or a regional anesthesia or a combination between the two can be equally used. Regional anesthesia can be performed as an epidural or spinal blockade and they provide the advantage of an awake patient in case of intraperitoneal bladder perforation which can be identified by the appearance of abdominal pain. The stimulation of the obturator nerve, which is located close to the lateral wall of the bladder during the TURBT can provoke an obturator nerve-reflex with contraction of the adductor muscle of the leg, which consequently determines a sudden movement of the leg that can lead to a bladder perforation. Two options are available to prevent this phenomenon; one method consists of paralyzing the patient with a short-acting depolarizing drug that, however, can be only used only if the patient is in general anesthesia. The second method consists of the "obturator nerve block" which can be obtained with several techniques. One of them consist of the direct injection of Lidocain through a long needle, inserted 2 cm lateral and caudal to the pubic tubercle and the needle is walked off the inferior border of the superior ramus of the nerve and it enables to block the main trunk before it divides. Another technique consists on the transvesical block; after using a nerve stimulator to detect the nerve on the lateral bladder wall, 10 ml of 1% lidocaine are slowly injected through the working channel of a cystoscope. According to own clinical experience, a semi-filled bladder reduces the risk of an obturator nerve reflex during resection of the tumor at the lateral walls of the bladder.

Antibiotic Prophylaxis

Intravenous antibiotic prophylaxis at the time of anesthesia is recommended for this surgery to prevent infectious complications. The type of antibiotic prophylaxis should be decided on the base of the resistance profile within the region of the treating hospital. A preoperative urine culture should be performed in case of suspicious urine assessed via dip-stick, and any detected infection should be treated before the procedure according to the pathogen spectrum.

Surgical Technique

The position is the same adopted for a classic cystoscopy. The patient is placed supine in a low lithotomy position: the knees should be separated enough to allow a comfortable manipulation of

the instruments. Before the surgical procedure, a bimanual examination should be performed unless the tumor is clearly small and noninvasive: the bladder should be palpated bimanually between a finger in the rectum or vagina and the other surgeon's hand, which is applied over the abdomen in the lower part. Usually, the presence of a palpable disease indicates the invasion of the muscle, either within or through the bladder wall. The bimanual palpation should be repeated at the end of the TURBT. A 24 Fr resectoscope has to be lubricated and inserted into the urethra. An accurate visual inspection of both anterior and posterior urethra with a 0° lens attached to a camera should be carried out. In case of resistance during the urethral passage, any forcing should be avoided. The procedure is pursued with the aid of irrigation either of sterile water or glycine 1.5%. Once the bladder is reached, all its surface should be accurately examined to establish a plan for the sequence of resection with a 30° lens (authors' preference), alternatively with 12°, 70°, or 120° lens. The urine ejaculation from both ureteric orifices should be observed searching for possible hematuria from the upper tract; in case of its detection, a separate urine sample should be collected for a cytologic evaluation. The bladder capacity should be evaluated, which is important in cases of a repeat resection. TURBT is best performed with the bladder half full since an empty bladder increases the risk of bladder perforation and a full bladder of overdistention. Each visible tumor should be resected systematically and completely if possible and submitted separately for histopathologic evaluation. The presence of detrusor muscle in the specimen is required. The resection is performed with a resectoscope equipped with a cutting monopolar or bipolar loop, similar to the one used for transurethral resection of prostate. The cutting mode should be activated before the contact between the loop and the tissue; this seems to be the only way to ensure a visually controlled penetration. There are two basic approaches to perform a TURBT: staged resection and en-bloc resection. A staged TURBT is performed in several phases (Fig. 1). First, the exophytic portion of the tumor is resected. Then, the next layers of tissue are resected in a similar fashion until the base of the tumor is reached. Finally, the base of the tumor is resected. En-bloc resection may be used for small tumors, generally those <3 cm in the greatest dimension (Fig. 2). The advantages of an en-bloc resection include more accurate pathologic assessment due to the decreased cautery artifact, the avoidance of tumor fragmentation, and the preservation of the spatial orientation of the tumor relative to the bladder wall. However, no study found superiority of en bloc resection, but available evidences suggest safety and its oncologic equivalence compared to the staged TURBT (Kramer et al. 2017). A separate sample of the ground of the resection including the muscle should be performed in order to avoid an understaging. Since the coagulation of neoplastic tissue is very difficult, the coagulation of the wound should be performed after the cut on the healthy tissue, from the margins to the inner area.

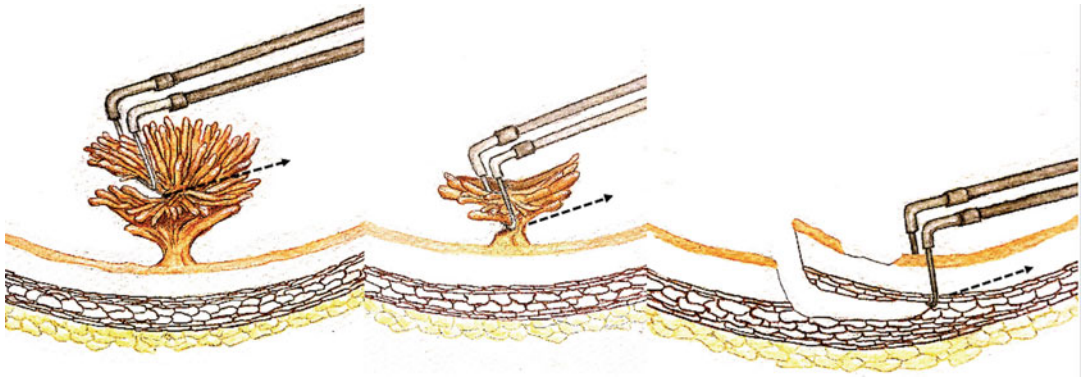

Fig. 1 Antegrade staged transurethral resection

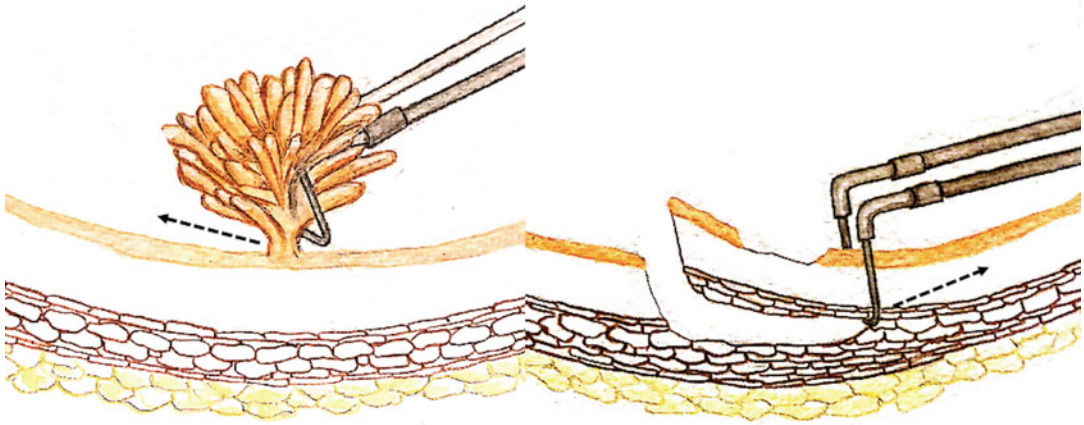

Fig. 2 Retrograde "en bloc" transurethral resection

As already before mentioned, at the end of the TURBT, the bimanual examination should be repeated before the insertion of the catheter. The bladder should be emptied, and any possible residual tumor has to be carefully palpated to determine the depth of the invasion, the eventual invasion of adjacent organs, and the potential fixation to the pelvic wall. In case of non-muscle-invasive bladder cancer, the probability to palpate a lesion bimanually is low. At the end of the procedure, a three-way transurethral catheter (at least 20 Charrier) should be inserted; continuous irrigation with sodium chloride 0.9% is recommended to clear and prevent clots. The catheter should be maintained for 24 h in case of superficial resections and more (at least 2–3 days) in case of deep or extended resection.

Special Conditions

Tumors in Bladder Diverticulum

By definition, tumors in bladder diverticulum do not have a muscular layer between themselves and the serosa. This feature makes the resection of this type of tumors challenging due to the high risk of bladder perforation. In general, small lesions with the appearance of low-grade tumors can be treated safely with a combination of resection and fulguration whereas large or high-grade tumors should be treated with diverticulectomy, partial or radical cystectomy.

Involvement of the Ureteral Orifices

Resection can be safely performed to remove tumors located close to the ureteral orifices, whereas cautery should be used as little as possible, given the high risk of subsequent stenosis.

Tumors in Bladder Dome

Resection of these tumors can be very challenging because of the difficulty in reaching the tumor and the high risk of intraperitoneal perforation if the resection is too deep especially in older women who have thin bladder walls. To help the resection, the surgeon or an assistant can applicate a pressure just above the pubic symphysis (Fig. 3) and the patient can be placed in the Trendelenburg position.

Biopsies During TURBT

Biopsies are recommended for all suspicious areas detected during a TURBT. Moreover, random biopsies of a unsuspicious bladder urothelium

Fig. 3 Resection of tumors in bladder dome

should be performed especially in patients with previous or suspected CIS (van der Meijden et al. 1999) since it can be present also in a normal-looking mucosa or in case of discordance between cytology and cystoscopy. Biopsies of the prostatic urethra should be taken in case of known or suspected CIS, tumors located on the bladder neck, positive cytology with macroscopic negative bladder (Mungan et al. 2005), or when are alterations of urethral mucosa are visible.

Complications of TURBT

The overall rate of complications of TURBT is low. The most frequent minor complications are development of irritative symptoms and minor bleeding which can occur in the immediate postoperative period. Major complications are rarer and consist mainly of uncontrolled hematuria and bladder wall perforations which are more frequently extraperitoneal, treated with a prolonged maintenance of the transurethral catheter. On the contrary, intraperitoneal perforations require a surgical repair.

Photodynamic Diagnosis (PDD) and Narrow Band Imaging (NBI)

Conventionally, cystoscopy and TURBT are performed with a white light. Given the high rates of residual or recurrent tumors after a white light cystoscopy, new technologies have been developed to improve the visualization and the detection of bladder diseases.

PDD

PDD consists of preoperative intravesical instillation of a fluorophore that is a precursor in the heme biosynthesis pathway. Hexylaminolevulinate (HAL) and 5-aminolevulinic acid (5-ALA) have been used for this technique. The 5-ALA is converted in all nucleated cells into an active fluorescent molecule, the protoporphyrin IX (PPIX), which in normal conditions is rapidly converted to heme. Tumor cells have a different metabolism compared to those of a normal urothelium, and these differences lead to a selective accumulation of PPIX which is about five times higher in neoplastic cells (Krieg et al. 2000). The fluorescence of PPIX is achieved by the presence of pyrol rings, and PPIX emits red light (635 nm) when exposed to a blue light (around 400 nm). About 1 h before the planned TURBT, 50 ml of solution of a fluorophore is instilled into the bladder through a transurethral catheter. The fluorescent cystoscopy is performed with a rigid cystoscope combined with a light source called D-light and should be done with an empty bladder. PDD showed a higher sensitivity and a lower specificity compared to white light endoscopy in detection of BCa, with a high rate of false-positive (Mowatt et al. 2011) even if artifact fluorescence is usually less intense than the one determined by a tumor. Moreover, a recent meta-analysis demonstrated a reduced recurrence rate in patients who underwent PDD-guided TURBT (Chou et al. 2017) compared to those treated with the white light endoscopy. The use of PDD is currently recommended in several cases. Firstly, in every patient with a new presentation of non-muscle-invasive BCa. Therefore, tumor detection is higher in patients evaluated with white light plus PDD compared to those evaluated with the white light alone (Mowatt et al. 2011), and as already mentioned, recurrence and progression rates are significantly lower (Chou et al. 2017; Gakis and Fahmy 2016). Moreover, PDD is particularly helpful in detection of CIS (Daneshmand et al. 2018) and improves quality of resection (Geavlete et al. 2010). Secondly, in patients with positive cytology and negative white light cystoscopy since it has been shown that PDD detect tumors in approximately 30% of patients with this condition. And finally, PDD is indicated for the treatment of multifocal recurrent tumors.

NBI

NBI takes advantage of the hypervascular nature of bladder cancer to enhance the contrast with the normal urothelium. It consists of modified optical filters applied to the light source of a video endoscope system which filter the light into two bandwidths of 415 and 540 nm. The intensities of blue and green light are increased, and these two narrow bandwidths are strongly absorbed by hemoglobin in hypervascular neoplastic tissues. Several studies reported the advantage of NBI in detection of non-muscle-invasive BCa compared to white light endoscopy and in recurrence especially in patients with low-risk tumors (pTa low grade, $<$30 mm, no CIS) (Naito et al. 2016).

Role of re-TURBT

It is not always possible to achieve a complete resection of the tumors since often the lesions are too big or located in areas difficult to reach with the resectoscope. Sometimes the incompleteness of the TURBT is caused by the necessity of a limited anesthesiologic time due to patient's comorbidity or to the need to interrupt the procedure for the occurrence of intraoperative complications. In any case, the rates of residual tumors after the initial TURBT are high and variable according to grade of the lesions (higher for T1 high grade tumors) (Gontero et al. 2016). Moreover, several studies have demonstrated that the understaging of tumors during the initial TURBT is common and the probability increases when the muscle is absent in the pathologic specimen (Herr 1999). A re-TURBT is recommended in all cases of macroscopic incomplete initial resection, when the muscle is not present at pathologic evaluation and in all T1 and high-grade tumors, because in these cases, a re-TURBT

decreases rates of recurrences and progressions (Gontero et al. 2016). When indicated, the second TURBT should be performed 2–6 weeks after the first operation.

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How Endoscopy Founded Modern Urology

20

Friedrich H. Moll and Dirk Schultheiss

Contents

Abstract

Within the urologist daily work, the cystoscope, the deriving techniques in diagnosis and therapy, and the "view into the cavity" remain one of the most important activities, which define the specialty, as a specialty of its own. The knowledge about these "stories" helps us to understand our daily work in a more comprehensive way. The visualization together with the development of microscopy and histology served the purposes of a science-oriented medicine to be "objective."

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Introduction

The word endoscopy (from Greek ἔνδον éndon, intern, and σκοπεῖν skopein, to examine, to monitor) derives from the old Greek language and means "to examine within, looking inside." Early specula have been unearthed that credit us of primitive endoscopy of human cavities like the vagina or the bladder. The urinary system received high attention and became a major field of research in visualization of the human body because it was easily accessible.

A story of the endoscope starts a cohort of information about urology, endoscopy in general for laypersons, medical professionals, and medical historians. It seems that the cystoscope, which is the base for most of all modern endoscopes, stays at its beginnings. Further on many historians and medical historians lined out that the cystoscope is the defining instrument of the specialty which had its scientific roots as a specialty of its

own in the first quarter of the nineteenth century (Netzhat 2011; Reuter et al. 1999; Engel 2007).

The concept of examining the body's interior and its organs dates back to ancient times. The *Hippocratic Corpus* records perhaps the first successful rudimentary efforts at endoscopy, which used a speculum in order to outline fistulas, and later, Galen's Levicom refers to an object which is an anal speculum (Moran 2014a).

Early Attempts at the Turn to the Nineteenth Century

Attempts to bring light directly into the human body had been initiated by Philipp Bozzini of Frankfurt (1773–1809), who in 1806 introduced his "Lichtleiter" (light conductor) in an effort to study organs and human body cavities (Figdor 2002). The Lichtleiter was a sharkskin-covered instrument housing a candle within a metal chimney. A mirror on the inside reflected light from the candle through attachments into the urethra, the vagina, or the pharynx. Short after its beginnings, there were two ways: the one with the urine- or fluid-filled bladder or the other with the air-irrigated bladder (Schultheiss et al. 1999). This development was remarkable. It was the first use of reflected light as a source of illumination. Unfortunately Bozzini was censured for his ingenuity since the intended use of the instrument was considered an unnatural act under contemporary mores. The name of several pioneers was connected with the endoscope up to the presentation of a routinely usable cystoscope by Maximilian Nitze (1848–1906).

The instrument by the French Pierre Salomon Segalas (1792–1875) in 1826 was constructed by adding an extra candle as a light source (Segalas 1827). He presented a cannulated catheter which drained the bladder and facilitated the inspection of the bladder cavity. This device was constructed from a gum elastic material in order to improve the safety and comfort of the procedure. Despite some improvement, this "speculum urethra-cystique" similarly failed to enable effective inspection of the bladder and was primarily used in female patients.

The instrument of Francis Cruise (1834–1912) of Dublin is another milestone in presenting endoscopy in medical and urological routine (Cruise 1865).

Antonin Jean Desormeaux (1814–1894) is credited with coining the word "l'endoscopie," a term he introduced, along with his revamped device, to the Academy of Sciences in Paris on July 20th, 1853, and the first functional endoscope which enabled a greater number of physicians to proceed in endoscopic examinations. He was also the first to successfully use the endoscope to operate on living patients. One of the major improvements in this instrument was the use of a gasogene lamp, which was constructed of a mixture of alcohol and turpentine and provided much superior illumination to previous technologies and improvements in focusing the light coming from the endoscope (Reuter et al. 1999; Netzhat 2011; Desmoreaux 1867) (Fig. 1).

For the USA, the names of the instruments of John D. Fisher (1798–1850) of Boston and Phillip Skinner Wales 1860 should be mentioned here (George Tiemann and Co 1872). As reported, Fisher conceived of his "instrument for the illumination of dark cavities" (a name later changed to the more prosaic "esophagus mirrors") in 1824 while still a medical student. He subsequently published his findings in 1827 in the Philadelphia Journal of Medical and Physical Sciences. It was a cumbersome elongated and angled speculum.

The Wales' instrument was produced by Horatio Kern, a well-known cutler in Philadelphia. Wales' instrument contains a metal shaft, again with a very acute beak, but it uses an ophthalmologic mirror to reflect light down the channel (Fisher 1827; Museum of Medico historical artifacts 2016).

The Dawn of the Cystoscope

In 1878, true endoscopy was born. In that year, Maximilian Carl-Friedrich Nitze (1848–1906), a German physician and proto-urologist, presented the first working cystoscope (Halling and Moll 2016; Herr 2006, which he had created in

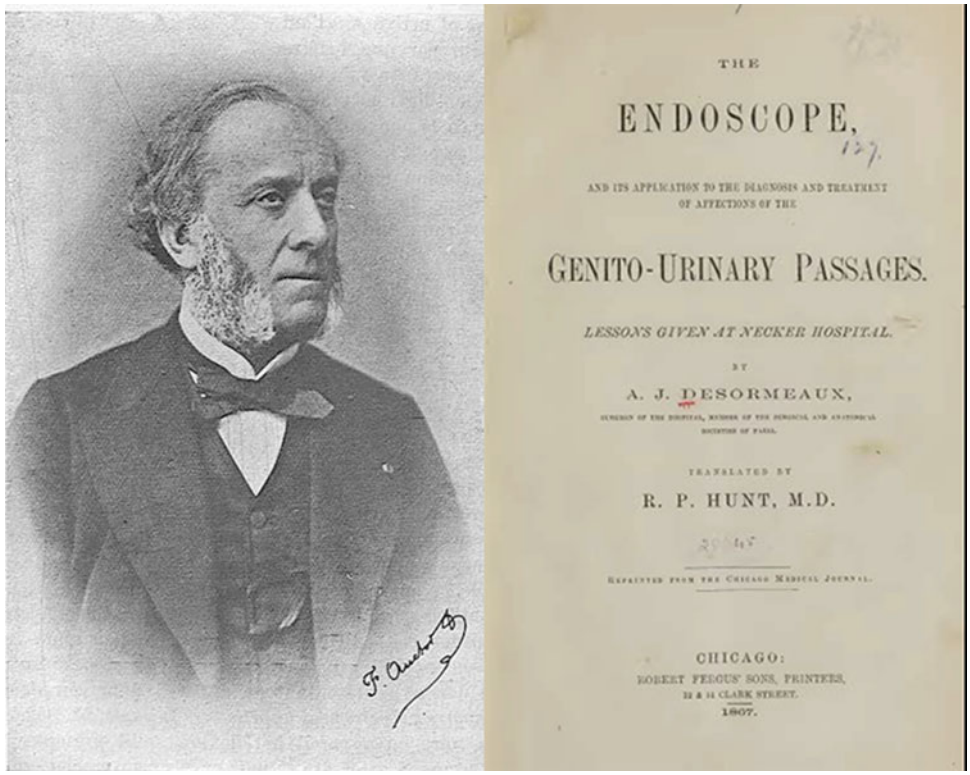

Fig. 1 Left A. J. Desormeaux (1814–1894) from Pousson, A., Desnos, E. (1914). Encyclopédie française d'urologie, Doin et fils, Paris p 286; frontpage of A. J. Desormeax's The Endoscope in its English translation by R. P. Hunt, Fergus' Sons, Chicago, by courtesy of Museum, Library and Archives, German Society of Urology, Repo Keyn. During the middle and the last quarter of the nineteenth century, translations of famous texts and books were a major source for international communication about very new scientific developments

collaboration with the Viennese cutler Joseph Leiter (1830–1892) (Newell 1887) (a prototype model had been developed together with the cutler Wilhelm Deicke (1834–1913) and was presented on a cadaver in 1876 at Stadtkrankenhaus Dresden (Saxony) (Nitze 1881; Reuter and Reuter 1998; Moll et al. 2015) (Fig. 2).

The Nitze/Leiter cystoscope was a landmark discovery, but it was by no means perfect. His idea was to place lenses into the tubes at prescribe distances to focus the image at an ocular. The instrument's biggest drawback was the tungsten wire used for lighting, which got very hot and required a complicated water-cooling system (Engel 2007). When Nitze could improve the instrument with the so-called mignon bulb, a low-amperage light bulb constructed like a miniaturized Edison bulb that was small enough to fit into the tip of a cystoscope, the instrument's application was much more usable. These bulbs enabled the development of cheaper and easier-to-use instruments. The only problem was that light bulbs burn out, often at the most inopportune moments, like within the procedure. The Electro Surgical Instrument (Quarrier and Rabinowitz 2017) under the direction of Henry Koch and Charles Preston, the head electrician, created what has become known as the mignon bulb. This story is often forgotten in the history of endoscopy and urology (Engel 2007; Moran 2010). Nitze himself regarded this as a milestone of progress: "In one simple step, the cystoscope was transformed form a complicated and technically difficult instrument into an instrument easy to use." Due to the pitfalls of these bulbs which enabled the development of easier-to-use

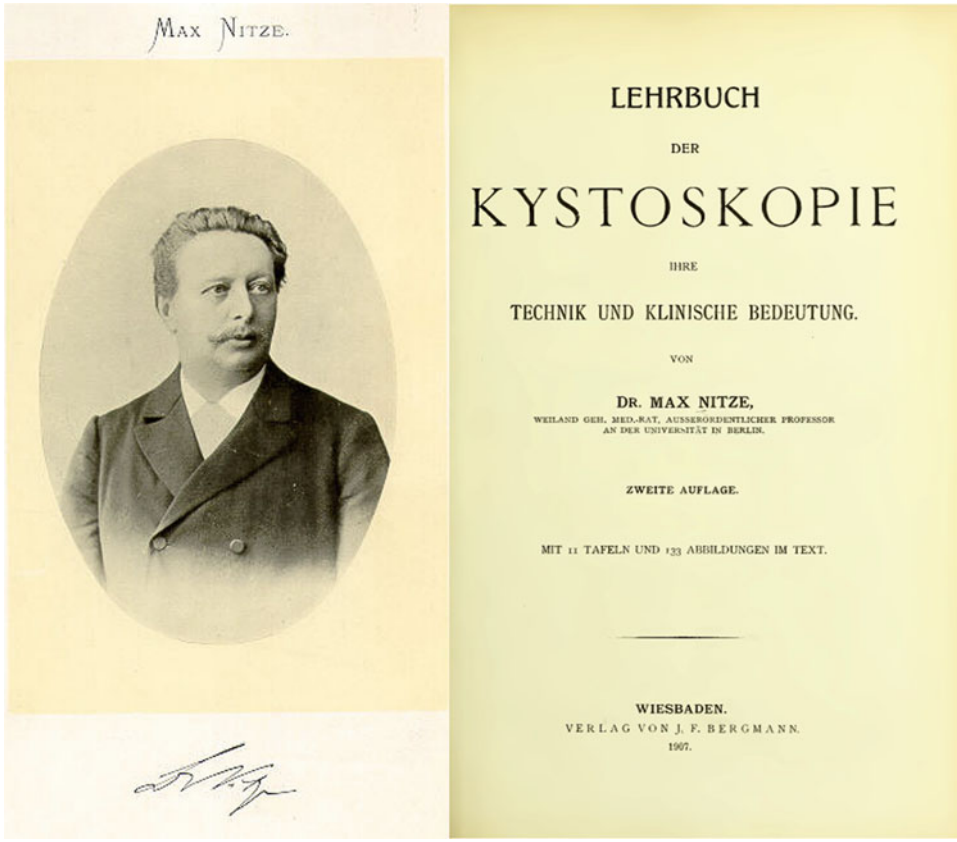

Fig. 2 The only photographical image of Max Nitze (1848–1906) (*left side*) which founded the remembering culture of this pioneer in urology, here in the edition "Galerie hervorragender Ärzte und Naturforscher (gallery of famous physicians and scientists), publishing house J. F. Lehmann, Beilage (supplement) Münchener Medizinischer Wochenschrift, without year imprint, light print, unsigned, Museum, Library and Archives, German Society of Urology. On the right the frontpage (frontispiece) of the second edition of Nitze's textbook, J. F. Bergmann, publishing house, Wiesbaden, by courtesy Museum, Library and Archives, German Society of Urology, Repro Keyn, with permission

instruments, some physicians, however, were still using simple instruments not a subject to such failures (Fig. 3).

Howard A. Kelly (1858–1943), the chair of the Department of Obstetrics and Gynecology at Johns Hopkins in Baltimore, for instance, used a small speculum-like tube that was used with the patient in the knee-chest position. Initially, it had neither a light nor a lens system attached to it (Schultheiss et al. 1999). Up to that time, repairing of a cystoscope especially in foreign countries and overseas (USA, Canada, and South America) was difficult and needs time because most of the major manufacturers and cutlers like Hirschmann, Louis and H. Loewenstein, Georg Wolff (1873–1938), or Josef Leiter were located in Germany or Austria-Hungary.

Reinhold Wappler (1870–1933), a young cutler, immigrated to New York from Oranienbaum, Germany, in 1890. Soon after arriving, he set up his own company to produce an American cystoscope and to repair European instruments. One of the first instruments developed at the new workshop was the F. Tilden Brown (1853–1910) composite cystoscope (1899), an elegant set of instruments with a lens to look straightforward, one at a slight angle, and another at a right angle. Obturators that were used to insert the instrument

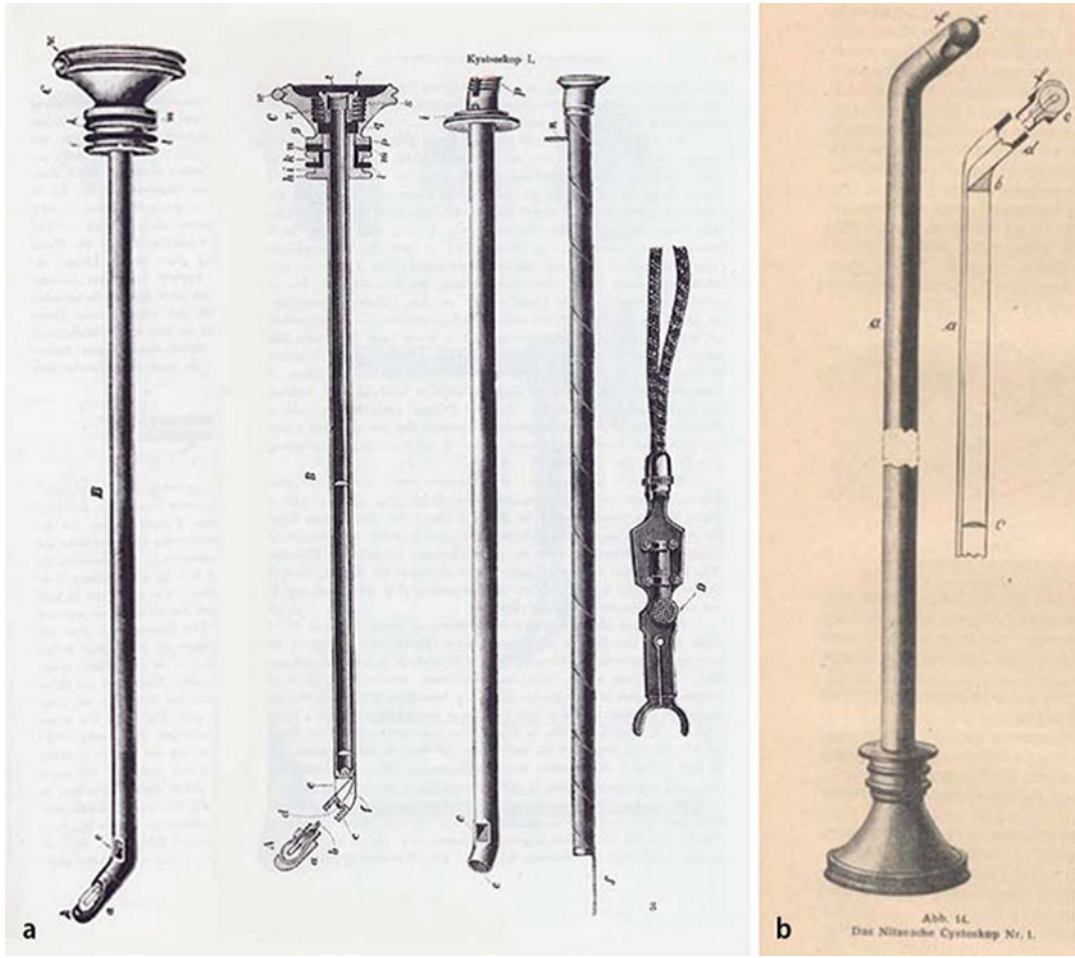

Fig. 3 A Nitze "Kystoskop" I (1887) on the left with mignon bulb. Nitze describes everything in detail (Nitze M (1907) Lehrbuch der Kystoskopie. Ihre Technik und klinische Bedeutung, 2. Aufl. Bergmann, Wiesbaden, S 33). Leopold Casper (right) laid much attention on the functionality (Casper L (1905) Handbuch der Kystoskopie (textbook of cystoscopy), 2nd edition, Thieme, Leipzig, p 14), Museum, Library and Archives, German Society of Urology, Repro Keyn, with permission

blindly were exchanged for the lens system. Wappler developed a new telescopic objective lens embodying a hemispherical lens, with William K. Otis (1860?–1906) (Otis 1893), for which he was granted his first US patent (Schultheiss et al. 1999; Reuter and Reuter 1999; Reuter 2000; Barnes 1959; Edmonson 1997).

One of such innovators, who is credited with highest respect, was the German Leopold Casper (1859–1959) (Moll et al. 2009) whose name is equivalent to the name of Max Nitze. His catheterizing cystoscope of 1895 was the first to employ an ureterizing cystoscope which fits for men and women at every time and not by accident. Casper was the first to reproduce constant results in ureteral catheterization. This instrument was not easy to use. It employed a complex mirror system between the eyepiece and the shaft, but it had one big advantage: It allowed ureteral catheterization easily without rigid angle. However, the instrument did not have a deflector to guide the catheter tip into the urethral orifice that would come later by the Cuban-born French Joaquin Albarran (1860–1911). This instrument was fitted with a

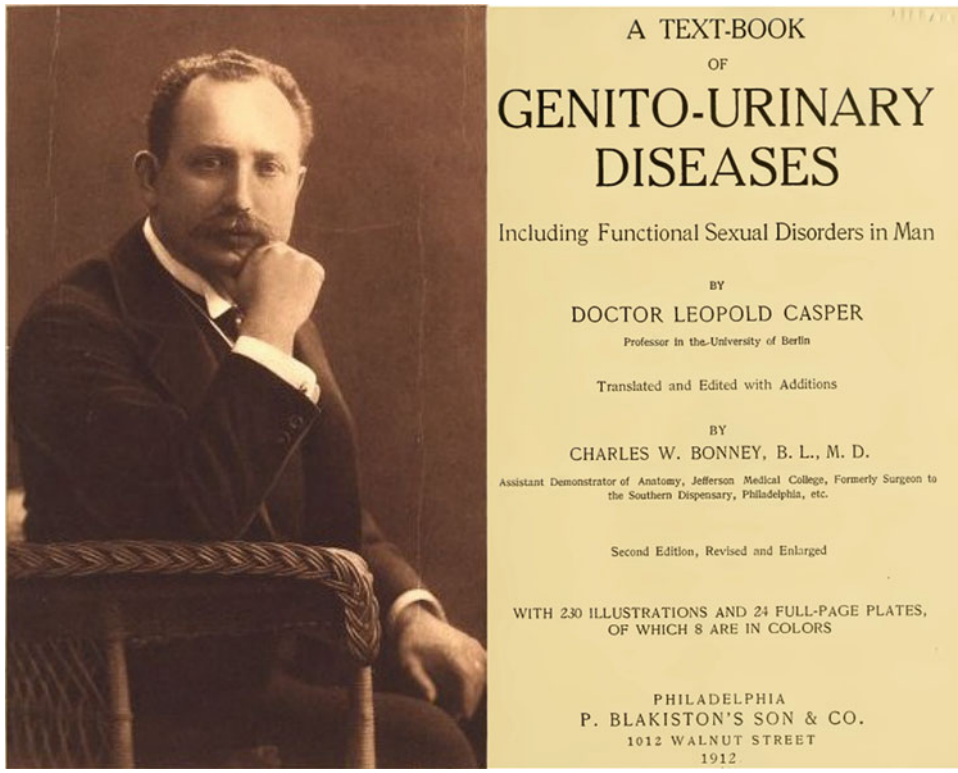

Fig. 4 Leopold Casper (1859–1959) about 1900 (left) and frontpage of the second edition of the English edition of his textbook on genitourinary diseases, Blakiston's Son & Co publishing house, by courtesy Museum, Library and Archives, German Society of Urology, Repo Keyn, with permission

special pusher to handle the ureteral catheter. This led ultimately to an intense and very public rivalry with Max Nitze, whom he eventually sued in the courts over a matter of priority (Fig. 4).

Important Developments

The employment of ureteral catheterization was the base to outline functional renal testing by Leopold Casper and Paul F. Richter (1868–1934) (Richter lost his position at III. Medical Clinic of the Charité Hospital after 1933 due to the atrocities of the Nazis), a well-refined system of some chemical investigations to outline the function of each kidney. This tool made kidney surgery more safe and effective (Casper 1903). Later on chromocystoscopy by Eugen Joseph (1879–1933) and Friedrich Voelcker (1872–1955) with the dye indigo carmine often replaced the use of an ureteric catheter, because the expulsion of the dye could be visualized directly (Moll 1996) (Fig. 5).

In the USA, Leo Buerger (1879–1943) a Viennese immigrant to New York, who based his design on an instrument by F. Tilden Brown of New York, invented the "working horse of American urology." The instrument was then produced by the Wappler Electric Company (later ACMI, Gyrus/ACMI, Olympus since 2008) for nearly five decades. It was easy to use, enabled catheterization of the ureters, and provided an excellent image. Virtually every urologist owned one or two of these instruments. Up to now a refurbished instrument is the award for the best scientific lecture during the history meeting of each American Urological Association (AUA) meeting.

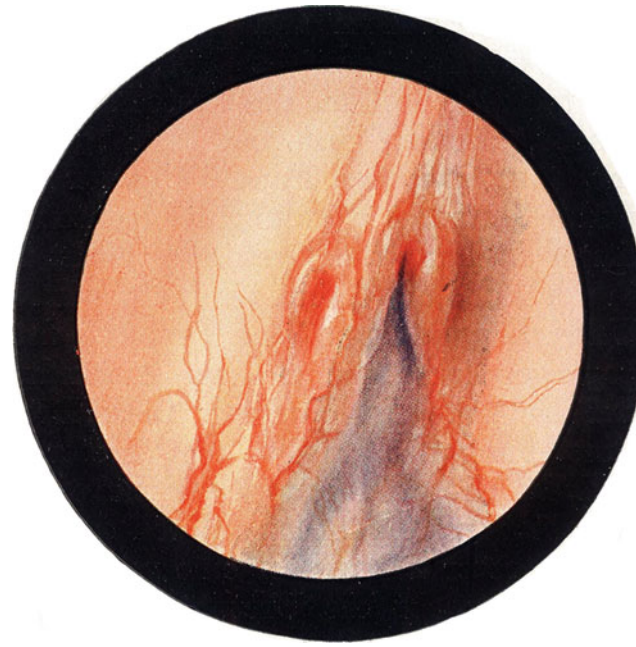

Fig. 5 Ostium duplex outlined with indigo carmine, Fig. 46, from Eugen Joseph, Lehrbuch der diagnostischen und operative Cystoskopie, Julius Springer, 1929, with permission of the Springer Publishing House. Repro Keyn, with permission

Within the field of treating bladder tumors, Nitze proposed operating cystoscopes with cold and hot wire loops for galvanocautery (Nitze 1895). After having finished his postgraduate studies in Prague, Vienna, and Berlin, Edwin Beer (1876–1938) of the Mount Sinai Hospital in New York applied a technique of utilizing a high-frequency monopolar current (Oudin current) to treat lesions within the bladder, a method that revolutionized the treatment of bladder tumors. For this outstanding contribution, he received the first gold medal awarded by the International Urological Society during their meeting at Brussels in 1927 (Jardin and Moll 2011; Beer 1910). Later on the fulguration techniques were displaced by resection techniques during the 1920s (Moll and Pelger 2015; Zorgniotti 1984) (Fig. 6).

Ureteroscopy: The Second Step in Outlining the Urinary Tract by Endoscope

In the field of urology, the development of the ureteroscope is the second major application of endoscopy in urology dating back to the 1970s. Just in 1929 H. H. Young (1870–1945) and R. McKay stumbled into the ureter of a child with posterior urethral valves (Young and McKay 1929; Dewan 1997). Tobias Goodman not only passed a 11Fr pediatric cystoscope into the ureters, and he was the first to perform interventional surgery to the upper tracts by fulgurating a low-grade transitional cell tumor within the ureter (Goodman 1997). In 1980, Enrique Perez-Castro Ellendt and Antonio Martinez-Pineiro developed longer instruments that allowed the visualization of the entire urinary tract, and the era of nephro-ureteroscopy began (Perez-Castro and Martinez-Piniero 1980). In parallel flexible fiber instruments to refine diagnostics were designed (Marshall 1964; Takagi et al. 1971; Takayasu and Aso 1974; Moran 2014b; Moll et al. 1990).

While often physicians are focused on the technical development of the instruments, it must be outlined that the real and important meaning of the invention of the endoscope in the history of science is the change of the diagnostic view. Within the emerging specialty of urology, the sense of vision became the most important diagnostic tool to receive the knowledge of diagnostics. The sounding utilized for diagnostic measurement

Fig. 1.

Fig. 2.
PLATE IX

Fig. 6 (**a**) Papillomatous tumor of the bladder, (**b**) appearance 8 days after Galvano-cauterization from the textbook of Georges Luys, (1870–1953) *Treatise about cystoscopy and urethroscopy* translated by Abraham Leo Wolbarst (1872–1978), Mosby, St. Louis, 1918, p. 160, Repro Keyn, with permission

within the bladder cavity was replaced by vision. Utilizing an endoscope had the advantage to enable the physician to document his findings by drawings and later on by photographies. So the results were saved on a data sheet (paper, film, or register) and could be brought to a wider public. This also meant that within several stages a documentation was possible, which enabled the physician to present and demonstrate a progression of a pathological finding in detail. At the beginning of that process, the physician had to "learn" to see in order to interpret the new "pictures" in a proper way. Visualization served the purposes of science-oriented medicine to be objective and to document the examination results. The pictures were self-evident and objective. Therefore many atlases and textbooks of cystoscopy and endo-urology up to now with detailed descriptions of the findings were published, because the pictures were not self-evident itself but must be outlined with a detailed text. So a combination of picture and text was needed to develop an endoscopic viewing in order to interpret an endoscopic findings properly. This enabled a broader public of physicians to learn, to interpret, and to train the new methods. A canon of a special tradition of words and pictures was established. On that base special pictures followed which laid the base for the "evidence of the pictures." As extracorporeal light sources had proven to be ineffective, attempts were made to bring light sources to the interior of the body. The reconstruction of this process can help to understand the background and knowledge of endoscopy today (Martin 2012; Martin and Fangerau 2011a, b; Burri 2008).

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21 Early-Invasive Urothelial Bladder Carcinoma and Instillation Treatment of Non-muscle-Invasive Bladder Cancer

Wolfgang Otto, Maximilian Burger, and Johannes Breyer

Contents

Abstract

Stage T1 non-muscle-invasive bladder cancer (NMIBC) is a very special subentity of urothelial bladder carcinoma showing progression in up to 50% within 5 years after first diagnosis. This chapter recalls recommended diagnosis and treatment of early-invasive bladder cancer in special and conservative adjuvant instillation treatment of NMIBC in general. In the end, indications of immediate and early cystectomy of NMIBC are discussed.

Keywords

Early-invasive bladder cancer · Stage T1 · Prognosis · Intravesical chemotherapy · Bacillus Calmette-Guérin · Early cystectomy

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Introduction

Early-invasive urothelial bladder cancer is a non-muscle-invasive bladder tumor at stage T1 with various clinical outcomes. While one third shows never recurrence, another third of patients recurs under progression and must be cystectomied to prevent death of disease that occurs at the level of stage T2 disease (Shahin et al. 2003).

Diagnosis of Stage T1 Bladder Cancer

Diagnostic assessment of stage T1 bladder cancer includes several steps that require increasing invasiveness and result in the histopathological verification of the urothelial carcinoma. The clinical suspicion has to lead to further investigation, as screening for bladder cancer is not recommended (Krogsboll et al. 2015).

Clinical Symptoms

Hematuria is the leading symptom in patients with bladder cancer, with the majority of the patients presenting with asymptomatic macroscopic hematuria (Kamat et al. 2016). Only 2–4% of the patients presenting with mircoscopic hematuria have bladder cancer (Sharp et al. 2013). Nonetheless, recurring microhematuria in combination with one of the known risk factors (past or current smoking, male sex, exposure to chemicals, etc.) demands further investigation (Sharp et al. 2013). Patients without hematuria suffer from a delayed diagnosis (Mansson et al. 1993). Other symptoms that may indicate towards bladder cancer are: urgency or dysuric symptoms.

Physical Examination

Physical examination cannot reveal stage T1 bladder cancer (Babjuk et al. 2016), but it should be performed to reveal a potential hydronephrosis through flank pain. Papillary or solid stage T1 tumor in or near the ureteral orifice can cause a hydronephrosis.

Ultrasound

Transabdominal ultrasound is recommended to detect visible intraluminal tumors of the bladder (Babjuk et al. 2016). Furthermore, differential diagnoses of hematuria like renal tumor, renal stone, or a hydronephrosis, as a result of obstruction by urolithiasis or urothelial carcinoma, can be detected.

Imaging

Radiologic imaging should be used in selected cases and is not recommended in routine diagnosis of bladder cancer (Babjuk et al. 2016). Multidetector-row CT (MDCT) has a sensitivity of 79%, specificity of 94% and accuracy of 91% and is not recommended for routine use in the detection of primary bladder cancer (Babjuk et al. 2016; Jinzaki et al. 2016). Intravenous urography (IVU) or computed tomography (CT) is able to detect papillary tumors of the upper urinary tract but not recommended due to the low incidence of findings (Babjuk et al. 2016; Goessl et al. 1997; Palou et al. 2005; Holmäng et al. 1998). The MDCT-scan of the abdomen has the highest sensitivity (93.5–95.8%), specificity (94.8–100%), and accuracy (94.2–99.6%) in detection of upper urinary tract urothelial carcinoma (UTUC) and thus should be the first option (Babjuk et al. 2016; Jinzaki et al. 2016). The IVU is inferior concerning sensitivity (75.0–80.4%), specificity (81.0–86.0%), and accuracy (80.8–84.9%) (Jinzaki et al. 2016). The MDCT can show smaller masses, is not impaired by intraabdominal gas, and can distinguish tumors from blood clots or stones (Jinzaki et al. 2016). Further information that can be acquired through MDCT is lymph node status and intrarenal tumors. Thus the IVU is recommended as an alternative if CT is not available (Babjuk et al. 2016; Nolte-Ernsting and Cowan 2006). MDCT and retrograde urography have similar sensitivity and specificity with MDCT being a not invasive procedure (Razavi et al. 2012). In case of contrast allergy, pregnancy or in young patients MRI of the abdomen can be performed but has several

limitations like a poorer resolution, various artefacts, and large studies comparing MRI to MDCT are missing (Vikram et al. 2009).

Imaging of the upper urinary tract should be considered in case of bladder tumor in the trigone, which has an incidence of 7.5% concomitant UTUC (Palou et al. 2005) and in follow-up of multiple and high risk tumors (Millán-Rodríguez et al. 2000).

Urinary Cytology

Examination of voided urine or bladder-washing specimens is performed to detect exfoliated tumor cells. The quality of urinary cytology depends on several parameters. The sensitivity depends on tumor grade, as the reported sensitivity for high grade or G3 tumors is 84%, for low grade or G1 tumors is 16% and for CIS is 60%, respectively (Yafi et al. 2015; Casey et al. 2015). Furthermore, evaluation of urinary cytology has high interobserver variability but specificity can raise up to 90% in experienced observers (Babjuk et al. 2016; Raitanen et al. 2002). Thus cytology can be considered in patients with CIS, G3, or high grade tumors in addition to cystoscopic evaluation. Negative urinary cytology does not exclude bladder cancer, whereas an urothelial carcinoma anywhere in the urothelial tract can result in a positive urinary cytology.

Voided first morning urine should not be used due to cytolysis because of the long contact to toxic substances within the urine (Layfield et al. 2004). The urine specimen should be collected 3–4 h after the last voiding and processed as soon as possible (Layfield et al. 2004). Urine washings with sterile isotonic solution concomitant to cystoscopy can also be used (Layfield et al. 2004). Intravesical infections, stones, intravesical instillation therapy, and low cell count can affect the quality of evaluation (Babjuk et al. 2016).

Urinary Marker Tests

Given the low sensitivity of urinary cytology especially for low grade tumors, various noninvasive urine tests have been the focus of many studies (Lokeshwar et al. 2005; Glas et al. 2003; van Rhijn et al. 2005; Vrooman and Witjes 2008; Lotan et al. 2010; Yutkin et al. 2010; Agarwal et al. 2008). Table 1 shows the sensitivities and specificities of the different tests compared to urinary cytology. The accuracy of urinary test systems is of course impaired by urinary infections, urolithiasis, and other malignant diseases of the urinary tract or manipulation.

To date, none of the urinary marker tests is recommended in the routine diagnosis of (primary) bladder cancer and none can reduce follow-up cystoscopies (Babjuk et al. 2016). As outlined above, there is also no application of these tests in bladder cancer screening. Few indications remain – especially for low or intermediate risk tumors – where urinary tests may give additional information to the golden standard cystoscopy. As the early-invasive T1 bladder cancer always displays a high risk tumor, follow-up should always include frequent cystoscopy and cytology and urinary marker tests are irrelevant in this situation (Babjuk et al. 2016).

Table 1 Sensitivities and specificities of the different urinary tests (adapted from (Babjuk et al. 2016))

Test system	Sensitivity (%)	Specificity (%)	Sensitivity for high grade tumors (%)
Urinary cytology	16–84	90	84
UroVysion (FISH)	30–86	63–95	66–70
Microsatellite analysis	58–92	73–100	90–92
Immunocyt/uCyt+	52–100	63–79	62–92
Nuclear matrix protein (NMP) 22	47–100	55–98	75–92
BTA stat	29–83	56–86	62–91
BTA TRAK	53–91	28–83	74–77
Cytokeratins	12–88	73–95	33–100

Cystoscopy

Despite the improvement in urine tests or imaging, cystoscopy remains the golden standard in the diagnosis of bladder cancer. Cystoscopy is regularly performed in an outpatient setting. Flexible instruments are recommended for the examination in men (Babjuk et al. 2016; Aaronson et al. 2009). In symptoms suggestive for bladder cancer, the visual examination of the bladder through cystoscopy can reveal papillary or solid lesions that have to be followed by transurethral resection of the bladder (TUR-B) and histological evaluation. Cystoscopy should be performed schematically and subtle to make every area visible. If concomitant Cis is suspected – usually displayed by a flat and red lesion – cystoscopy and histological evaluation should be complemented by urinary cytology and multiple biopsies (Kurth et al. 1995).

Treatment of Stage T1 Bladder Cancer

Transurethral Resection

After detection of papillary, solid or flat lesions via cystoscopy, transurethral resection of the bladder (TURB) always is the first step in bladder cancer treatment. It should clarify the diagnosis and macroscopically remove the complete tumor burden (Babjuk et al. 2016). There are different strategies to resect bladder tumors: small masses should be cut out en bloc, while larger ones are resected in fractions separated in the exophytic part of the tumor, the detrusor muscle, and the tumor surrounding areas. Random biopsies should be taken in cases of suspect cytology without macroscopic tumors from the four bladder walls, the trigone, and dome of the bladder to assess macroscopically hardly detectable carcinoma in situ (CIS). In our days, random biopsies were replaced by photodynamic diagnosis (PDD) that could show an increase of 23% in detection of CIS (Kausch et al. 2010). For exophytic non-muscle-invasive bladder cancer (NMIBC) PDD results in a statistically significantly better recurrence-free survival over all NMIBC risk groups and due to decrease of hospitalization in a reduction of tumor-related costs (Otto et al. 2009).

High rates of residual tumor burden in stage T1 bladder cancer of up to 65% and the danger of under-staging in initial TURB of 20% demonstrate the need of second resection in this patient group 2–6 weeks after initial TURB (Patschan et al. 2017; Hautmann et al. 2009). Due to high risk of recurrence and progression in early-invasive bladder cancer in every case of stage T1 bladder cancer, further treatment is essential.

Further Treatment Options

The guidelines of the leading international associations of urology recommend at least some sort of instillation therapy in every case of NMIBC. This applies especially for stage T1 bladder cancer, where at least long-term immunotherapy by intravesical Bacillus Calmette-Guérin (BCG) treatment should be performed and in some circumstances even early cystectomy is demanded, e.g., in high-grade stage T1 bladder cancer with associated CIS (Denzinger et al. 2008). Today European Organization for Research and Treatment of Cancer (EORTC) risk factors are decisive for prognostification of NMIBC.

The results of seven trials with 2596 patients were combined in the EORTC score to predict recurrence and progression of patients with NMIBC (Sylvester et al. 2006). The following clinical and pathological parameters have been included: number of tumors, tumor diameter, prior recurrence rate, stage, associated CIS, and grade (Table 2). The feasibility of this EORTC score for early-invasive bladder cancer at stage T1 is limited because the patients in these trials did not undergo a second TUR-B or receive maintenance BCG therapy. Furthermore, drugs for intravesical treatment have been used that are no longer used.

Thus the CUETO group developed a score for patients treated with intravesical BCG (Fernandez-Gomez et al. 2009). The following clinical and pathological parameters have been included: sex, age, prior recurrence status, number

of tumors, stage, concomitant CIS, and grade. Due to the more effective BCG treatment, the recurrence rates are lower than in the EORTC score, whereas the progression rates are only lower in high risk patients (Fernandez-Gomez et al. 2009). In patients treated with BCG, number of tumors and prior recurrence rate are the best predictors for recurrence. Regarding progression, stage and grade are the most important factors (Babjuk et al. 2016) (Table 3).

Considering grading, there is evidence that well-differentiated G1 tumors do not exist in stage T1 bladder cancer (Mikulowski and Hellsten 2005; Otto et al. 2011). Furthermore, in early-invasive bladder cancer at stage T1, the WHO1973 classification, that discriminates G1, G2, and G3 tumors is more suitable in prognosis prediction than the two-armed WHO2004/2016 classification that discriminates between low-grade and high-grade tumors (Otto et al. 2011; May et al. 2010).

Interobserver-variability leads to 40–50% non-conforming results regarding staging Ta vs. T1 and grading (May et al. 2010; Murphy et al. 2002; Bol et al. 2003; van Rhijn et al. 2010a). The reproducibility of the WHO2004/2016 classification is not superior to the WHO1973 classification (May et al. 2010; Rhijn et al. 2010b; Mangrud et al. 2014).

Table 2 EORTC risk calculator for disease recurrence and progression. (Adapted from Sylvester et al. 2006)

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2–7	3	3
≥8	6	3
Tumor diameter		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/year	2	2
>1 recurrence/year	4	2
Stage		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5

Intravesical Chemotherapy

Indeed EORTC risk factors remain the only established parameters in supporting the treatment decision of NMIBC. Whether intravesical chemotherapy or immunotherapy should take place depend on the probability of recurrence or progression. Where recurrence is the foremost risk of patients, intravesical chemotherapy is recommended. Patients with low risk of recurrence

Table 3 Probability of disease recurrence and progression according to EORTC score. (Adapted from Babjuk et al. 2016)

Recurrence score	**Probability of recurrence at 1 year (%)**	**Probability of recurrence at 5 years (%)**	**Recurrence risk**
0	15 (10–19)	31 (24–37)	Low
1–4	24 (21–26)	46 (42–49)	Intermediate
5–9	38 (35–41)	62 (58–65)	Intermediate
10–17	61 (55–67)	78 (73–84)	High
Progression score	**Probability of progression at 1 year**	**Probability of progression at 5 years (%)**	**Progression risk**
0	0.2 (0–0.7) %	0.8 (0–1.7)	Low
2–6	1 (0.4–1.6) %	6 (5–8)	Intermediate
7–13	5 (4–7) %	17 (14–20)	High
14–23	17 (10–24)	45 (35–55)	High

only demand an immediate instillation of chemotherapy, which reduces the 2-year recurrence rate statistically significant (Hinotsu et al. 1999). Further instillation treatment is not suitable in these cases.

For patients with intermediate or high risk of recurrence, adjuvant intravesical chemotherapy is recommended. Advantage of chemotherapy with foremost mitomycin C (MMC) instillations was proven for tumor recurrence but not progression in initial and recurrent NMIBC (Huncharek et al. 2000; Huncharek et al. 2001). There is no clear recommendation concerning duration of intravesival chemotherapy, mostly continued for 1 year (Sylvester et al. 2008).

Intravesical Immunotherapy

Especially for high risk NMIBC concerning recurrence and progression various meta-analyses could show that Bacillus Calmette-Guérin (BCG) is superior to MMC instillation treatment and other substances for intravesical treatment, e.g., epirubicin (Järvinen et al. 2009; Sylvester et al. 2010). Early-invasive bladder cancer should be treated by BCG instillations after reresection. Six weekly instillations should be mandatory, maintenance therapy is recommended (Böhle et al. 2003). Only these patients could show a statistically significant reduction of progression rate, but a distinct schedule could not be established yet. Indeed it should endure at least 1 year with up to 27 instillations up to 3 years (Lamm et al. 2000).

BCG Failure and Early Cystectomy

Immediate and early cystectomy describes radical cystectomy that is performed in patients with NMIBC either without instillation treatment or after NMIBC recurrence after failure of intravesical therapy. Based on the classification described above, stage T1 early-invasive bladder cancer always displays a high risk or even highest risk situation, where early cystectomy at least should be considered as an alternative to the bladder sparing approach by instillation therapy. Besides the clinical and pathological parameters indicative for early cystectomy, this is an individual decision that has to integrate patient's age, physiological and mental status. It has to be considered that more than 30% of the T1 tumors are understaged in TURB (Patschan et al. 2017; Hautmann et al. 2009; Denzinger et al. 2008). Established indications for early cystectomy are: BCG-failure, T1G3 recurrence after BCG-treatment, refusal of BCG-treatment, and T1G3 tumor in diverticulum because of the lack of muscle layer (Babjuk et al. 2016; Golijanin et al. 2003).

Early cystectomy for early-invasive bladder cancer should always include lymph node dissection, due to understaging and about 9–18% lymph node metastases in radical cystectomy specimens of T1G3 bladder cancer (Kulkarni et al. 2010).

Besides these indications, morbidity and mortality of radical cystectomy have to be considered. Early cystectomy for stage T1 bladder cancer provides the best oncological safety, which is dearly bought by incontinence, sexual dysfunctions and a perioperative 90-day mortality of up to 9% (Aziz et al. 2014). The lack of strong suggestive parameters for immediate or early cystectomy in combination to the side effects results in an individual treatment decision in high risk or highest risk T1 bladder cancer.

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Urothelial Carcinoma In Situ and Treatment of Bacillus Calmette-Guérin Failures

22

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Abstract

Despite its superficial growth, urothelial carcinoma in situ is an aggressive disease with high recurrence and progression rates. Macroscopic as well as microscopic diagnosis is challenging.

Bacillus Calmette-Guérin (BCG) is the most effective therapy for high-risk bladder cancer. In case of failure no other intravesical therapy has shown convincing results to be used in clinical routine. Radical cystectomy remains from an oncologic point of view the most effective therapy.

Introduction

Noninvasive flat urothelial tumors exhibit a wide spectrum of characteristics that vary from inflammatory, atypia, paraneoplastic, and clearly malignant. Moreover, denuded urothelium, inflammatory processes, and radiation-induced alterations make its differential diagnosis challenging.

Urothelial Dysplasia

Urothelial dysplasia is defined as a flat lesion with appreciable cytologic and architectural abnormalities that are believed to be preneoplastic but are not sufficient to be characterized as carcinoma in situ (CIS). Indeed, urothelial dysplasia is characterized by cohesive cells with mildly abnormal nuclear changes. Nuclear crowding, prominent nucleoli, and abnormal mitotic figures may be present. Umbrella cells can be found in dysplastic cells but not in CIS, helping in the differential diagnosis. These characteristics are mainly found in the basal layer, with a transition toward the luminal layer. Usually the urothelium is present in all its layers, but there can be an exfoliation of the more mature cells, exposing deeper altered layers.

Similarly to CIS, genetic instabilities like allelic loss of chromosome 9 and mutations in fibroblastic growth factor receptor 3 (FGFR3) are not infrequent, and are postulated to be the earliest genetic abnormality responsible for the transformation from normal tissue to atypia and dysplasia (Mhawech-Fauceglia et al. 2006).

The clinical relevance of urothelial dysplasia and its role as a precancerous lesion remains under debate. However, patients with a history of bladder cancer presenting with dysplasia are at risk for recurrence as it can progress into CIS in approximately 60% of the cases and need, therefore, a close follow-up (Cheng et al. 1999).

Carcinoma In Situ

CIS is a flat lesion of the surface urothelial layer composed of cells with high cytologic grade that per definition do not invade the lamina propria. While in T1 and higher stages concomitant CIS is found in about 50–60% of the cases, primary CIS is a relatively rare entity with a prevalence of about 3% of all new bladder cancer diagnoses (Moch et al. 2016). According to the TNM classification, CIS is a superficial cancer but, unlike low-grade Ta and T1, it elicits an aggressive behavior. Older studies published before the introduction of BCG therapy described the natural history of CIS. In these retrospective series, the average incidence of subsequent development of invasive disease was about 50%, and mainly in patients with diffuse CIS (Utz et al. 1969).

Macroscopy

Macroscopically it presents as a flat hyperemic area which mimics isolated inflammatory lesions or it may not be visible at all, making its diagnosis on white light cystoscopy challenging. Its occurrence can be isolated, diffuse, or concomitant with solid tumors. In the latter case, CIS can present as an erythematous area around the tumor and can be considered an extension of it.

Microscopy

Cells are large, pleomorphic, and chromatin clumping, and abnormal mitotic figures are common.

Nuclei are large, irregular, and hyperchromatic and present severe nuclear atypia as well as loss of cellular polarity. Loss of umbrella cells is characteristic in CIS and helps in the differential diagnosis with dysplasia. Cells are not cohesive and can easily exfoliate in the bladder (Lopez-Beltran et al. 2015). A typical CIS is depicted in Fig. 1.

Interobserver variability is high, even among experienced pathologists and despite many decades of efforts to develop pathologic classifications that reflect clinical behavior (Sharkey and Sarosdy 1997; Murphy et al. 2002)

Molecular Biology

Histopathological and molecular analyses support two major pathways in the pathogenesis of urothelial cancer. In the first one, normal urothelium degenerates to low-grade noninvasive disease. In the second one, normal urothelium develops CIS and subsequent muscle-invasive disease. There is also a third proposed pathway in which hyperplasia/dysplasia develops from normal urothelium and degenerates to high-grade papillary carcinoma and subsequent muscle-invasive disease (Fig. 2) (Knowles 2008).

Molecular studies have shown that the conversion of normal urothelium to dysplasia is associated with chromosome 9 deletions in 75% of cases, TP53 overexpression in 50%, and increased cellular growth in all cases (Mallofré et al. 2003).

Several other oncogenes and tumor suppressor genes, like fibroblast growth factor receptor-3 (*FGFR3*) and *RB1*, are involved in the genesis of CIS. The identification of combinations and sequences of these gene-alterations is essential for the understanding of the tumor own biology and the improvement of prediction models and is the focus of ongoing translational studies (Goebell and Knowles 2010; Robertson et al. 2017).

The differentiation between CIS and dysplasia using only histological feature is often difficult for pathologists. In this case, immunohistochemistry

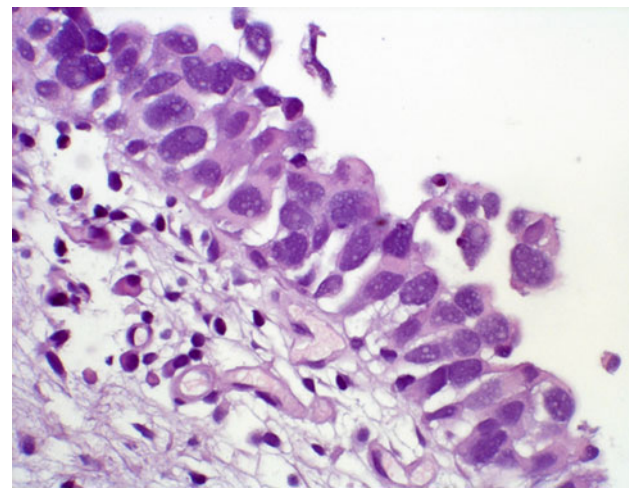

Fig. 1 Microscopic appearance of a carcinoma in situ of the urinary bladder. (Courtesy of Prof. A. Haitel, Department of Pathology, Medical University of Vienna, Austria)

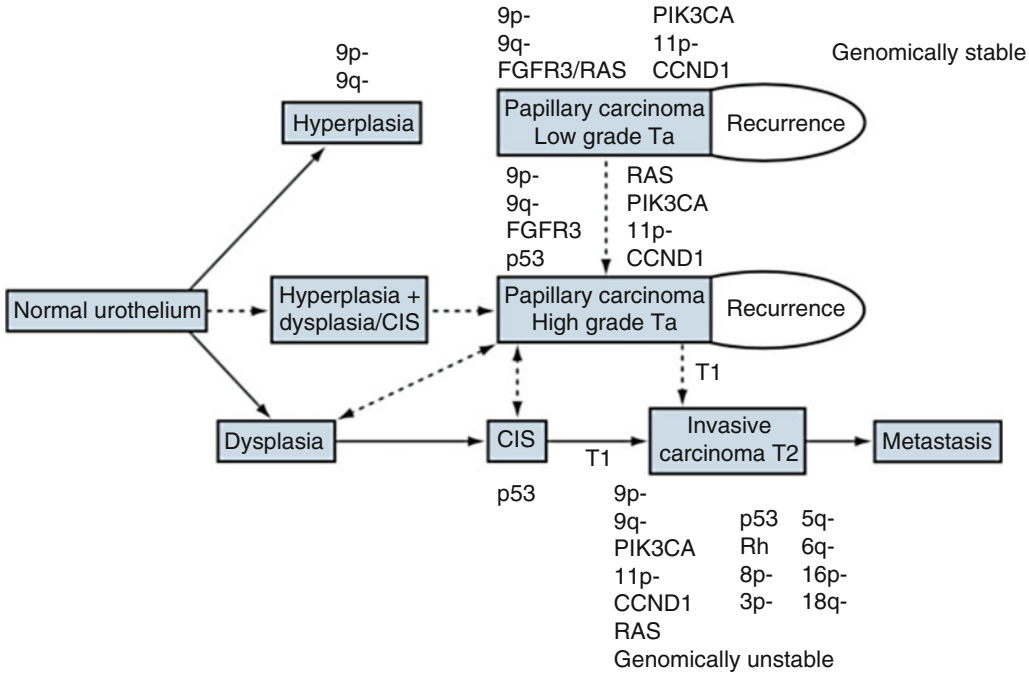

Fig. 2 Molecular pathway for the pathogenesis of development of papillary low-grade bladder cancer and carcinoma in situ. (Knowles 2008)

can help in the differential diagnosis. Usually CIS shows a p53 overexpression and genetic aberrations, particularly of chromosome 9 and 17 (Hopman et al. 2002; Knowles 2008; Goebell and Knowles 2010). Alterations in the *FGFR3* gene play a major role in low-grade cancer and demark a subpopulation with good prognosis and low recurrence rates whereas *FGFR3* mutations are a rare finding in high-grade tumors and CIS (Hernández et al. 2006).

The expression of cell-cycle proteins (i.e., p53 and p21) or adhesion molecules (E-cadherin) has been associated with clinical outcomes (Shariat et al. 2001, 2003), but their use as biomarkers in clinical routine is still limited due to lacking consensus definitions of assays and thresholds across the board.

A difference must be made between primary and concomitant CIS as they are two different tumor entities on molecular as well as prognostic level. Indeed, chromosome 9 loss is infrequent in the first one, while the latter has genetic alterations and molecular expression profiles similar to the concomitant tumor. Both have high *TP53* mutation rates and/or LOH of chromosome 17 (Hopman et al. 2002). This expression signature underlines the different pathways in carcinogenesis and development of papillary and invasive bladder cancer. Concomitant CIS probably represents a precursor stage of the main tumor. In summary, the genetic instability that characterizes CIS easily allows the occurrence of further alterations and, consequently, the development of invasive disease.

Clinical Implications

If symptomatic, patients with primary CIS present with irritative symptoms that are similar to those of a bacterial cystitis. Hematuria, gross or microscopic, can be present.

Clinical diagnosis is difficult, particularly under office white light cystoscopy, which can often be unremarkable. The definitive diagnosis comes often later in the work-up as part of mapping or TURB with enhanced imaging, such as photodynamic diagnosis (PDD).

Despite the apparently harmless definition, its clinical behavior is highly aggressive and if untreated progression rates to muscle-invasive

bladder cancer (MIBC) are as high as 60% (Lamm et al. 1998). Since the introduction of intravesical bacillus Calmette-Guérin and its report by Morales et al. in 1976, the natural history of CIS has changed and its progression to an extensive disease has become even more rare.

Clinical manifestations of CIS can be distinguished in:

- Asymptomatic focal primary CIS, which is the earliest and least aggressive form of the disease
- Symptomatic diffuse primary CIS
- CIS associated with prior or concurrent Ta or T1 urothelial carcinoma

CIS Diagnosis

The detection of CIS consists of a combination of cytological examination of exfoliated cells in urine and histological evaluation of random bladder biopsies under white light cystoscopy.

In case of suspected CIS or positive cytology without evidence of tumor in the bladder, the recommendation grade from the European Association of Urology guidelines for mapping biopsies of normal looking urothelium (grade B) and from the prostatic urethra (grade C) is low.

New imaging technologies have been developed in order to improve the detection rates and are currently widely used in clinical routine.

Photodynamic Diagnosis

PDD makes use of optical imaging agents instilled in the bladder before cystoscopy. These compounds induce the endogenous production of the photosensitizer protoporphyrin IX which accumulates selectively in neoplastic cells. If the cystoscopy is performed with light source of 380–470 nm (blue light), protoporphyrin IX is activated and induces emission of fluorescence light (693 nm) enhancing the detection and diagnosis of bladder cancer.

PPD has higher sensitivity (92% vs 71%) but lower specificity (63% vs 81%) when compared to white light cystoscopy (Mowatt et al. 2011). Moreover, it can detect up to 40% more CIS (Burger et al. 2013) and reduce recurrence but not progression rates (Rink et al. 2013).

Two photodynamic agents, 5-aminolevoulinic acid (ALA) and its derivate hexaminolevulinate (HEX), have been extensively investigated and are therefore mainly used in clinical routine. None of the two substances has shown a superiority in tumor detection compared to the other (Burger et al. 2009).

Both agents are precursors in the formation of the photoactive intermediate protoporphyrin IX and other photoactive protoporphyrins. After excitation with light at wavelengths between 360 and 450 nm, protoporphyrin IX returns to a lower energy level inducing fluorescence. The fluorescence from tumor tissue appears bright red and demarcated, whereas the background normal tissue appears dark blue. Protoporphyrin IX is not only accumulated in tumor cells but in general in all cells with an increased metabolism, including inflammatory cells. This increases the false positive rates in patients with urinary tract infection, recent TURB or intravesical BCG instillation within the last 3 months, although sensitivity still is higher than with white light in these cases. It is therefore advised to treat the infection or wait at least 6 weeks after the last BCG instillation. The use of PDD during TURB allows the detection of more tumors and a more radical resection. This has also a beneficial effect on recurrence rates with an absolute reduction of 10% in the first year of follow-up (Burger et al. 2013).

Narrow-Band Imaging

Narrow-band imaging reduces the whole spectrum of white light to two wavelengths, namely 415 nm blue light and 540 nm green light. These two wavelengths are the peak light absorption of hemoglobin allowing an enhanced visualization of hypervascular tumor tissue. The main advantage of this procedure, compared to PDD, relies on the avoidance of disposable materials and intravesical instillation prior to cystoscopy.

Several other visualization technologies for tissue differentiation have been developed and are mainly based on digital filters. These technologies will probably make the use of white light cystoscopy alone obsolete in the near future.

Cytology

Urine cytology on exfoliated cells is a powerful, fast, and cost-effective tool in the diagnosis and surveillance of bladder cancer. Urine cytology has a sensitivity of 28–100% for CIS but is highly investigator-dependent. Moreover, several factors like urinary tract infections, urinary stones, indwelling catheters but also incorrect retrieval and fixation of the urine can affect the quality of the material. It is imperative that all this information is reported to the pathologist to increase the value of the analysis.

The Paris Working Group has recently proposed a standardized reporting system for reporting and classifying urinary samples also considering clinical aspects of patient management.

- Adequacy of urine specimens (Adequacy)
- Negative for high-grade urothelial carcinoma (Negative)
- Atypical urothelial cells (AUC)
- Suspicious for high-grade urothelial carcinoma (Suspicious)
- Low-grade urothelial neoplasia (LGUN)
- High-grade urothelial carcinoma (HGUC)

In conclusion, isolated CIS is a highly aggressive disease with high progression rates to invasive disease if untreated. Its diagnosis is often challenging even if the development of new diagnostic imaging technologies has allowed a more accurate identification during endoscopic procedures.

The overall impact of better detection of concomitant CIS remains under debate because it may not alter management of patients who have high-risk NMIBC but its prognostic role in these patients, as well as in those with MIBC, is significant and essential for a more accurate risk stratification of urothelial cancer (Shariat et al. 2007a; Palou et al. 2012; Wheat et al. 2012; Youssef et al. 2011).

Therapy of CIS

Adjuvant intravesical BCG instillation after TURB has shown to reduce recurrence rates and at least delay progression when compared to TURB alone or in combination with intravesical chemotherapy. It is therefore the standard therapy for high-risk NMIBC. Intravesical BCG can potentially treat residual papillary lesions but should not be used as a substitute to complete transurethral resection. In this context, the treatment of CIS represents a completely different scenario. Indeed, transurethral resection is mainly restricted to small biopsies and a complete resection can never be guaranteed because of the before mentioned limitations. Therefore, adjuvant treatment with BCG is indicated and essential in every patient with CIS (Casey et al. 2015; Chade et al. 2010b). Particularly, patients with primary CIS treated with CIS have a 26% better response rate at 6 months compared to those with concomitant CIS or secondary to a papillary NMIBC (Chade et al. 2010a).

In the case of extensive disease, immediate radical cystectomy can be offered, achieving excellent long-term results, but in a relevant number of cases this would result in an overtreatment.

As shown in the subgroup analysis of the SWOG 8507 trial (Lamm et al. 2000) maintenance BCG cycles are of paramount importance for the long-term response to therapy. However, the optimal duration of maintenance is still under investigation. Nevertheless, in patients with high-risk disease 3 years of maintenance are more effective than 1 year for reducing recurrence (Cambier et al. 2016).

Response rates to BCG for CIS are excellent and range from 72% to 93%. On the other hand, 50% of these patients will experience recurrence and may develop progression eventually, requiring a lifelong follow-up (Takenaka et al. 2008; Sylvester et al. 2002). In patients with CIS persistence after a first induction cycle, a second induction can achieve complete response. Therefore, final response to therapy should be assessed after 6 months.

Patients with CIS are also at a higher risk of developing extravesical recurrence like in the upper urinary tract and prostate, resulting in worse survival outcomes. In the case of prostatic presentation, CIS invades only the epithelial lining of the prostatic urethra or the prostatic ducts and should be clearly differentiated from

urothelial cancer invading the prostatic stroma, which per definition is a T4a stage. The presence of prostatic CIS concomitant with primary pT1G3, represents an independent adverse prognostic feature. Therefore, the biopsy of the prostatic urethra is of paramount prognostic importance for an accurate risk stratification (Palou et al. 2012).

These cases can be treated with adjuvant BCG, but results are not optimal owing to the short exposure time of cancer cells to the agent.

Several BCG strains are available. One EORTC meta-analysis showed no difference in terms of reduction of progression to muscle-invasive disease (Sylvester et al. 2002). The choice which strain to use relies on clinical expertise and local availability.

Definition of BCG Failure

Defining a patient as failure requires particular attention as it drives relevant therapy decisions. Therefore, it must be assured that the patient has received an adequate and sufficiently long therapy schedule.

Recurrent or persistent disease after an induction cycle was in the past generally defined as BCG failure. This generalization, also due to the heterogeneity of older studies, does not accurately describe the possible scenarios associated with therapy duration time to recurrence and histopathologic features at the time of relapse. Indeed, all these characteristics have independent prognostic features and cannot be, therefore, generalized. Non-high-grade recurrence after BCG, for example, should not be considered as BCG failure.

The EAU guideline panel has categorized BCG failure in three categories which are reported in Table 1.

There are also a small number of patients who are defined as BCG intolerant because of the toxicity. These patients experience severe side effects that necessitate therapy interruption and prevent further instillations and are therefore at higher risk for recurrence.

As mentioned before, it is important to remember that the declaration of BCG failure can take up to 6 months. Indeed, 40–60% of patients that do not respond to a first induction cycle may respond to a second course. Further courses of BCG beyond two are not recommended because the failure rate is ≥80% of the cases (Sylvester et al. 2005). Patients who fail therapy within 6 months after the last instillation seem to have the same prognosis as those who are BCG refractory. The International Bladder Cancer Group summarizes these patients as "BCG unresponsive" (Kamat et al. 2016). The EAU guideline panel has proposed an algorithm for the treatment of BCG-failed NMIBC patients (Fig. 3).

Table 1 Categories of unsuccessful treatment with intravesical BCG

Whenever a muscle-invasive bladder cancer is detected during follow-up
BCG-refractory tumor: If high-grade, non-muscle-invasive papillary tumor is present at 3 months. Further conservative treatment with BCG is associated with increased risk of progression If CIS (without concomitant papillary tumor) is present at both 3 and 6 months. If patients with CIS present at 6 months, an additional BCG course can achieve a complete response in >50% of cases If high-grade tumor appears during BCG therapy
High-grade recurrence after BCG. Recurrence of high-grade/grade 3 (WHO 2004/1973; Epstein et al. 1998; Sauter et al. 2004) tumor after completion of BCG maintenance, despite an initial response

Treatment of BCG Failure and Recurrence After BCG

Based on the categories defining BCG failure, a risk adapted treatment can be offered to the patients. Previous history, the individual situation, and the histopathological report should always be considered in the decision making.

Generally, with the exception of CIS, patients failing intravesical BCG therapy are unlikely to respond to a rechallenge. Therefore, more aggressive treatments with curative intent are advisable and radical cystectomy would be the first choice as stated by the EAU and AUA guidelines panels.

A second BCG induction can be offered in selected patients with intermediate-risk disease or with primary CIS.

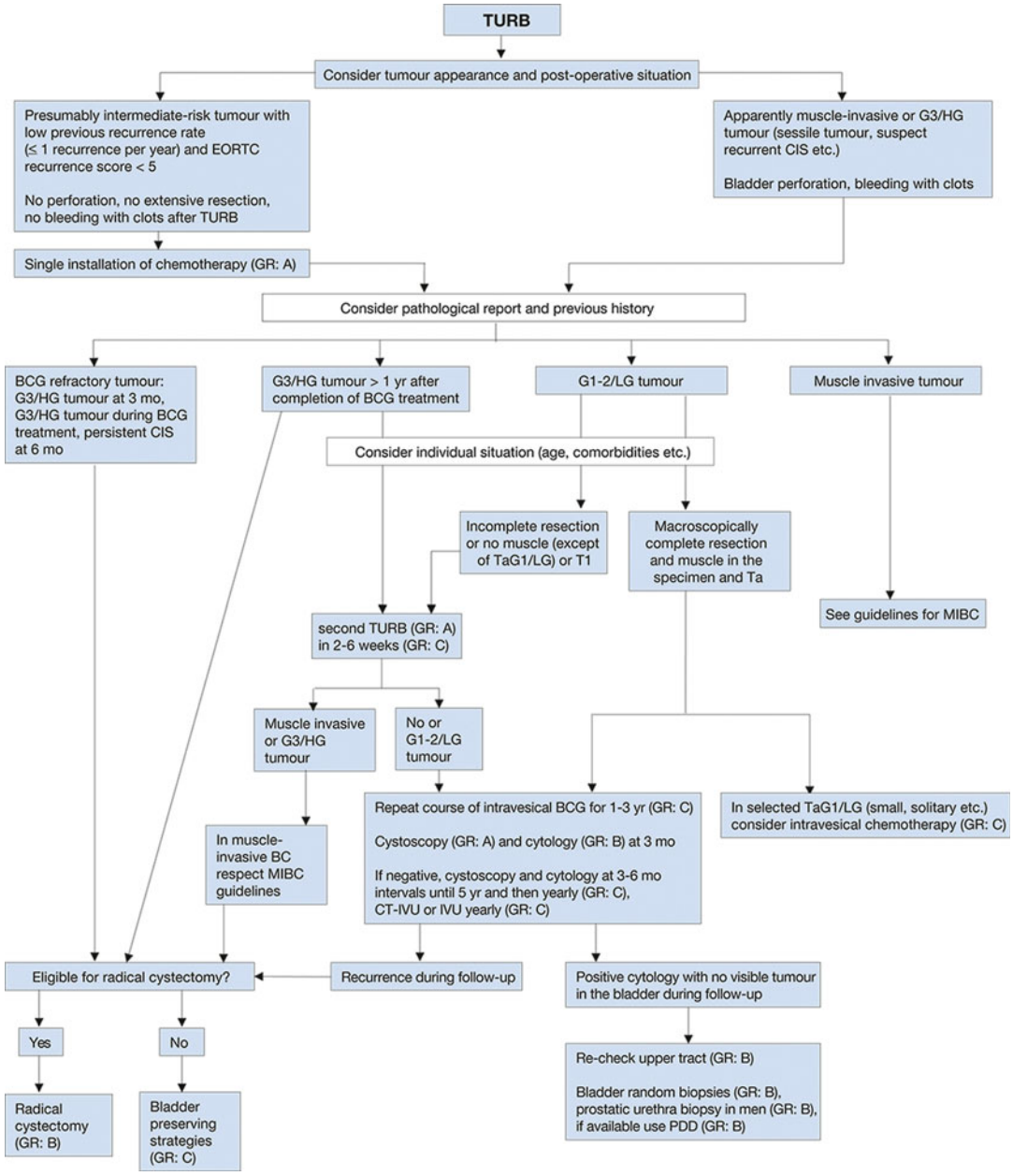

Fig. 3 Algorithm proposed by the European Association of Urology guideline panel for the treatment of NMIBC recurrence during or after intravesical BCG therapy. *BCG* bacillus Calmette-Guérin, *CIS* carcinoma in situ, *HG* high grade, *IVU* intravenous urography, *LG* low-grade, *PDD* photodynamic diagnosis, *TURB* transurethral resection of the bladder

Patients presenting adverse features such as concomitant diffuse CIS, multiple and/or large tumors that are not completely resectable endoscopically, tumors that involve the prostatic urethra or the distal ureter, some forms of variant histology of urothelial carcinoma and T1 tumors with lymphovascular invasion are at highest risk for disease progression and may not respond to BCG therapy at all. In these patients, immediate radical cystectomy (after the first diagnosis) or early radical cystectomy (after intravesical therapy failure) can be considered for therapeutic purposes.

The risks and benefits of a radical cystectomy for NMIBC should always be discussed with the patient, in a shared decision-making process. While in some cases immediate radical cystectomy may sound like an overtreatment with consequent impairment in quality of life, there are some aspects that should be considered as follows:

- If radical cystectomy is performed before progression to MIBC, in 80% of the patients a disease-free survival at 5 years can be achieved (Shariat et al. 2006).
- The clinical staging composed of TURB specimen and imaging can be inaccurate resulting in an upstaging of the patients in about 40% of the patients at the time of radical cystectomy (Shariat et al. 2007b; Tilki et al. 2010).

Several bladder-preserving therapies can be offered, but all of these therapy approaches are considered oncologically inferior to radical cystectomy.

Repeat BCG

In selected patients with disease persistence after a first induction course of BCG, a second induction course can be effective in about 50% of the cases, but response rates are not long lasting requiring a close follow-up. Patients who have failed two induction cycles will respond in only 20% of the cases to further courses of BCG. These patients are at higher risk of progression and develop metastases in about 50% of the cases. A third induction cycle is, therefore, not recommended (Catalona et al. 1987; Rosevear et al. 2011; Steinberg et al. 2016).

Combination of BCG with IFN-a

Due to high costs and nonsuperiority to BCG monotherapy, the use of INF-a in combination is reserved for BCG failure. In this setting, salvage low-dose BCG plus INF-a therapy can achieve response rates similar to those of induction cycle in BCG-naïve patients and about 50% disease-free survival rates after 24 months (Joudi et al. 2006).

Response rates depend on the number of previous induction cycles and respective failures. Indeed, patients treated with low-dose BCG plus INF-a for CIS after two or more prior BCG failures have a 14–23% disease-free survival after 2 years. Patients with only one failure or naïve patients have a 57% vs 69% disease-free survival, respectively (Rosevear et al. 2011).

Intradermal Priming

To further improve the response rates, the combination of BCG with more immunostimulating drugs has been experimentally proposed. The intradermal injection of BCG vaccine itself, stimulates the production of cytotoxic T cells and increases the infiltration of the bladder if secondarily exposed to BCG. A quadruple therapy consisting of intravesical solution with one-third dose BCG, 50 million units IFN, and 22 million units interleukin-2, along with a 250-mcg subcutaneous sargramostim injection has been proposed, but data on treatment tolerability and long-term outcomes are limited (Steinberg et al. 2017). One ongoing prospective trial (NCT02326168) is investigating the effect of intradermal priming.

MCNA

The use of other immunomodulatory drugs like MCNA, an agent comprised of mycobacterial cell wall fragments complexed with biologically active nucleic acids, derived from the nonpathogenic Mycobacterium Phlei has been reported, but their use is still experimental (Morales et al. 2015).

Early Cystectomy

High-grade NMIBC is an aggressive disease with many cases progressing to muscle-invasive disease despite complete transurethral resection and adjuvant intravesical therapy.

Therefore, in BCG failure a more aggressive approach is imperative to achieve optimal disease control. The term early radical cystectomy refers to a procedure performed before the classical indication of muscle-invasive disease but in patients who have already failed one previous treatment cycle. It must be differentiated from immediate radical cystectomy, where the procedure is performed immediately after the diagnosis of NMIBC. Although this may sound as overtreatment, there are some considerations that have to be made.

Not every BCG failure has the same prognosis. Patients who fail BCG therapy after 6 months have a significant higher risk of recurrence and progression to muscle-invasive disease when compared to those patients who fail therapy further on (Herr and Dalbagni 2003). Moreover, patients who experience disease progression after opting for a bladder preserving management also tend to have worse oncologic outcomes and a 10% reduced overall survival after 5 years compared to those who are muscle invasive at the first diagnosis (Lerner et al. 2009; Moschini et al. 2016).

If radical cystectomy is performed in T1 stage, patients have a 13% higher cancer-specific survival when compared to those with T2 stage (77.5% vs 64.5%) (Shariat et al. 2006).

It has also been reported that patients with BCG refractory CIS treated with radical cystectomy have 39% rate of upstaging and a 6% risk of lymph node metastasis (Tilki et al. 2010)

All these data support extirpative surgery and its performance at an early moment in the course of the disease to achieve the best oncologic result. Nevertheless, the risk of progression must be weighed against the morbidity and the change in quality of life after radical cystectomy.

Despite all international guidelines support early radical cystectomy, a survey performed in 2003 showed that only one fifth of the American urologists would advise patients with high-grade NMIBC after two BCG failures for radical cystectomy or radiotherapy (Joudi et al. 2003).

Intracavitary Chemotherapeutic Agents

Thiotepa (triethylenethiophosphoramide) is an alkylating agent approved for the adjuvant treatment of NMIBC. It can significantly reduce recurrence rates, but since the results of prospective randomized trials have shown the superiority of BCG (Martínez-Piñeiro et al. 1990), its use is limited in high-risk disease. No data are available on its efficacy in the treatment of BCG failure.

Valrubicin is approved by the FDA for the therapy of BCG refractory CIS. In a pivotal study, complete response at 6 months could be achieved in 21% of the cases (Steinberg et al. 2000). However, more recent studies have shown a complete response at 6 and 12 months only in 18% and 16.4% of the cases, respectively (Dinney et al. 2013).

The use of gemcitabine after BCG failure seems promising, but actual data rely on small sample sizes. The SWOG S0353 trial, for example, enrolled 58 patients who had undergone at least two prior BCG courses. The results showed a recurrence-free survival of 21% after 24 months in patients treated with gemcitabine (Skinner et al. 2013).

Intravesical taxanes have also been studied in BCG failure, but results are preliminary and their use is restricted to clinical trials. A phase I trial, for example, has shown a 3-year recurrence-free survival of 25% if docetaxel is administered with a course of 6 weekly instillations (Barlow et al. 2013). Nanoparticle albumin-bound paclitaxel has an increased solubility and reduced toxicity compared to docetaxel. Its use has been reported in a phase I/II study showing a response in 36% of the patients after 6 weeks (McKiernan et al. 2014).

In summary, intravesical chemotherapies are still not used in clinical routine as salvage therapy because of several limitations. Cohorts evaluated in clinical trial are small and heterogeneous, the follow-up is short and no standardized instillation schedule could be defined. Moreover, the pharmacodynamics of the drug itself, its toxicity, and the limited depth of penetration in the tissue limit their use.

Device-Assisted Intravesical Chemotherapy

Intravesical chemotherapy has shown to be not as effective as BCG. Therefore, there has been almost no role for the use of intravesical chemotherapy after BCG failure. In the past years, new device-assisted intravesical therapies have been developed to allow a deeper penetration of the drug in the tissue and improve, therefore, its effectiveness. Microwave-induced hyperthermia (MIH) and electromotive intravesical chemotherapy (EMDA) have emerged as alternative therapies for the high-risk NMIBC, and their use has been supported by a certain level of evidence also as salvage therapy in BCG refractory patients.

MIH

MIH acts on different layers. The hyperthermia itself induces cell degeneration, inhibits angiogenesis, and acts in synergism with chemotherapy. A specific catheter provided with microwave antennas must be placed in the bladder and connected to an external device which provides continuous irrigation and 915-MHz microwaves. The target temperature is set to 41 °C and 44 °C for a total irrigation duration of 60 min.

A prospective trial compared intravesical chemohyperthermia versus BCG in an adjuvant setting and showed no significant difference in recurrence rates after 2 years, but the trial was prematurely closed due to slow accrual (Arends et al. 2016).

In the case of BCG failure, EMDA can keep progression rates under 5% and achieve a recurrence-free survival of 85% and 56% after 1 and 2 years, respectively. The administration of maintenance cycles seems to play a relevant role in outcomes improvement (Nativ et al. 2009), but prospective randomized trials are needed in order to confirm these findings. Different chemotherapeutic agents have been used, but their efficacy is comparable (Arends et al. 2014).

EMDA

EMDA takes advantage of iontophoresis to improve the penetration of chemotherapeutics in the tissue. A voltage gradient of 15–20 mA is applied through a pad on the abdominal skin and an electrode in the bladder. Therapy cycles have a duration of 30 min and MMC is mainly used. One randomized controlled trial comparing sequential BCG and EMDA versus BCG alone has shown a 16% reduction in recurrence and 12.6% reduction in progression rates (Di Stasi et al. 2006). No trials have investigated the role of EMDA in BCG failure.

Photodynamic Therapy

In this procedure photosensitizing agents are injected intravenously or administered orally. Light delivered by different laser systems is then locally applied in the bladder and activates the drug. The experience with photodynamic therapy in BCG failure is limited. Small trials have shown response rates between 12% and 50% but high adverse events rates, particularly cardiotoxicity and hemodynamic instability, associated with the oral administration of 5-aminolevulinic acid.

Radiation Therapy

Radiation therapy in the treatment of NMIBC is generally restricted to those individuals who refuse or are unfit for radical cystectomy after the failure of intravesical therapy.

For the treatment of BCG failure, there is only limited data from small retrospective studies. It must also be kept in mind that patients included in these studies were treated with combined chemoradiotherapy after progression to MIBC (Wo et al. 2009). Radiation therapy is therefore generally not recommended for BCG-failed NMIBC patients.

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Local Treatment, Radical Cystectomy, and Urinary Diversion

23

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Abstract

The open technique of radical cystectomy (RC) has become an efficacious and safe procedure for patients with muscle-invasive or high-risk non-muscle-invasive bladder cancer. Disease-free survival probabilities range from 60% to 70% at 5 years and from 50% to 65% at 10 years. In recent years, more focus has been placed on quality of life after RC. There is evidence that nerve-sparing techniques have a beneficial effect on short- and long-term continence rates in patients with continent urinary diversion. Furthermore, advances in robotic surgery have turned robot-assisted RC (RARC) into a potential alternative to the open procedure. While RARC has not shown benefit in terms of complication outcomes or perioperative morbidity, short-term oncologic data for RARC appear acceptable (bearing in mind that selection bias in most series precludes definitive conclusions). There is general consensus, however, that pelvic lymph node dissection (PLND) should be performed in every case of RC. From observational data, a more extensive PLND template is associated with higher detection rate of lymph node metastasis and lower adjusted risk of mortality. The results of two prospective, randomized trials comparing extended and standard templates are highly anticipated. Following RC, urinary diversion is mandatory. Ileal conduits are most commonly performed, while continent cutaneous urinary diversions represent a valid alternative. Orthotopic bladder substitution allows preservation of an intact body image and normal voiding function and thus of a normal lifestyle, though it requires careful patient selection, meticulous surgical technique, conscientious postoperative patient instruction, and lifelong follow-up.

Introduction

Since Whitmore and Marshall's report of the first radical cystectomy (RC) series of the modern era in 1962, the procedure has seen substantial improvements in efficacy and safety along with advances in anesthesia. Today, RC with pelvic lymph node dissection (PLND) remains the mainstay of therapy for patients with clinically localized muscle-invasive bladder cancer and high-risk or refractory non-muscle-invasive bladder cancer, and it offers the best chance of cure for these patients (Clark et al. 2016). The most frequently used urinary diversions are ileal conduit and orthotopic bladder substitution. For the latter, long-term daytime and nighttime continence rates as high as 90% and 70%, respectively, have been reported (Furrer et al. 2016a). Advances in anatomical knowledge and surgical technique have spurred increased use of nerve-sparing techniques, allowing better preservation of sexual function and continence (Furrer et al. 2016b).

More recently, as minimally invasive techniques are being applied in a growing number of urologic centers, the value of robot-assisted RC (RARC) as an alternative to open RC has been debated. And while there is little doubt that PLND should be performed in conjunction with RC, general consensus on the extent of the dissection template has not been reached.

This chapter will review the experience with open RC in terms of oncologic and complication outcomes; will discuss ongoing controversies on the value of nerve-sparing techniques, RARC, and the extent of PLND; and will give special

consideration to the different forms of urinary diversion following RC.

Radical Cystectomy: Preoperative Assessment

Clinical staging of the primary tumor is based on analysis of the pathologic specimen provided by endoscopic resection as well as bimanual examination under anesthesia. Despite some controversy regarding its value in the context of modern imaging, examination under anesthesia has recently been shown to still independently improve the ability to determine local tumor stage (Rozanski et al. 2015).These procedures are completed by performing computed tomography or magnetic resonance imaging of the abdomen and pelvis, including excretory phase to exclude involvement of the upper urinary tract, in addition to bone scintigraphy. Importantly, transurethral resection should be limited to a single, site-directed biopsy in the case of a macroscopically solid, invasive tumor for which the biopsy will only confirm the indication for cystectomy. Complete resection of such tumors should be avoided in order to minimize the risk of tumor cell dissemination into the bloodstream. The pathologic work-up should include biopsies of the distal prostatic urethra in men and of the bladder neck in women in the case of visible disease or when a continent urinary diversion is contemplated.

It has to be emphasized that, although universally used, clinical staging remains relatively inaccurate. As many as 25% of ≥cT3 patients are over-staged compared to final pathologic classification (Svatek et al. 2011). Furthermore, 30–50% of patients undergoing RC are clinically understaged (Ficarra et al. 2005; Svatek et al. 2011). More specifically, approximately 75% of patients with clinical T2 disease may be upstaged at RC (Ficarra et al. 2005), and up to 45% of patients with clinically non-muscle-invasive disease may harbor stage T2 disease or higher at RC (Ficarra et al. 2005; Svatek et al. 2011). Looking to the future, steady advances in imaging modalities may improve the accuracy of clinical staging in patients with bladder cancer.

Oncologic Outcomes of Radical Cystectomy

RC is associated with acceptable survival rates, though oncologic outcome trends show that bladder cancer survival has not improved in the last three decades (Zehnder et al. 2013). This may be due to changes in patient selection and the lack of effective systemic chemotherapy and points out that more than just surgery is required to treat bladder cancer. Neoadjuvant chemotherapy, which is addressed elsewhere in this book (see ▶ Chap. 25, Peri-operative Chemotherapy for Muscle-Invasive Bladder Cancer), is associated with a modest absolute benefit in overall survival of 5% at 5 years, provided cisplatin-based combination regimens are used (Advanced Bladder Cancer Meta-Analysis Collaboration 2005). In an exciting new development for the urologic and oncologic communities, the immune checkpoint inhibitor atezolizumab was approved in May 2016 by the US Food and Drug Administration for the second-line treatment of patients with metastatic bladder cancer. Atezolizumab is the first anti-programmed death ligand 1 monoclonal antibody for bladder cancer and also the first agent approved for bladder cancer in decades. The role of atezolizumab and other immune checkpoint inhibitors in the neoadjuvant and adjuvant settings is being explored in prospective trials, and this new class of drug could eventually lead to survival improvements in patients undergoing RC.

Survival Probabilities After Radical Cystectomy

Prognosis after RC depends primarily on tumor and nodal stage (Stein et al. 2001; Madersbacher et al. 2003; Dotan et al. 2007). Outcome data from selected major RC series are summarized in Table 1, though comparisons of different

Table 1 Oncologic outcomes in selected major series of open radical cystectomy

Reference	Location	No. pts	Follow-up, median	RFS	DSS	OS	Notes
Bruins et al. (2014)	Netherlands	245	6.3 years	67%, 5y	NA	58%, 5y	No neoadjuvant or adjuvant chemotherapy
Chromecki et al. (2013)	International	4118	44 months	60%, 5y 57%, 10y	66%, 5y 60%, 10y	53%, 5y 19%, 10y	22% of pts received adjuvant chemotherapy
Dotan et al. (2007)	United States	1589	NA	NA	71%, 5y 66%, 10y	NA	11% and 17% of pts received neoadjuvant and adjuvant chemotherapy, respectively
Ghoneim et al. (2008)	Egypt	2720	6.7 years	56%, 5y 50%, 10y	NA	NA	49% squamous cell carcinoma, 10% adenocarcinoma No neoadjuvant or adjuvant chemotherapy
Hautmann et al. (2012)	Germany	1100	38 months	70%, 5y 66%, 10y	71%, 5y 67%, 10y	58%, 5y 44%, 10y	No neoadjuvant or adjuvant chemotherapy
Jensen et al. (2012b)	Denmark	265	45 months	64%, 5y	72%, 5y	67%, 5y	No neoadjuvant or adjuvant chemotherapy
Madersbacher et al. (2003)	Switzerland	507	31 months	62%, 5y 50%, 10y	NA	59%, 5y 37%, 10y	No neoadjuvant or adjuvant chemotherapy
Shariat et al. (2006)	International	888	39 months	58%, 5y 52%, 10y	66%, 5y 59%, 10y	NA	2% of pts received neoadjuvant radiation therapy and 5% neoadjuvant chemotherapy; 5% received adjuvant radiation therapy and 26% adjuvant chemotherapy
Stein et al. (2001)	United States	1054	10.2 years	68%, 5y 60%, 10y	NA	66%, 5y 43%, 10y	18% of patients received preoperative radiation therapy and/or chemotherapy
Yafi et al. (2011)	Canada	2287	35 months	48%, 5y	67%, 5y	57%, 5y	3% of pts received neoadjuvant chemotherapy; 19% received adjuvant chemotherapy

pts patients, *RFS* recurrence-free survival, *DSS* disease-specific survival, *OS* overall survival, *y* year, *NA* not available

series must be cautiously made because of differing selection criteria. Overall, at least 30–40% of all patients will relapse within 5 years following surgical resection of their tumor. With surgery alone, 5-year recurrence-free survival decreases from 76% in patients with pT1 tumors to 74% in those with pT2 tumors, 52% for pT3 tumors, and 36% for pT4 tumors (Madersbacher et al. 2003). Five-year disease-specific survival rates are 93% for ≤pT1, 74% for pT2N0, 66% for pT3N0, and 46% for pT4N0 tumors (Hautmann et al. 2012).

Outcomes for Patients with Lymph Node Metastases

Lymph node involvement is found in 17–35% of all RC patients and is universally accepted as a predictor of poor prognosis (Stein et al. 2001;

Madersbacher et al. 2003; Dotan et al. 2007; Ghoneim et al. 2008; Zehnder et al. 2011; Jensen et al. 2012a; Tarin et al. 2012; Simone et al. 2013). At 5 years, recurrence-free survival probabilities range from 24% to 35% and overall survival probabilities from 18% to 32% (Stein et al. 2001; Madersbacher et al. 2003; Tarin et al. 2012). However, the number of lymph node metastases is significantly associated with increased risk of cancer-specific death, as patients with 1 positive node have a hazard ratio of 1.9 (95% confidence interval [CI] 1.04–3.46) compared to 4.3 (95% CI 2.25–8.34) for patients with $\geq$2 nodes (Tarin et al. 2012). Excluding the patients who received neoadjuvant chemotherapy did not alter these results. Similar studies have found that a larger metastatic burden is associated with poor prognosis, with a threshold of 1 positive lymph node being the most significant (Dotan et al. 2007; Jensen et al. 2012a). Another important prognostic factor for patients with lymph node metastases is the presence of extracapsular extension, which independently confers a more than twofold higher risk of recurrence (Fleischmann et al. 2005).

Local Recurrence and Quality of Surgery

Isolated local recurrences occur in 1–6% of patients with organ-confined tumors, in 7–13% of those with non-organ-confined tumors, and in 13% of node-positive patients (Stein et al. 2001; Madersbacher et al. 2003; Dhar et al. 2008). Local recurrence is closely associated with the presence of positive surgical margins at RC (Dotan et al. 2007). The presence of positive surgical margins is an independent predictor of survival even in advanced disease (Novara et al. 2010), and nearly all patients who develop local recurrence die of their disease (Herr et al. 2004); this may merely reflect the malignant potential of the tumor, but it is also plausible that adequate surgical technique is critical, including radical, complete excision and avoidance of tumor cell spillage during transection of the ureters and the urethra.

The place of RC as a critical component of therapy has been highlighted by Herr, who reported muscle-invasive recurrence in 38% and noninvasive recurrence in 25% of patients who refused RC after a complete response to chemotherapy (Herr 2008). Considering the subset of these patients who subsequently died of their disease, this would amount to an additional mortality of 30% due to RC refusal, assuming that all patients would have survived had they undergone their planned postchemotherapy RC. Furthermore, several lines of evidence underline the importance of surgery quality for optimizing outcomes. In a sub-analysis of the Intergroup trial, the major neoadjuvant chemotherapy trial conducted in the United States, only 43% of RC were done by fellowship-trained urologic oncologists, and only 13% of surgeons performed more than five RC during the study (Herr et al. 2004). Significant predictors of overall survival and local recurrence were negative surgical margins and the removal of $\geq$10 lymph nodes after adjusting for pathologic stage and delivery of neoadjuvant chemotherapy. Not surprisingly, surgical margins and number of lymph nodes removed were associated with each other. Further analysis of the Intergroup trial suggested that RC performed by urologic oncologists and at academic centers was associated with more extensive PLND and lower rates of positive surgical margin. In confirmation of this result, several studies have demonstrated that high hospital volume and high surgeon volume are each associated with better overall survival (Fairey et al. 2009; Kulkarni et al. 2013). Altogether, these data imply that RC should be performed in high-volume referral centers to achieve the best outcomes.

Conditional Survival After Radical Cystectomy

The concept of conditional survival implies that the patient who survives for a certain duration

after RC has improved prognosis compared to immediately after RC. Ploussard et al. evaluated whether conditional survival applies for muscle-invasive bladder cancer (Ploussard et al. 2014). Analyzing a multicenter cohort, the authors found that 5-year overall survival probabilities improved in patients who survived a certain time after RC: 5-year conditional overall survival probability was 58% immediately after RC, 61% after 1 year, 66% after 2 years, 71% after 3 years, 73% after 5 years, and 74% after 10 years. These improvements were observed across all tumor stages but were more pronounced for patients with adverse pathological characteristics. Therefore, the prognosis of patients who underwent RC improves with longer time after surgical intervention, with increased survivorship associating with decreased risk of mortality.

Complications After Radical Cystectomy

Standardized Reporting of Complications

For many years, evaluation of complications following RC had been hampered by lack of uniformity in methodology and, consequently, underestimation of perioperative morbidity. In 2008, a group from the Memorial Sloan Kettering Cancer Center was the first to apply a standardized reporting system for defining 90-day morbidity of open RC (Shabsigh et al. 2009). Complications were graded using a system similar to the modified Clavien-Dindo system. In addition, complications were stratified into 11 categories by the organ system. This analysis included 1142 patients who underwent RC, of whom 724 (63%) received an ileal conduit and 418 (37%) a continent urinary diversion. A total of 735 (64%) patients experienced one or more complications within 90 days of surgery. The organ system most often involved was gastrointestinal (ileus, small bowel obstruction, colitis, etc.) followed by infectious (fever of unknown origin, urinary tract infection, sepsis, etc.) and wound-related complications. A total of 153 (13%) patients had grade 3–5 complications, i.e., complications that required more than oral or intravenous medications or blood transfusions. Overall, complication rates in the Shabsigh study were significantly higher than in previously published works (ranging from 27% to 41% within 30 days and 28% to 34% within 90 days) (Stein et al. 2001; Boström et al. 2009), highlighting the importance of strict complication reporting. Indeed, subsequent studies that examined complications using the standardized reporting system found 90-day complication rates that ranged from 49% to 56% (Novara et al. 2009; Svatek et al. 2010).

Perioperative Mortality After Radical Cystectomy

Thirty-day mortality rates after RC range from 1% to 3% (Stein et al. 2001; Madersbacher et al. 2003; Ghoneim et al. 2008; Shabsigh et al. 2009; Hautmann et al. 2012). Most of these events are due to cardiovascular, pulmonary, or infectious complications. However, in older people the early mortality rate can be as high as 11% (Froehner et al. 2009); because of age and/or comorbidity, these patients have lower reserves to tolerate surgical stress compared to younger patients. Comorbidity has been shown to be an independent predictor of perioperative mortality as well as of overall survival and disease-specific survival after RC (Fairey et al. 2009; Mayr et al. 2012). Thus, the patient's comorbidity profile, biological age, and performance status are critical factors that should be taken into account when discussing RC and its associated mortality and risk of complications. Importantly, in-hospital mortality rates after RC are higher with low-volume centers and surgeons who only occasionally perform RC, compared to high-volume centers and experienced RC surgeons (Konety et al. 2005). Together with the abovementioned evidence that high hospital volume and high surgeon volume are associated with better survival outcomes after RC, it is an established view that a demanding procedure such as RC should be performed in referral centers.

Nerve-Sparing Radical Cystectomy and Continent Urinary Diversion

Clinical Evidence in Favor of Nerve Sparing

Since the introduction of nerve-sparing techniques 30 years ago, it has been continuously debated whether they improve urinary continence in patients who undergo RC and continent urinary diversion. Data from the University of Bern supported a positive association between nerve sparing and daytime and nighttime continence for patients with an ileal orthotopic bladder substitution, with nerve-sparing patients having a 40% higher chance of being continent (Turner et al. 1997; Kessler et al. 2004). Similarly, Colombo et al. reported continence rates at 24 months after RC of 89% for daytime and 57% for nighttime after nerve-sparing RC compared to 78% and 55% after non-nerve-sparing RC (Colombo et al. 2015). More recently, the long-term impact of nerve sparing was evaluated in patients with an orthotopic bladder substitution who survived $\geq$10 years (Furrer et al. 2016b). Patients with any nerve sparing achieved daytime continence faster than those without nerve sparing (3 months vs 6 months; $p = 0.003$). In multivariable analyses, any type of nerve sparing was associated with a borderline significant higher likelihood of daytime continence (odds ratio 2.51, 95% CI 0.97–6.47, $p = 0.057$), which was mainly driven by bilateral nerve sparing (odds ratio 6.83, 95% CI 1.33–35.00, $p = 0.02$). Furthermore, any nerve sparing was associated with >twofold higher likelihood of nighttime continence (odds ratio 2.28, 95% CI 1.06–4.94, p = 0.04). These data paralleled those from studies that evaluated the long-term beneficial effect of nerve sparing on continence for patients who underwent radical prostatectomy (Burkhard et al. 2006). Finally, a further development in RC has been the possibility of sparing one or both seminal vesicles in selected patients, which resulted in a high probability of preserving potency while preserving oncologic efficacy (Ong et al. 2010).

Rationale for Nerve Sparing from Anatomical and Physiological Studies

Recent advances in anatomic and physiologic understanding of the neurovascular bundles, and their relationship to surrounding structures, lend support to the concept of nerve sparing for patients who receive an orthotopic bladder substitution. The distal branches of the lower part of the inferior hypogastric plexus lie within a plate between the bladder and rectum, run at a distance of <2 mm along the dorso- and ventrolateral aspect of the seminal vesicles, and end as the paraprostatic neurovascular bundle to innervate the urethral sphincter and erectile organs (Alsaid et al. 2011). Thus, the seminal vesicles represent an essential anatomical landmark. These nerves continue dorsolaterally in the angle between the bladder neck and the prostate to the base of the latter. Further down, using neural immunostaining and computerized planimetry, Ganzer et al. demonstrated that the proportion of autonomic periprostatic nerve surface was highest dorsolaterally, i.e., between the 7 and 9 o'clock positions (Ganzer et al. 2008). A certain number of nerves were found in the ventrolateral and dorsal positions. These results agreed with those from others (Sievert et al. 2008; Alsaid et al. 2011). In addition, the overall nerve surface area was the largest at the base versus the mid-level and apex. Interestingly, the ratios of periprostatic nerves over nerves entering the prostatic capsule ranged from 1.9 at the apex to 3.6 at the base. These findings mean that for every nerve leaving the neurovascular bundle and branching out into the prostate, 2–4 may finally contribute to other functions such as continence and erectile function. Further support is provided by studies that documented that at the prostate apex and urethra levels, some fibers innervate the urethral sphincter, while others form divisions that reach the corpora cavernosa and the corpus spongiosum (Alsaid et al. 2010, 2011).

The functional role of the autonomic nerves has been delineated in several studies. Autonomic periprostatic nerves consist of cholinergic and adrenergic, i.e., parasympathetic and sympathetic, as well as sensory fibers (Alsaid et al. 2010). Intraoperative stimulation of the neurovascular

bundle during radical prostatectomy results in a significant increase in urethral pressure (Takenaka et al. 2007). Furthermore, intraoperative electrophysiological confirmation of nerve sparing by monitoring intracavernous or intraurethral pressure changes was positively associated with postoperative continence status (Kaiho et al. 2005). It could be demonstrated that increased sensory threshold of the membranous urethra after orthotopic bladder substitution was associated with higher risk of postoperative incontinence (Hugonnet et al. 2001); this is possibly due to loss of sensation of urine entering the urethra, which precludes guarding reflex or voluntary contraction of the external urethral sphincter. A similar study was performed in radical prostatectomy patients, demonstrating that impaired urethral sensitivity was associated with incontinence (Catarin et al. 2008). A comparative analysis was done of urethral parameters for men who underwent nerve-sparing or non-nerve-sparing cystectomy with an orthotopic bladder substitution. The results showed that the nerve-sparing group had higher maximal pressure profiles as well as greater functional urethral length (El-Bahnasawy et al. 2006). Concordant findings were reported in women, where functional urethral length and maximal urethral closing pressure were significantly associated with continence (Gross et al. 2015).

Taken together, the available evidence suggests that denervation of the urethra results in stress incontinence mainly due to reduced urethral outlet resistance and diminished functional length of the membranous urethra. Thus, nerve sparing is recommended on the non-tumor-bearing side in unilaterally located tumors. Bilateral nerve sparing may be offered in medially located tumors and in patients with non-muscle-invasive disease. However, it has to be noted that confounding factors may also play a role, namely, anatomical and functional characteristics of the outlet before RC, mechanical or thermal sphincter damage during RC, low-capacity reservoir with reduced compliance, elevated end fill pressures or pressure spikes, presence of infected urine causing reservoir wall contractions resulting in occasional sudden urine loss, overflow incontinence due to infra-neovesical outlet obstruction, and patient age or compliance.

Nerve-Sparing Radical Cystectomy: Safety and Technique

There is a legitimate concern that nerve sparing may jeopardize oncologic efficacy because of inadequate tumor resection. However, currently there are no data that substantiate this hypothesis. Data from the University of Bern showed that nerve sparing was not associated with high risk of local recurrence (Turner et al. 1997), which was in line with other reports (Vallancien et al. 2002). In the RC series of the University of Bern, where nerve sparing is performed whenever possible, isolated local recurrence rates were 3% in patients with organ-confined tumors, 11% in those with non-organ-confined tumors, and 13% in those with positive lymph nodes (Madersbacher et al. 2003). In another major series, from an institution where there is no particular focus on the use of nerve sparing, isolated recurrence rates were 6% and 13% in patients with organ-confined and non-organ-confined tumors, respectively (Stein et al. 2001). Thus, nerve-sparing techniques appear to be safe, provided the patient has gone through an appropriate selection process and the procedure is performed in a center with expertise. In men, the plane of dissection is close to the seminal vesicle toward the base of the prostate, staying in close contact to the vesicoprostatic angle and avoiding damage to the paraprostatic neurovascular bundle (Fig. 1). In women, the autonomic nerves of the dorsomedial bladder pedicle are spared around the cervix uteri, in the cervicovesical angle, and along the ventrolateral paravaginal plane, avoiding any dissection further dorsally than the 2 or 10 o'clock position. Incision of the endopelvic fascia should be close to the bladder neck, thereby avoiding injury to the paraurethral structures including the autonomic nerves.

Robot-Assisted Radical Cystectomy

Following successful adoption of minimally invasive techniques in kidney and prostate surgery, the last decade has seen a growing interest in RARC. RARC gives the surgeon improved visualization and dexterity as well as filtering of any tremor. In

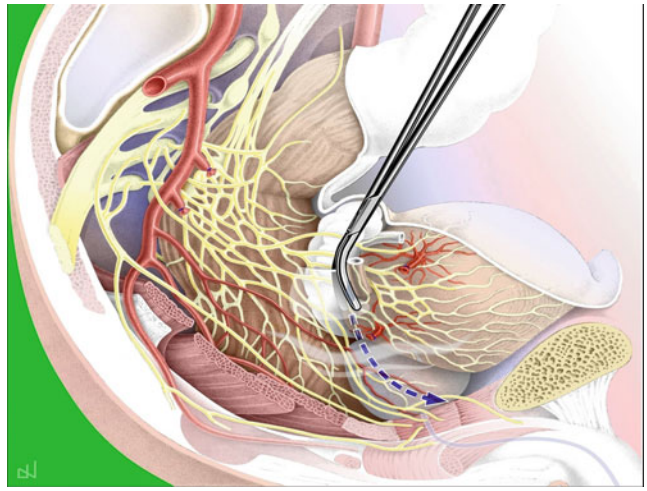

Fig. 1 Schematic drawing depicting the nerve-sparing technique on the non-tumor-bearing side. Dissection is performed in three steps: (1) The periprostatic fascia is incised and cleaved in order to mobilize the neurovascular bundle; (2) the plane close to the seminal vesicle is dissected, taking care to keep the dissection plane away from the pelvic plexus, which is located dorsolateral to the seminal vesicle; and (3) dissection is continued toward the vesicoprostatic angle between the bladder wall, seminal vesicle, and base of the prostate (From Studer 2015)

addition, the pneumoperitoneum provides a tamponade effect, minimizing intraoperative blood loss. However, among the surgical options in patients who need RC, the status of RARC remains a matter of debate. Proponents of RARC emphasize the potential for improvement in perioperative morbidity and quicker recovery. Critics of RARC highlight the lack of long-term survival outcomes, the possible impact on recurrence patterns (Nguyen et al. 2015; Albisinni et al. 2016), and longer operative times and costs (Bochner et al. 2015). Furthermore, before discussing complication and survival outcomes, it needs to be stressed that most reports on outcomes of RARC to date have included younger and healthier patients with lower disease burden, which reflects the expected selection bias when a new surgical technique is introduced (Wang et al. 2008).

Complications After Robot-Assisted Radical Cystectomy

In the Memorial Sloan Kettering Cancer Center and CORAL randomized trials, there were no significant differences in complication rates between open RC and RARC (Bochner et al. 2015; Khan et al. 2016). Using the standardized reporting system of complications, the International Robotic Cystectomy Consortium reported 30-day and 90-day complication rates of 41% and 48%, respectively. Gastrointestinal, infectious, and genitourinary complications were most common (Johar et al. 2013).

Oncologic Outcomes After Robot-Assisted Radical Cystectomy

The introduction of RARC into surgical practice has been accompanied by legitimate concerns regarding its oncologic efficacy. Rates of positive surgical margins, an important surrogate of surgical quality and survival, range from 7% to 15% for RARC and globally have shown equivalency to the open procedure (Ng et al. 2010; Khan et al. 2016; Raza et al. 2015). Nevertheless, for extravesical disease treated with RARC at high-volume centers, rates of positive surgical margins were higher than those reported in the open RC literature (17–20% for RARC compared to 9–14% for open RC) (Hellenthal et al. 2010;

Dotan et al. 2007; Novara et al. 2010; Johar et al. 2013). Furthermore, the lymph node yields reported for RARC have been similar to those of open RC (Ng et al. 2010; Bochner et al. 2015). However, due to variability in patients' anatomy, surgical technique, the template applied and pathologic processing, the number of lymph nodes retrieved is only a crude measure of surgical quality, precluding definitive conclusions.

A recent review of oncologic outcomes after RARC documented 3-year disease-free survival, cancer-specific survival, and overall survival probabilities of 67–76%, 68–83%, and 61–80%, respectively (Yuh et al. 2015). The rates of disease-free survival, cancer-specific survival, and overall survival probabilities at 5 years were 53–74%, 66–80%, and 39–66%, respectively. However, most studies had short follow-up. The most mature data were published by the International Robotic Cystectomy Consortium. With a median follow-up of 67 months, Raza et al. reported 5-year recurrence-free survival, disease-specific survival, and overall survival probabilities of 67%, 75%, and 50%, respectively (Raza et al. 2015). It is noteworthy that in this cohort of 743 patients, 62% had organ-confined disease and 40% had stage pT1 or lower disease.

Robot-Assisted Radical Cystectomy: Challenges Ahead

Recently, Nguyen et al. suggested that recurrence in atypical locations may be more frequent after RARC compared to open RC (Nguyen et al. 2015). In a single-surgeon cohort of 120 open RC and 263 RARC patients, overall recurrence rates were not different between the two techniques. However, while the distribution of distant recurrences within 2 years was similar, peritoneal carcinomatosis occurred in 21% of RARC patients who recurred compared to 8% of open RC patients who recurred. Similarly, extra-pelvic lymph node metastases were found in 23% of RARC patients who recurred and 15% of open RC patients who recurred. These findings were particularly worrying since the RARC group had lower tumor stage than the open group. In a further study, Albisinni et al. analyzed a cohort of 311 patients who underwent laparoscopic RC and had $\leq$pT2N0R0 stage at final pathology. Unexpectedly, 27 (9%) of these patients experienced disease recurrence within 24 months, leading the authors to hypothesize that the surgical technique/peritoneum may have played a role in the development of early recurrences (Albisinni et al. 2016). Evidence derived from laboratory-based studies suggests that the pneumoperitoneum may increase the risk of bladder cancer cell seeding in the peritoneal cavity (Ost et al. 2008). Furthermore, tumor cell seeding may be enhanced via a chimney effect due to continuous insufflation and desufflation. Therefore, more studies are needed to evaluate the potential link between pneumoperitoneum and peritoneal carcinomatosis in the clinical setting, because the pneumoperitoneum may be the only major technical difference between open RC and RARC when RARC follows the principles of oncologic surgery.

Furthermore, data are scarce for short- and long-term functional outcomes, especially in patients with a continent urinary diversion, as well as health-related quality of life after RARC. Another hurdle to the implementation of RARC is that many surgeons who start performing this procedure have no or only limited experience with open RC. This may prove detrimental to the patient in terms of perioperative morbidity and survival, as a laparoscopic surgeon lacking broad surgical expertise may not be able to follow the technical and oncological principles of open surgery when faced with the need for conversion.

Collectively, the available data suggest that RARC is feasible; however, caution is warranted when considering RARC to treat locally advanced disease. Given the wealth of unanswered questions for RARC, it is important to understand that open RC remains the gold standard for the treatment of muscle-invasive cancer. Looking ahead, the ongoing randomized RAZOR trial comparing open RC and RARC may provide further insight into the role of RARC.

Pelvic Lymph Node Dissection

Pelvic Lymph Node Dissection as Staging Procedure

Accurate cancer staging identifies the extent and location of the tumor, helps define malignant potential, and forms the basis for the best therapeutic management. In bladder cancer, adjuvant chemotherapy is recommended in patients with pT3-T4a and/or node-positive disease at RC (Clark et al. 2016). Nevertheless, current imaging studies for evaluation of bladder cancer still lack diagnostic accuracy in the staging of pelvic lymph nodes, with reported sensitivity for the detection of lymph node metastasis of about 75% at best. In the future, the capacity to detect diseased nodes preoperatively may be improved by new imaging concepts that include diffusion-weighted MRI and conventional or diffusion-weighted MR lymphangiography using ultrasmall superparamagnetic particles of iron oxide. Thus, for the time being, histopathologic examination of a PLND template remains the most accurate staging procedure. The number of positive nodes, the metastatic volume, and the presence of nodal extracapsular extension can be obtained, detailed information that is helpful for patient counseling about the risk of progression and for stratifying men who may benefit from adjuvant chemotherapy.

Necessity of Pelvic Lymph Node Dissection

PLND at RC is currently recommended by major oncologic societies (Clark et al. 2016). A population-based study conducted by Abdollah et al. found patients who had no PLND to have higher 10-year probabilities of cancer-specific and overall mortality compared to those who had PLND, after adjusting for baseline clinicopathological variables (hazard ratio 1.33, 95% CI 1.24–1.44 for cancer-specific mortality, and hazard ratio 1.29, 95% CI 1.22–1.37 for overall mortality) (Abdollah et al. 2012). An updated analysis from the same authors included propensity score matching to reduce potential bias and demonstrated that PLND compared to no dissection was associated with improved all-cause and cancer-specific survival, in particular in patients $\leq$75 years or with low-risk comorbidity profile (Larcher et al. 2015). Similar retrospective institutional analyses documented lower risk of mortality with PLND compared to no dissection in patients undergoing RC (Herr et al. 2004). Despite this, PLND is still omitted in approximately 20% of RC patients (Abdollah et al. 2012).

Extent of Pelvic Lymph Node Dissection

Although the available evidence supports PLND, there is an ongoing debate on the extent of the template, particularly regarding the proximal boundaries. Several templates have been described and definitions are not uniform. Generally speaking, the limited variant includes lymph nodes in the obturator fossa and along the external iliac vessels up to the iliac bifurcation. The standard template additionally removes lymph nodes along the internal iliac vessels. Extended PLND includes all of these regions plus lymph nodes along the common iliac vessels up to the crossing of the ureters or to the aortic bifurcation. For instance, at the University of Bern, limits of the extended PLND template are (Fig. 2) the mid-common region where the ureter crosses the iliac vessels cranially, the circumflex iliac vein and femoral canal distally, the genitofemoral nerve laterally, the bladder medially, and the floor of the obturator fossa and the internal iliac vessels dorsally, including skeletonization of the tissue lateral and medial to the internal iliac vessels. In addition, lymph nodes located in the fossa of Marcille, that is, dorsolateral to the proximal external iliac vessels and dorsal to the junction of the ureters with the common iliac vessels, are removed (Fig. 3). This template is in agreement with a single photon emission computed tomography/computed tomography mapping study and would incorporate 92% of all primary lymphatic landing sites of the bladder (Roth et al. 2010).

A bi-institutional retrospective study demonstrated 13% rate of lymph node metastasis in patients who underwent limited PLND compared

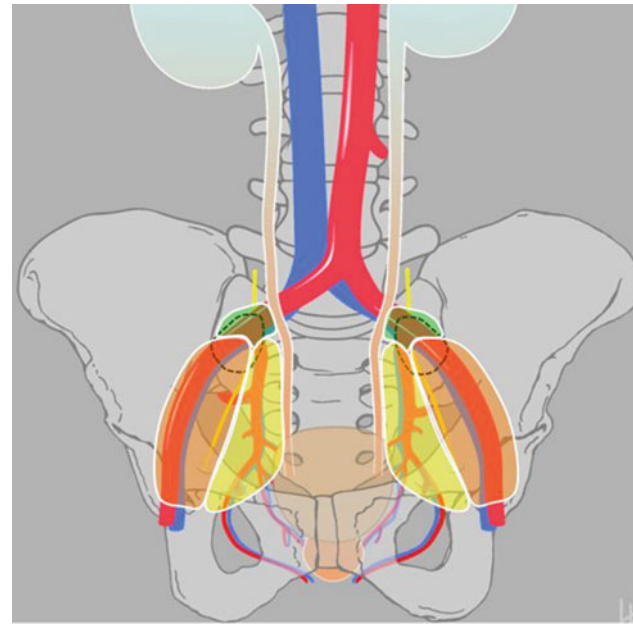

Fig. 2 Template for pelvic lymph node dissection used at radical cystectomy at the University of Bern. The *orange*, *yellow*, and *green* regions represent the external iliac, internal iliac, and common iliac regions, respectively. The regions delineated by *dashed* lines represent the fossa of Marcille

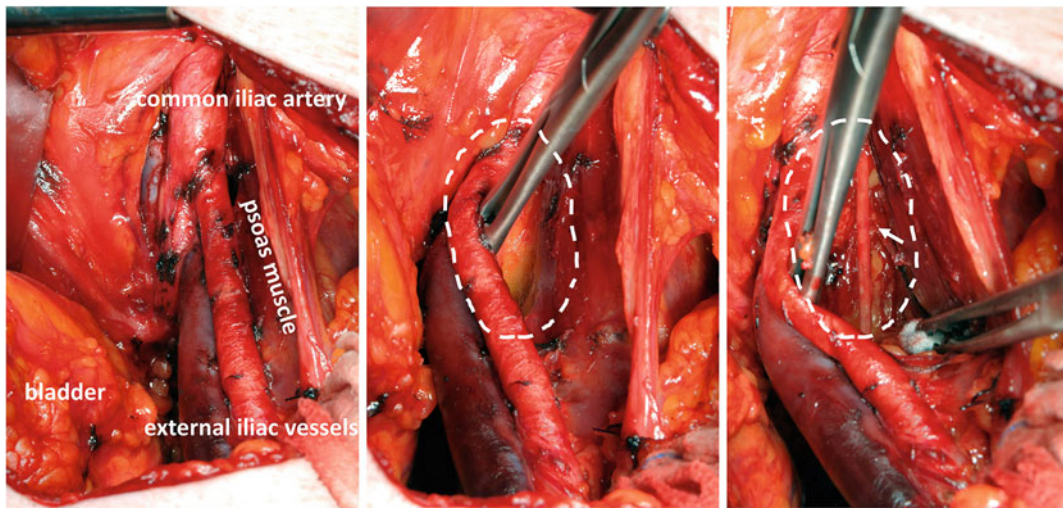

Fig. 3 Dissection of the fossa of Marcille. *Left*: the surface of the external iliac and common iliac vessels up to the ureter crossing has been cleared. *Middle*: access to the fossa of Marcille (*dotted-dashed* line) is gained by medial retraction of the external iliac vessels. *Right*: after removal of the fatty, connective, and lymphatic tissue, the space medial to the psoas major including the obturator nerve (*arrow*) is fully exposed

to 26% in those who underwent extended PLND. Recurrence-free and overall survival probabilities were significantly worse for patients who underwent limited PLND regardless of nodal status (Dhar et al. 2008). These results echoed those from similar retrospective cohort studies comparing different variations of limited versus extended dissection (Herr et al. 2004; Jensen et al. 2012b; Simone et al. 2013). A recent analysis from the Memorial Sloan Kettering cohort found that patients with pN3 disease (13% of the entire cohort) had a 42% cancer-specific survival rate at 3 years (Tarin et al. 2012). The authors consequently hypothesized that routine removal of

common lymph nodes at RC can cure some patients with metastases in this location and confers an approximate 5% improvement in disease-specific survival (42% of 13%), which is comparable to the survival benefit achieved with neoadjuvant chemotherapy. A recent meta-analysis compiled the results of 11 retrospective studies on standard or extended PLND. Although limited by the lack of uniformity in template definitions, variability in surgeon experience, and differences in patient characteristics, the study found an overall odds ratio of 1.63 (95% CI 1.28–2.07) for 5-year recurrence-free survival in favor of the extended template (Mandel et al. 2014).

A more extensive lymph node dissection appears to be beneficial even if the patient has pathologically proven lymph node metastases (Dhar et al. 2008; Abol-Enein et al. 2011; Jensen et al. 2012b; Simone et al. 2013). For instance, Abol-Enein et al. reported 5-year recurrence-free survival rates of 48% for the extended template and 28% for the limited template in node-positive patients (Abol-Enein et al. 2011). Dhar et al. found 5-year overall survival rates of 34% for extended lymph node dissection and 7% for limited lymph node dissection (Dhar et al. 2008). Multivariable analyses confirmed that extended PLND is an independent predictor of survival in node-positive patients (Abol-Enein et al. 2011; Jensen et al. 2012b; Simone et al. 2013). There is also evidence that extended PLND is associated with lower rates of local recurrence (Dhar et al. 2008; Jensen et al. 2012b; Abdi et al. 2016). This is important because local recurrences, particularly in the fossa of Marcille, are often exceedingly painful and a major quality-of-life issue for patients with relapsing disease.

A super-extended dissection has been described, which comprises lymph nodes medial to the ureters at the level of the common iliac bifurcation and at the aortic bifurcation up to the inferior mesenteric artery (Zehnder et al. 2011). However, tissue dissection in these regions may damage autonomic nerves descending along the aorta. Furthermore, patients with node metastases in the para-aortic regions usually have additional nodes involved. In fact, disease-free survival was not improved in a retrospective study comparing super-extended and extended PLND (Zehnder et al. 2011). Thus, a super-extended template may compromise potency and continence in patients who are candidates for an orthotopic bladder substitution (Furrer et al. 2016b), while the additional survival benefits are not definite.

The interpretation of retrospective studies is hampered by varied definitions of dissection templates or the sole use of lymph node yield to define the template. Therefore, two randomized trials comparing limited and extended templates have been launched. The trial from the Association of Urogenital Oncology and the German Cancer Association has randomized 375 patients with high-grade pT1 or muscle-invasive urothelial bladder cancer in the first phase III trial (NCT01215071). Limited PLND includes the obturator, external iliac, and internal iliac regions bilaterally. Extended dissection additionally included the deep obturator fossa, presacral, paracaval, interaortocaval, and paraaortal nodes up to the inferior mesenteric artery. The first results of this trial were presented at the 2016 meeting of the American Society of Clinical Oncology (Gschwend et al. 2016). The median number of lymph nodes removed was 19 in the limited arm and 32 in the extended arm. The 5-year recurrence-free survival rates were not statistically different between the two groups (62% in the limited arm versus 69% in the extended arm; $p = 0.3$). Five-year cancer-specific survival probabilities were not statistically different either: 66% in the limited arm and 78% in the extended arm ($p = 0.1$). The second trial (Southwest Oncology Group 1011; NCT01224665) was opened in August 2011 in the United States and calls for accrual of 620 patients and randomization of 564 patients who will undergo limited or extended PLND. Unlike the German trial, the US trial is allowing patients who have received neoadjuvant chemotherapy to enroll.

Urinary Diversion

One of the drawbacks of RC is that it requires urinary diversion in patients with at least one renal unit. Incontinent forms, such as ureterocutaneostomy or ileal conduit, are relatively easy to perform and represent the most commonly

performed urinary diversion procedures. On the other hand, in the nonacademic setting, only 10–30% of surgeons perform continent urinary diversions such as orthotopic bladder substitution and continent cutaneous urinary diversion. Preoperative variables that dictate which type of urinary diversion can be performed are local tumor status; renal, hepatic, and intestinal function; capability to perform clean intermittent catheterization or pelvic training; and the individual patient's preferences and compliance.

Ileal Conduit

The ileal conduit is the most commonly performed urinary diversion. The technique is straightforward and minimizes the risk of postoperative complications. It is associated with a lower risk of metabolic disturbances than continent diversion because the diverted urine comes into contact with a smaller area of bowel epithelium. Therefore, it is well suited for patients with limited renal function. The ileal conduit should also be the diversion of choice in elderly patients, in patients with severe comorbidities, and in those who are noncompliant, i.e., unwilling or unlikely to comply with the stringent aftercare associated with continent diversion. Another indication is tumor of the urethra/prostatic urethra in men and of the bladder neck in women. Finally, an ileal conduit or alternatively a continent catheterizable urinary reservoir is indicated in patients in whom extension of the tumor does not allow for nerve sparing on either side, thus precluding urinary diversion with an orthotopic bladder substitution. The main disadvantage of ileal conduit is impaired body image because of the stoma.

Rectosigmoid Bladder/Mainz Pouch II

In 1852, Simon was the first to pull the ureters through the wall of the sigmoid colon into the lumen in a patient who died 2 days later from septic complications. Later on, the rectosigmoid reservoir was detubularized (Mainz pouch II), which led to significant improvements in urinary continence as well as renal function (Fisch et al. 1993). Advantages of the rectosigmoid reservoir include preservation of body image and use of the genuine anal sphincter as outlet valve with minimal risk of dysfunction. The surgical technique is relatively simple. Careful follow-up is warranted as hyperchloremic acidosis is common even with good renal function, and alkali substitution is necessary lifelong. The risk of secondary malignancy at the location where the urine first comes into contact with the colon mucosa should be considered, and yearly colonoscopies beginning 5–10 years later are recommended.

Heterotopic Continent Catheterizable Urinary Reservoir/Mainz Pouch I

A continent catheterizable reservoir is usually constructed using a detubularized ileocecal segment, such as for the Mainz pouch I or the Indiana pouch. The Mainz pouch I is constructed with 12 cm of cecum and 24–36 cm of terminal ileum and can, less commonly, be used for an orthotopic reservoir as well (Pfitzenmaier et al. 2003). It is not indicated in patients with limited renal function, noncompliance, or inability to perform self-catheterization. Antirefluxive mechanisms consisting of tunneling the ureters submucosally into the cecum are used to protect the upper urinary tract, combined with a catheterizable antirefluxive continence mechanism in the umbilical area. As an alternative, an ileal reservoir can be used. The appendix is most frequently used as a continent catheterizable outlet valve because of the relatively low complication rate. In the absence of a suitable appendix, the fallopian tube or a short segment of ileum can be reconfigured according to the Yang-Monti technique. The umbilicus is best suited for stoma creation for both cosmetic and functional reasons. The stoma is hidden in the umbilicus, and the tract to the reservoir is the shortest possible given the absence of subcutaneous fatty tissue. Thus, the risk of kinking or false routes is kept low compared to longer

subcutaneous tunnels, e.g., in the suprapubic area. The heterotopic continent catheterizable urinary reservoir is an elegant alternative in patients for whom an orthotopic bladder substitution is not feasible, namely, involvement of the urethra with tumor and/or sphincter dysfunction. Quality of life is comparable with orthotopic continent diversion. However, revision surgeries are not uncommon, as the outlet valve may become incontinent or catheterization may become difficult because of stomal stenosis. Furthermore, in up to one third of all patients, removal of the ileocecal valve results in periodic stool frequency due to too rapid loss of bile acids. In addition, 25% of all patients will develop bile acid stones or renal stones. Importantly, one third of patients will require long-term sodium/potassium citrate substitution to prevent metabolic acidosis. Finally, one third of patients who do not get regular vitamin B12 substitution will develop vitamin B12 hypovitaminosis when the ileocecal area is used for continent urinary diversion (Pfitzenmaier et al. 2003).

Continent Orthotopic Urinary Diversion

The breakthrough in urinary diversion came when the tubular bowel segments were reconfigured into a spheroidal, minimally contractile reservoir in order to avoid the coordinated peristalsis that causes incontinence (Studer 2015; Hautmann et al. 2006). Reservoir compliance is best when using ileum only (Paananen et al. 2014). Patients with reservoirs made from ileum may experience episodes of salt loss syndrome and severe metabolic acidosis mainly in the early postoperative phase only. However, provided the patient has normal renal function, long-term alkali substitution is less frequently required (Furrer et al. 2016a). Furthermore, when using ileum only and leaving the terminal ileum as well as the ileocecal valve intact, the problem of vitamin B12 malabsorption and bile acid loss with frequent stool, gallbladder stones, and renal calculi formation is much less pronounced.

Urinary diversion with an ileal orthotopic bladder substitution following RC has been performed worldwide for more than 30 years (Studer 2015; Hautmann et al. 2006). The procedure has high patient acceptance because it is associated with preservation of body image. The main advantage of an orthotopic bladder substitution is that the low-pressure reservoir is anastomosed to the patient's genuine sphincter. Timed spontaneous voiding takes place every 3–5 h. However, there are restrictive selection criteria for this type of diversion: i) good renal function is a prerequisite, ii) meticulous preservation of sphincter and at least unilateral nerve sparing must be possible, iii) proactive postoperative patient management is required, and iv) lifelong patient follow-up is mandatory for timely detection of complications before irreversible damage occurs (Studer 2015). Because ileal orthotopic bladder substitution is the most common form of continent urinary diversion, the critical points that must be adhered to are summarized in the following sections.

Continent Orthotopic Urinary Diversion: Patient Selection

During endoscopic resection or biopsy of the tumor, biopsies from the distal prostatic urethra in male patients or from the bladder neck in female patients must exclude the presence of tumor at this level. However, carcinoma in situ is not an absolute contraindication for orthotopic urinary diversion since these patients can be cured with topical bacillus Calmette-Guerin therapy (Giannarini et al. 2010). Furthermore, the patient must be aware that early postoperative urinary incontinence is likely and that she/he will have to follow an active rehabilitation process for 2–3 months. Adequate renal function (serum creatinine $\leq$150 μmol/L or glomerular filtration rate $>$ 50 ml/min) is mandatory, as significantly impaired renal function would not allow for compensation of metabolic acidosis. Normal liver function is required because of the increased ammonia load in case of infected urine in the orthotopic bladder substitution.

Continent Orthotopic Urinary Diversion: Surgical Technique

Nerve-sparing techniques should be used at RC in patients who are candidates for an orthotopic bladder substitution. This is because, as described in section "Nerve-Sparing Radical Cystectomy and Continent Urinary Diversion," preservation of the autonomic innervation to the urethra is associated with better continence outcomes that are maintained over time (Turner et al. 1997; Kessler et al. 2004; Furrer et al. 2016b). The puboprostatic ligaments in male patients and pubourethral ligaments in female patients are preserved. Whenever possible from an oncologic standpoint, the uterus is preserved as this results in better functional outcomes (Gross et al. 2015).

At the time of orthotopic bladder substitution construction, both the ileocecal valve and the most distal 25 cm of ileum are preserved intact in order to avoid accelerated bowel transit time, vitamin B12 loss, bile acid-induced diarrhea, and kidney/gallbladder stones. The reservoir is made by detubularizing the distal 40–44 cm of the bowel segment and using the proximal 12–14 cm as a tubular afferent limb (Fig. 4). The ureters are implanted in refluxive fashion. Importantly, the anastomosis of the orthotopic bladder substitution to the membranous urethra must be flat and wide open. Care is taken to avoid a funnel-shaped outlet with its associated risk of kinking, with consequent outlet obstruction and residual urine (Fig. 5).

Continent Orthotopic Urinary Diversion: Follow-Up

After removal of the urethral catheter, the patient is required to void in a sitting position at 2-hourly intervals during daytime and 3-hourly intervals during nighttime, mainly by relaxing the pelvic floor, if needed accompanied by only slight abdominal straining. Sphincter training is performed by contracting the sphincter regularly according to specific instructions. The presence of

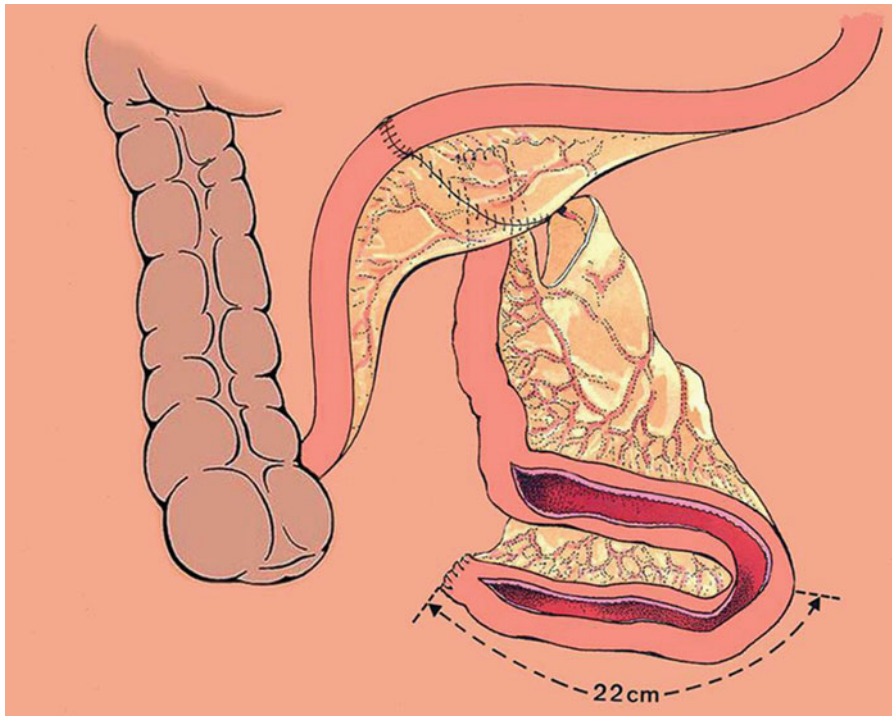

Fig. 4 Construction of the orthotopic bladder substitution. Both ends of the isolated segment of the reservoir are closed and the distal 44-cm-long portion along the antimesenteric border are opened while leaving the proximal 10–12-cm-long portion as the afferent isoperistaltic tubular segment (From Studer 2015)

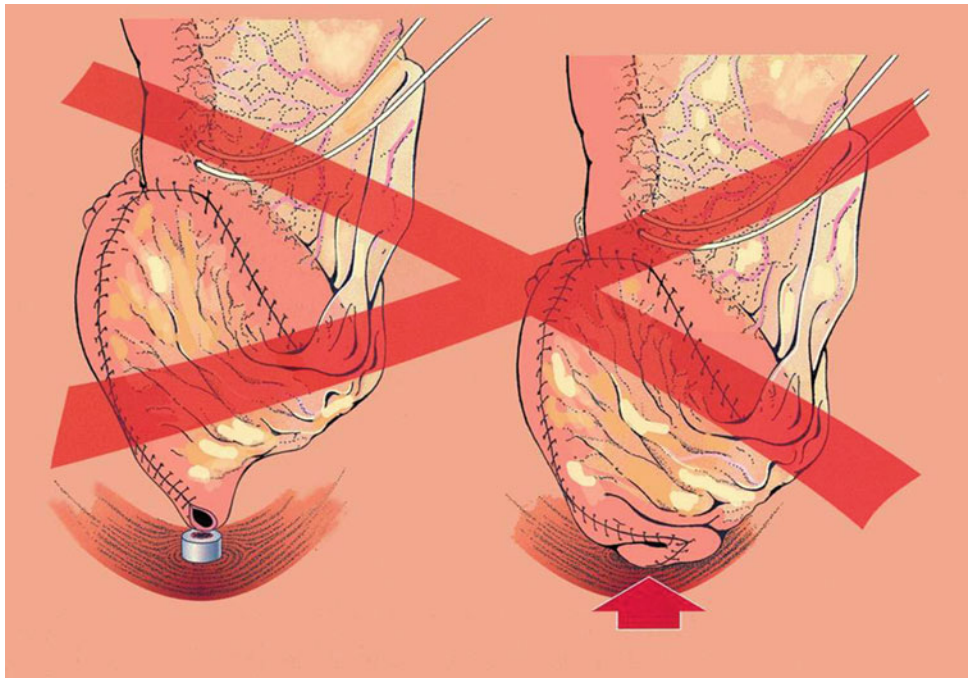

Fig. 5 How not to construct the orthotopic bladder substitution. Creating a funnel-shaped anastomotic end should be avoided since this leads to kinking and obstruction of the reservoir (From Studer 2015)

residual urine is checked on a daily basis and base excess in the venous blood gas is checked every 2 days. The patient should increase salt and fluid intake in order to prevent salt loss syndrome and/or metabolic acidosis. As soon as the patient has a stable metabolism and is able to retain urine for 2 h, she/he must increase the voiding interval to 3 h and later to 4 h in order to increase the functional capacity of the reservoir to 500 ml. A meticulous, lifelong follow-up is necessary in order to assure optimal reservoir function and to avoid long-term complications (normal upper tract, no residual urine, no infection, no acidosis, good functional capacity of 400–500 ml, and urinary continence) (Studer 2015).

Continent Orthotopic Urinary Diversion: Quality of Life and Complications

Factors that impact quality of life in patients with urinary diversion are physical functioning, interpersonal relationships, psychosocial stress, urinary continence, spontaneous micturition, and preserved sexual function, among others. There is general agreement that quality of life is better in patients with an ileal orthotopic bladder substitution than in those with an ileal conduit (Cerruto et al. 2016). This may, however, reflect the fact that patients who receive an ileal conduit usually are older and have more comorbidities. Regarding the risk of complications after urinary diversion, Nieuwenhuijzen et al. evaluated 281 patients who underwent RC and urinary diversion with ileal conduit, Indiana pouch, or orthotopic bladder substitution and found no differences in the risk of developing major complications between these types of urinary diversion (Nieuwenhuijzen et al. 2008). Similarly, in the Memorial Sloan Kettering series, the type of urinary diversion was not an independent predictor of major complications (Shabsigh et al. 2009).

Studies of renal function after urinary diversion have been heterogeneous in methodology and definitions, making it difficult to compare results across studies. Overall, there is no evidence that continent diversion is associated with

a higher risk of decreased renal function (Eisenberg et al. 2014; Jin et al. 2012). In the series from the University of Bern evaluating patients with ileal conduit or orthotopic bladder substitution, urinary tract obstruction (ureteroileal stricture, stomal stenosis, parastomal hernia) was the leading cause of deterioration of renal function regardless of the type of urinary diversion (Jin et al. 2012). These findings once again emphasized the importance of regular follow-up after surgery.

In all, continent forms of urinary diversion allow for the preservation of body image by circumventing the need for a wet stoma and external collection device. However, precise surgical technique and meticulous, lifelong follow-up are critical to achieve excellent long-term functional outcomes.

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Multimodality Treatment for Bladder Conservation

24

Oliver J. Ott

Contents

Abstract

Standard treatment for muscle-invasive urothelial cancer of the bladder is radical cystectomy. Multimodality treatment, including initial transurethral resection of the bladder tumor (TUR-B), followed by concurrent radiochemotherapy (RCT) has been shown to produce survival rates comparable to those of radical cystectomy. With these bladder conservation approaches, (salvage) cystectomy has been reserved for patients with incomplete response or local muscle-invasive relapse. During the past three decades, organ preservation by multimodality treatment has been investigated in prospective series from single centers and cooperative groups, with far more than 1000 patients included. Five-year overall survival rates in the range of 50–60% have been reported, and approximately 80% of the surviving patients maintained their own bladder. Clinical criteria helpful in determining patients for bladder preservation include such variables as small tumor size (<5 cm), early tumor stage, a visibly and microscopically complete transurethral resection, absence of ureteral obstruction, and no evidence of pelvic lymph node metastases. On multivariate analysis, the completeness of TUR-B was found to be one of the strongest predictive factors for overall survival. Patients at greater risk of recurrence after initial

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complete response are those with multifocal disease and extensive associated carcinoma in situ at presentation. Close coordination among all disciplines is required to achieve optimal results. Future investigations will focus on optimizing radiation techniques including all possibilities of radiosensitization (e.g., concurrent radiochemotherapy, additional deep regional hyperthermia), and incorporating more effective systemic chemotherapy, and proper selection of patients based on predictive molecular makers.

Introduction

According to the World Cancer Report 2014, bladder cancer is the ninth most common cancer worldwide, and urothelial carcinoma is the most frequent histological type (>90%). Tobacco smoking remains the most important cause of bladder cancer. Arsenic and some occupational exposures could also occasionally lead to bladder cancer. Only 30–40% of patients with muscle-invasive cancers survive 5 years or longer (McGuire 2016). Standard procedure for muscle-invasive bladder cancer (≥T2) is the immediate radical cystectomy with pelvic lymphadenectomy, which provides local control rates of 90–95%. But, especially for tumors with perivesical invasion (≥T3b) the local control rates are not satisfying with surgery alone. Furthermore, up to 50% of the patients with bladder cancer die due to distant metastases during the course of disease. Especially but not only for these patients, the deprivation of bladder's voiding function means a substantial loss of quality of life, even despite of contemporary surgical reconstruction techniques. Multimodality treatment including initial TUR-B followed by concurrent radiochemotherapy (RCT) for bladder conservation offers a valuable treatment alternative not only for patients unfit or unwilling for radical surgery (Ploussard et al. 2014a; Retz et al. 2016).

Patient Selection

From the practical point of view, at least three patient subgroups can be discriminated, which present themselves with different general health and bladder cancer disease status (Fig. 1). The proper differentiation of these groups has a major impact on the curative or palliative treatment intention.

The first patient subgroup usually presents in good general condition and a tumor limited to the bladder (≤T2) with no evidence of distant metastases. For this subgroup multimodality treatment with curative intention including TUR-B and RCT has proved to be a real alternative to radical cystectomy with comparable overall survival rates at 5 and 10 years (Weiss et al. 2008), and a long-term bladder preservation rate of 80% (Rodel et al. 2002), at least.

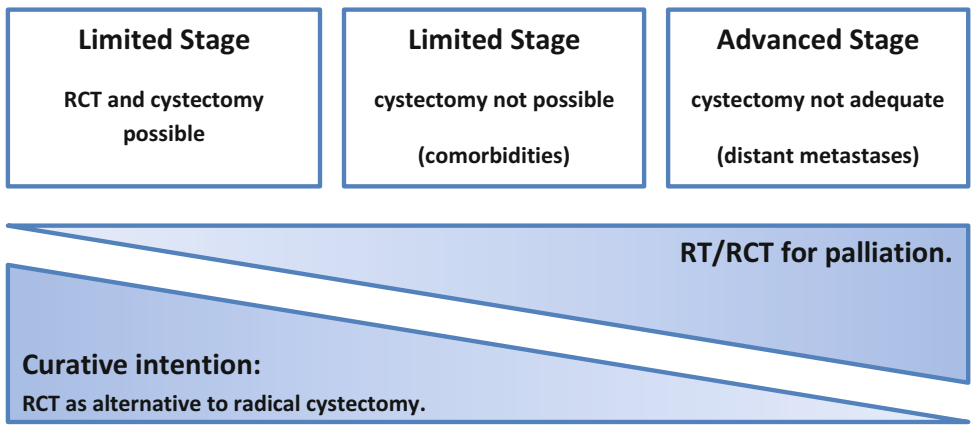

Fig. 1 Patient selection for bladder preservation (Abbreviation: *RCT* Radiochemotherapy, *RT* Radiotherapy)

The second subgroup also presents with a limited extension of the bladder carcinoma but with substantial comorbidities (e.g., severe dysfunctions of the heart or lungs), which could lead to an inacceptable risk regarding general anesthesia or surgical procedures. These patients present to the radiation oncologist not because they were aware of the advantages of the multimodality treatment approach for bladder preservation, but they were refused to be treated by the urologist. Unfortunately, because of the poor general condition this group of patients often cannot receive curative full-dose simultaneous RCT, which could lead to inferior results of the multimodality treatment approach.

The third subgroup of patients initially presents with distant metastases. Urologists usually refer these patients to the radiation oncologist for quality of life reasons. The treatment intention is palliative, and radiotherapy/RCT of the bladder cancer is usually given to prevent or treat local progression and tumor induced pain.

Patients at greater risk of new tumor development after initial complete response are those with multifocal disease and extensive associated carcinoma in situ at presentation. Anemia has also been shown to predict reduced local control as well as a higher rate of distant metastases and death from bladder cancer (Gospodarowicz et al. 1989). Clinical criteria helpful in determining patients for bladder preservation include such variables as small tumor size (< 5 cm), early tumor stage, a visibly and microscopically complete TUR, absence of ureteral obstruction, and no evidence of pelvic lymph node metastases.

Over the past years, some working groups found correlations between predictive molecular markers and clinical treatment outcomes after radical cystectomy and multimodality treatment for bladder conservation in small to medium size retrospectively analyzed patient cohorts.

Weiss et al. analyzed survivin expression as a predictive marker for local control in 48 patients with high-risk stage T1 bladder cancer treated with TUR-B and RCT. Survivin was not expressed in normal bladder urothelium but was overexpressed in 67% of the tumors. With a median follow-up of 27 (3–140) months, elevated survivin expression was significantly associated with an increased probability of local failure ($p = 0.003$) (Weiss et al. 2009). Choudhury et al. found that low pretreatment tumor MRE11 expression was associated with worse 3-year cancer-specific survival compared with high expression (43.1% vs. 68.7%, $p = 0.012$) in 86 patients who received radiotherapy for bladder cancer. In a control group of 88 patients who received radical cystectomy, MRE11 expression was not associated with cancer-specific survival (CSS). High MRE11 expression in the combined radiotherapy cohort had a significantly better 3-year cancer-specific survival compared with the high-expression cystectomy cohort (69.9% vs. 53.8%, $p = 0.021$). In this validated immunohistochemistry study, MRE11 protein expression was shown as a predictive factor associated with survival following bladder cancer radiotherapy (Choudhury et al. 2010). Laurberg et al. evaluated the expression of TIP60 and MRE11 and their predictive value for the treatment-specific outcome of localized invasive bladder cancer in 3 cohorts with a total of 583 patients who received either radical cystectomy or radiotherapy for bladder cancer. TIP60 protein expression was a predictive marker for cancer-specific survival after cystectomy in two independent cohorts. TIP60 was the strongest predictive factor in multivariate analysis in patients receiving cystectomy. MRE11 was shown to be a predictive marker for cancer-specific survival (CSS) after radiotherapy. The authors concluded that TIP60 and MRE11 hold the potential to guide patients with invasive bladder cancer to either cystectomy or radiotherapy (Laurberg et al. 2012). Furthermore, Keck et al. reported on Neuropilin-2 and VEGF-C as potential predictive markers for treatment response after transurethral resection and radiochemotherapy in 247 muscle-invasive bladder cancer patients. Neuropilin-2 expression emerged as a prognostic factor in overall survival (HR: 3.42; 95% CI: 1.48–7.86; $p = 0.004$) and was associated with a 3.85-fold increased risk of an early cancer-specific death (95% CI: 0.91–16.24; $p = 0.066$) in multivariate analyses. CSS dropped from 166 months to 85 months when Neuropilin-2 was highly expressed ($p = 0.037$). Patients with high

VEGF-C expression had a 2.29-fold increased risk of shorter cancer-specific survival (95% CI: 1.03–5.35; $p = 0.043$) in univariate analysis. CSS dropped from 170 months to 88 months in the case of high VEGF-C expression ($p = 0.041$). Additionally, Neuropilin-2 and VEGF-C coexpression was a prognostic marker for overall survival in multivariate models (HR: 7.54; 95% CI: 1.57–36.23; $p = 0.012$) (Keck et al. 2015). Bertz et al. described micropapillary morphology as a predictive marker for poor prognosis in 238 patients with urothelial carcinoma treated with transurethral resection and radiochemotherapy. The mere presence of micropapillary morphology did not affect prognosis. But in tumors with extensive (≥30%) micropapillary morphology, mean cancer-specific survival was significantly worse compared to conventional urothelial cancer (97 vs. 229 months, $p = 0.002$) (Bertz et al. 2016).

Prospective trials for further confirmation of the predictive value of molecular markers are still lacking, but there is a good future potential for more adequate patient selection for both radical cystectomy and multimodality treatment.

Teamwork Is Not Optional

Well-organized teamwork between the urologist, the pathologist, and the radiation oncologist is mandatory for successful bladder preservation. The basis of the combined modality approach is the TUR-B. Concurrent RCT starts 4 weeks after initial TUR-B. Another 6–12 weeks after the completion of RCT, an obligatory restaging TUR-B with multiple representative biopsies has to be performed by the urologist. A pathologically confirmed complete response (pCR) requires the absence of any endoscopically visible tumor, and any microscopic tumor in the biopsy specimen, as well as negative urine cytology. In case of complete remission, patients should be observed at 3-month intervals for the first year, at 6-month intervals until the fifth year, and every 12 months thereafter (Retz et al. 2016). In case of persistent or recurrent tumor, additional treatments, such as TUR-B followed by intravesical therapy for superficial or salvage cystectomy for muscle-invasive tumors, are recommended and should be initiated at the earliest opportunity. In summary, good collaboration plays a key role in the successful organ preserving combined modality treatment of bladder cancer. A comprehensive overview of the treatment algorithm is shown in Fig. 2.

Initial Transurethral Resection of the Bladder (TUR-B)

Preferably, the bladder cancer should be removed completely (R0-resection). Therefore, the TUR-B should be performed as radical as reasonable achievable without perforating the bladder wall. The quality of the TUR-B has to be confirmed by multiple representative biopsies from the basal and lateral resection margins of the tumor in order to confirm the completeness of the surgical procedure and to detect associated carcinoma in situ (CIS) or a multifocal growths pattern, which are well-known prognostic factors (Retz et al. 2016). A standardized protocol for the TUR-B in the context of bladder preservation was proposed firstly by Dunst et al. in 1994 (Dunst et al. 1994). For the majority of the patients with limited disease (≤pT2) a pCR should be achievable. For example, Weiss et al. (2006) reported on a series of 141 patients with high-risk T1-baldder cancer and found a multiple biopsy approved pCR rate of 56% (79/141). The quality of the TUR-B has been proven to be one of the most important prognostic factors for overall survival. Rodel et al. (2002) analyzed a total of 415 patients (high-risk stage T1 ($n = 89$) and muscle-invasive T2–4 tumors ($n = 326$) who received combined modality treatment with TUR-B followed by radiotherapy alone (126/415) or RCT (289/415) for bladder preservation. The 10-year overall survival rates were 50%, 33%, and 18% ($p = 0.003$) for patients with a complete resection (R0), microscopically (R1), and macroscopically residual disease (R2), respectively. On multivariate analysis, the completeness of TUR-B was found to be one of the strongest prognostic factors for overall survival (Rodel et al. 2002).

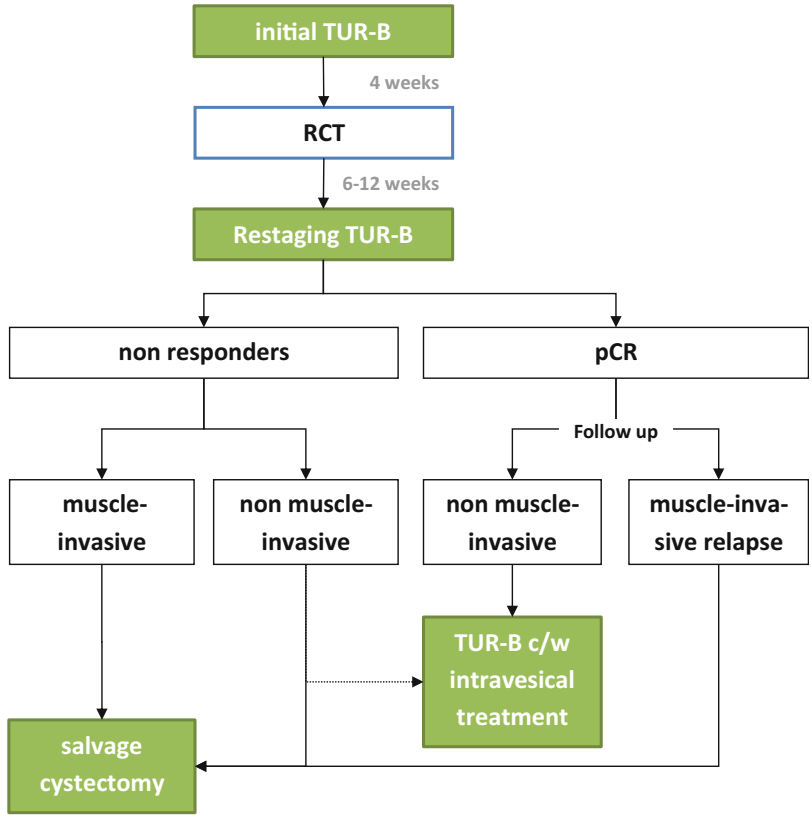

Fig. 2 Treatment algorithm for bladder preservation (Abbreviation: *TUR-B* Transurethral resection of the bladder cancer, *RCT* Radiochemotherapy, *pCR* Pathologically confirmed complete remission)

Radiotherapy

Radiotherapy as part of the multimodality bladder preserving treatment approach can be performed as conventionally fractionated *continuous course* up to a total dose of 55–60 Gy, or *split course* with an induction dose of 40 Gy followed by a consolidation boost of another 25 Gy in case of a pCR in the obligatory restaging TUR-B 4–6 weeks after the end of radiotherapy (Ploussard et al. 2014a; Retz et al. 2016; Rodel et al. 2002; James et al. 2012; Krause et al. 2011). Nonresponders with persisting muscle-invasive disease in the restaging TUR-B are advised to receive salvage cystectomy after 55–60 Gy (continuous course) or 40 Gy (split course) (Efstathiou et al. 2012). Up to date, no prospective trial has proved the superiority of one of the two treatment approaches (Ploussard et al. 2014a; Retz et al. 2016). For general radiobiological reasons it is recommended not to interrupt radiotherapy until reaching the complete dose to minimize undesirable repopulation effects among the tumor cells (Maciejewski and Majewski 1991; De Neve et al. 1995).

In Europe, radiotherapy is usually applied with single fraction doses of 1.8–2.0 Gy and five fractions per week (Rodel et al. 2002; James et al. 2012; Krause et al. 2011). Up to date there is no evidence that an accelerated fractionation schedule with two fractions per day is leading to better local control or overall survival rates. Actually, accelerated treatment schedules are leading to higher treatment-related toxicity (Retz et al. 2016; Efstathiou et al. 2012; Horwich et al. 2005). Reduction of overall treatment time and large fraction sizes should be avoided, especially when radiotherapy is combined with concomitant chemotherapy. New treatment techniques, such as image-guided and intensity-modulated radiotherapy, as well as interstitial radiotherapy in selected cases (unifocal, small bulk disease) or the use of particle therapy, in particular protons, may allow dose escalation with

the expectation to further improve tumor response and long-term local control (Hata et al. 2006; Henry et al. 2006; Pos et al. 2005, 2006).

The radiotherapy target volume for bladder conservation strategies is not well defined. While the majority of the centers include the whole bladder into the planning treatment volume (PTV), there were some attempts to spare or increase the local dose in distinct bladder areas to avoid toxicity or increase efficacy (Koning et al. 2012). In another phase III multicenter trial 219 patients were randomized to standard whole-bladder radiation therapy or reduced high-dose volume radiation therapy that aimed to deliver full radiation dose to the tumor and 80% of maximum dose to the uninvolved bladder. The primary endpoints for the radiation therapy volume comparison were late toxicity and time to locoregional recurrence. Reduced high-dose volume radiation therapy did not result in a statistically significant reduction in late side effects compared with standard whole-bladder radiation therapy, and noninferiority of locoregional control could not be concluded formally (Huddart et al. 2015).

The role of the elective irradiation of the pelvic lymphatics is unclear, but in many institutions the pelvic lymph node areas are included into the planning treatment volume because of an increasing likelihood of involved lymph nodes with more advanced tumor stages (Tunio et al. 2012). The total radiotherapy dose should not exceed 50 Gy in the elective areas and may be increased up to 60–66 Gy for macroscopic tumor tissue outside of the bladder as an additional boost irradiation (Ploussard et al. 2014a; Witjes et al. 2014).

Radiosensitization with Chemotherapy and Hyperthermia

During the past three decades several working groups proved the advantage of simultaneous RCT compared to radiotherapy alone within two prospective randomized trials and quite a number of further prospective and retrospective evaluations (Ploussard et al. 2014a; Retz et al. 2016; Rodel et al. 2002; James et al. 2012; Krause et al. 2011; Efstathiou et al. 2012; Coppin et al. 1996; Ploussard et al. 2014b). Cisplatin turned out to be the most effective chemotherapy agent for the treatment of locally advanced or metastasized urothelial cancer as well as for radiosensitizing purposes in the framework of a bladder preservation multimodality treatment approach (Witjes et al. 2014). In 1996, a small randomized Canadian trial with a total of 99 patients proved the superiority of RCT for the first time. Patients received either a preoperative or definitive radiotherapy randomly combined with or without Cisplatin (3×100 mg/m^2, q2w). After a follow-up of 6.5 years a better pelvic tumor control was reported for the Cisplatin arm ($p = 0.036$). Overall and distant metastasis-free survival rates were not different (Coppin et al. 1996).

One of the worldwide largest long-term evaluations regarding bladder conservation with a total of 473 patients showed that the concurrent Cisplatin-based chemotherapy not only significantly improved bladder-conservation rates but also median overall survival rates (70 vs. 28.5 months, $p < 0.001$) (Krause et al. 2011).

The British prospective BC2001 trial included a total of 360 patients, who randomly received radiotherapy alone or combined with a radiosensitizing concurrent chemotherapy with Mitomycin C (MMC; 12 mg/m^2, day 1) and 5-fluorouracil (5-FU; 500 mg/m^2, days 1–5 und 16–20). After a median follow-up of about 70 months a significantly improved locoregional control was found in the RCT group (HR 0.68, $p = 0.03$). The 5-year overall survival rates were 48% vs. 35% in favor of the RCT group, but the difference was statistically not significant ($p = 0.16$). Global early toxicity rates were not different (36 vs. 27.5%, $p = 0.07$), with a higher gastrointestinal toxicity in the RCT group (9.6 vs. 2.7%, $p = 0.007$). Grade 3–4 late toxicity rates were equal (RTOG grading: 15.7% after radiotherapy alone and 8.3% after RCT ($p = 0.07$); LENT/SOM grading: 51% vs. 54% ($p = 0.72$), respectively (James et al. 2012).

In randomized trials for several tumor entities (e.g., cervical carcinoma, anal cancer, rectal cancer, head and neck cancer, glioblastoma multiforme, breast cancer, and malignant melanoma) concurrent regional hyperthermia combined with radiotherapy and/or chemotherapy had been

shown to significantly further improve clinical endpoints. A comprehensive overview of the technique and additional effects of regional hyperthermia can be found in several reviews (van der Zee 2002; Wust et al. 2002; Horsman and Overgaard 2007; Moyer and Delman 2008).

In bladder carcinoma treatment two randomized trials showed significantly improved clinical results when adding hyperthermia to either chemotherapy (Colombo et al. 2003) or external beam radiotherapy (van der Zee et al. 2000). Colombo et al. randomly assigned 83 patients suffering from primary or recurrent superficial (Ta-T1) transitional cell cancer of the bladder to either intravesical instillation of Mitomycin C versus the same cytostatic agent in combination with local hyperthermia after complete TUR-B (Colombo et al. 2003). For intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) addition of hyperthermia reduced significantly the local recurrence rate at 2 years (17.1% vs. 57.5%, $p = 0.0002$).

Furthermore, van der Zee et al. could show that deep regional hyperthermia significantly increased the complete response rate (73% vs. 51%, $p = 0.01$) in locally advanced muscle-invasive bladder cancer (T2–T4) when combined with external beam irradiation (van der Zee et al. 2000).

It has been the ongoing policy at the Departments of Urology and Radiation Oncology at the University Hospitals of Erlangen, Germany, to use definitive radiotherapy with or without concurrent CT after conservative surgery for high-risk stage T1 and muscle-invasive (T2–4) bladder cancer since 1982 (Rodel et al. 2002; Dunst et al. 1994; Sauer et al. 1998; Weiss et al. 2007). To further advance in multimodal treatment of bladder cancer, we evaluated the effectiveness and safety of adding concurrent hyperthermia to our well-established combined modality bladder-sparing treatment for patients with high-risk stage T1 and T2 bladder cancer. In 45 patients with stage T1–2 bladder carcinoma who received RCT combined with concurrent deep regional hyperthermia, the pCR rate has been further improved in comparison to our historical data with radiotherapy or radiochemotherapy alone (Table 1) (Ott et al. 2009; Wittlinger et al. 2009).

In summary, simultaneous RCT either with Cisplatin or 5-FU and MMC is leading to better clinical results compared to radiotherapy alone and should therefore be regarded as standard treatment for patients, who want to preserve their own bladder. Future options for a further improvement of multimodality treatment may be an optimization of concurrent chemotherapy, e.g., with taxanes or gemcitabine, or the additive use of deep regional hyperthermia, or integration of hypoxia-modifying medication (Wittlinger et al. 2009; Caffo et al. 2011; Mitin et al. 2013; Choudhury and Cowan 2011; Choudhury et al. 2011; Hoskin et al. 2010). The use of radiotherapy alone is justified only for those patients who are unfit for concurrent chemotherapy at all.

Restaging TUR-B and Salvage Strategies

A restaging TUR-B is an indispensable part of the multimodality treatment approach for bladder conservation. The restaging TUR-B should

Table 1 Erlangen experience of bladder preservation (Weiss et al. 2007, 2008; Rodel et al. 2002)

Period	Cases [n]	T-category	TUR combined with	pCR [%]	5y-OAS [%]	5y-OAS, bladder preserved [%]
1982–1985	126	T1 (high risk)-T4	RT	61	40	37
1985–1993	95	T1 (high risk)-T4	RT + Carboplatin	66	45	40
1985–1993	145	T1 (high risk)-T4	RT + Cisplatin	82	62	47
1993–2006	112	T1 (high risk)-T4	RT + 5-FU/Cisplatin	88	74	61
2005–2008	38	T1 (high risk)-T2	RT + 5-FU/Cisplatin + RHT	95	80[a]	82[a]

TUR Transurethral resection, *pCR* Pathological complete remission, *5y-OAS* Overall survival probability at 5 years, *RT* External beam radiotherapy, *RHT* Regional deep hyperthermia

[a]: at 3 years of follow-up

be performed 6–12 weeks after completion of RCT, firstly to allow adequate tumor remission and secondly not to unnecessarily waste time to initiate required salvage treatments in patients with persisting tumor. Tumor biopsies from the former tumor area are regarded as necessary to safely discriminate between responders with a pCR and nonresponders (Retz et al. 2016).

In case of persisting (in the restaging TUR-B) or recurrent non-muscle-invasive (stage pTa-T1) urothelial cancer of the bladder (NMIBC) during follow-up, it may be individually decided to perform another TUR-B with or without intravesical therapy or a cystectomy for salvage treatment. For muscle-invasive disease, salvage cystectomy is strongly recommended. In the absence of a recurrence in very rare cases cystectomy may be considered as necessary because of severe bladder dysfunction during follow-up (Retz et al. 2016).

Comparison with Cystectomy Series and Conclusion

The primary goal of the bladder-sparing approach remains optimal patient survival. Thus, results of the organ-sparing approach need to be compared with the surgical standard. Bladder-sparing treatment has not yet been tested against primary cystectomy in randomized trials. Contemporary radical cystectomy series reported 5-year overall survival rates of 63–74% for NMIBC and 26–63% for muscle-invasive disease (Table 2). Despite the fact that comparisons between surgical series and bladder preservation protocols are hindered by the difference in pathologic and clinical staging – with the latter tending to understage the real tumor extent – the 5-year overall survival rates of these contemporary surgical series and the bladder sparing approaches lie in the same range (Table 2).

The use of organ preservation therapy for bladder cancer is a valid alternative to radical cystectomy in selected patients. Contemporary protocols utilize a combination of TUR-B, concurrent RCT, and often adjuvant chemotherapy. These approaches require close coordination among all disciplines involved. Future investigations will focus on optimizing radiation techniques and fractionation regimens as well as the incorporation of radiosensitizing agents (e.g., chemotherapy and/or hyperthermia) and more effective systemic therapy, and will explore the role of molecular markers and targeted biologic agents in the management of this disease.

Table 2 Comparison of the Erlangen data on bladder preservation with contemporary cystectomy series

Reference	Cases [n]	Median follow-up [months]	T-category	5y-OAS [%]	5y-OAS, bladder preserved [%]
Stein et al. (2001)	1024	122	T1 T2–4	74 55	51 38
Dalbagni et al. (2001)	300	65	T1 T2 T3–4	64 59 26	n.a.
Madersbacher et al. (2003)	507	45	T1 T2 T3–4	63 63 35	48 30 25
Hautmann et al. (2006)	788	35	T1–4	58	45
Shariat et al. (2006)	888	39	T1–4	59	n.a.
Erlangen data Rodel et al. (2002), Wittlinger et al. (2009), Krause et al. (2011)	525	35	T1 T2–4	71 56	50 34

5y-OAS Overall survival probability at 5 years, *RT* External beam radiotherapy, *n.a.* Not available

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Peri-operative Chemotherapy for Muscle-Invasive Bladder Cancer

25

Thomas Seisen, Benjamin Pradère, and Morgan Rouprêt

Contents

Abstract

The role of perioperative chemotherapy as an adjunct to radical cystectomy for muscle-invasive bladder cancer has been explored by several landmark randomized controlled trials over the past decades. On the one hand, a meta-analysis of level-I evidence and long-term results from the largest trials support the use of neoadjuvant chemotherapy, which is now advocated as the standard of care by most of the clinical guidelines worldwide. On the other hand, evidence supporting the use of adjuvant chemotherapy is more contentious. Specifically, several meta-analyses identified a survival benefit with the immediate postoperative delivery of cisplatin-based regimen, but the investigators identified multiple methodological limitations in the vast majority of included randomized controlled trials. Nonetheless, the use of adjuvant chemotherapy is currently considered for patients with adverse pathological features at radical

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cystectomy. The toxicity of both neoadjuvant and adjuvant chemotherapy is acceptable and well-aligned with what expected with cisplatin-based regimens. Given its greater response rate, the methotrexate, vinblastine, doxorubicine, and cisplatin combination is preferentially used in the neoadjuvant setting, while the gemcitabine plus cisplatin combination is more commonly delivered in the adjuvant setting because of its better toxicity profile. However, there is no prospective evidence suggesting a survival superiority of one regimen over the other. Finally, the comparative effectiveness of neoadjuvant vs. adjuvant chemotherapy has been poorly assessed in the current literature. Nonetheless, the only randomized controlled trial indirectly comparing both suggested no survival difference between the pre- and postoperative delivery of cisplatin-based chemotherapy.

Keywords
Urinary bladder neoplasms · Cystectomy · Drug therapy · Neoadjuvant therapy · Chemotherapy · Adjuvant · Cisplatin

Introduction

In the absence of clinical evidence suggesting a metastatic dissemination, radical cystectomy with pelvic lymph node dissection is currently considered as the standard of care for the local treatment of patients with muscle-invasive bladder cancer (Alfred Witjes et al. 2016). Nonetheless, the 5-year probability of overall survival after such procedure does not exceed 50–60% in expert centers, and a significant proportion of these individuals ultimately develop fatal intra- or extra-pelvic recurrence, likely due to the presence of micrometastases at the time of surgery (Grossman et al. 2003).

Striving to improve this paradigm, the efficacy of perioperative chemotherapy has been tested in multiple landmark randomized controlled trials over the past decades (International Collaboration of Trialists et al. 2011; Sternberg et al. 2015). Interestingly, there is a rationale for the exclusive use of neoadjuvant or adjuvant chemotherapy, although both present substantial limitations that may impact clinical practice. As such, several level-I evidence meta-analyses support either the systematic delivery of neoadjuvant chemotherapy for all muscle-invasive bladder cancer patients (Advanced Bladder Cancer Overview Collaboration 2005) or the selective delivery of adjuvant chemotherapy only in those with advanced disease after radical cystectomy (Leow et al. 2014).

Despite the potential advantages related to an adjuvant chemotherapy strategy, most of the current clinical guidelines advocate preferentially the first-line use of neoadjuvant chemotherapy (Alfred Witjes et al. 2016), given the higher quality of the overwhelming prospective evidence in favor of the preoperative infusion of cisplatin-based regimen. Nonetheless, important questions persist in terms of optimizing perioperative chemotherapy for bladder cancer in general.

Neoadjuvant Chemotherapy

Rationale for the Use of Neoadjuvant Chemotherapy

As opposed to an adjuvant chemotherapy strategy, the delivery of neoadjuvant chemotherapy offers several potential advantages in the framework of muscle-invasive bladder cancer management. First, the infusion of full-dose cisplatin-based regimen is largely facilitated by the better pre- vs. postoperative general condition of patients undergoing radical cystectomy and several postoperative complications such as renal failure have been reported to limit its use when indicated. This may impact the oncological outcomes associated with the delivery of adjuvant chemotherapy. In addition, adjuvant chemotherapy could delay the wound healing and increase the risk of infectious complications and/or fistula in the postoperative setting.

Second, it is well-established that the delivery of neoadjuvant chemotherapy allows to assess the response of the primary tumor to systemic chemotherapy at the time of surgery. Interestingly, individuals experiencing a downstaging of the

primary tumor (≤T1) could have a better prognosis than nonresponders. Furthermore, a complete pathologic response of the primary tumor has been shown to correlate with increased overall survival in a recent meta-analysis by Petrelli et al. (2014).

Based on this rationale and the proven efficacy of cisplatin-based regimen for metastatic bladder cancer, several landmark randomized controlled trials have explored the role of neoadjuvant chemotherapy prior to radical cystectomy for localized disease over the past decades.

Oncological Outcomes

Meta-analyses of Randomized Controlled Trials

Interestingly, discording results have been observed in the randomized controlled trials comparing neoadjuvant chemotherapy followed by local treatment vs. local treatment alone. The first large-scale study published in 1999 by the International Collaboration of Trialists included 976 patients from 106 institutions with cT2-T4 N0 bladder cancer to receive either three cycles of neoadjuvant cisplatin, methotrexate, and vinblastine ($n = 491$) or upfront local treatment ($n = 485$). Despite a benefit in terms of pathological downstaging, this randomized controlled trial showed no significant difference in overall survival between the two treatment groups after a median follow-up of 4 years (hazard ratio [HR]: 0.85; 95% CI, 0.71–1.02; $p = 0.075$) (Anon 1999). The absolute difference in 3-year overall survival was up to 5.5% (95% IC, from −0.5% to 11%), with corresponding rates of 55.5% in patients who received neoadjuvant chemotherapy and 50% in patients who received upfront local treatment. Similarly, no locoregional disease-free survival benefit was observed with the delivery of neoadjuvant chemotherapy (HR = 0.87; 95% CI, from 0.73 to 1.02, $p = 0.087$). However, there was a significant difference between the two treatment groups in terms of metastasis-free survival (HR = 0.79; 95% CI, from 0.66 to 0.93; $p = 0{\cdot}007$); this translated in an absolute difference in 3-year metastasis-free survival of 8% (95% CI, from 2% to 14%), 53% in the neoadjuvant chemotherapy group, and 45% in the upfront local treatment group.

Given that neoadjuvant chemotherapy was associated with a decreased risk of death from any cause in other reports, the Advanced Bladder Cancer group from the Cochrane collaboration performed a first individual patient data meta-analysis of level-I evidence in 2003 (Advanced Bladder Cancer Meta-analysis Collaboration 2003). This study included 2688 patients from 10 randomized controlled trials. The investigators found that, as compared to local treatment alone, the use of neoadjuvant platinum-based combination chemotherapy (most of the time cisplatin) was associated with a 13% overall survival benefit (hazard ratio [HR] = 0.87; 95% confidence interval [CI], from 0.78 to 0.98; $p = 0.016$); this translated into a 5% absolute benefit in 5-year overall survival (50% vs. 45%). In addition, the infusion of neoadjuvant platinum-based combination chemotherapy improved significantly overall ($p < 0.001$) and locoregional ($p < 0.001$) disease-free survival as well as metastasis-free survival ($p = 0.001$). However, a neoadjuvant single-agent cisplatin chemotherapy was not associated with an overall survival benefit as compared to radical cystectomy alone ($p = 0.26$). Accordingly, neoadjuvant platinum-based combination vs. single-agent cisplatin chemotherapy also significantly improved overall survival ($p = 0.044$) and disease-free survival ($p = 0.046$).

Further randomized controlled trials were conducted after this first meta-analysis, which did not include the second largest study from the Southwest Oncology Group published by Grossman et al. in 2003. In this report, the investigators randomized 317 patients with cT2-T4a bladder cancer to receive either three cycles of methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy ($n = 153$) or radical cystectomy alone ($n = 154$) (Grossman et al. 2003). Interestingly, a higher pathologic complete response rate was found in patients who received neoadjuvant chemotherapy (38% vs. 15%; $p < 0.001$), and there was only a trend toward adverse overall survival in patients treated

with radical cystectomy alone (HR = 1.33; 95% CI, from 1.00 to 1.76). Specifically, the 5-year overall survival was 57% in the neoadjuvant chemotherapy group and 43% in the radical cystectomy alone group ($p = 0.06$). Nonetheless, exploratory analyses showed that patients who received radical cystectomy were significantly more likely to experience cancer-specific death (HR = 1.66; 95% CI, from 1.22 to 2.45; $p = 0.002$).

As such, a second individual patient data meta-analysis has been undertaken by the Advanced Bladder Cancer group in 2005 to include 3005 patients from 11 randomized controlled trials (Advanced Bladder Cancer Overview Collaboration 2005). This updated analysis confirmed the overall survival benefit of neoadjuvant platinum-based chemotherapy as compared to local therapy alone (HR = 0.86; 95% CI, from 0.77 to 0.95; $p = 0.003$) with a 5% absolute improvement in 5-year overall survival. In addition, there was a significant disease-free survival benefit in patients who received neoadjuvant platinum-based combination chemotherapy (HR = 0.78; 95% CI, from 0.71 to 0.86; $p < 0.001$), equivalent to a 9% absolute improvement at 5 years.

Concomitantly, Winquist et al. performed a meta-analysis of summary data from 16 randomized controlled trials including 3315 patients (Winquist et al. 2004). Of these trials, 11 (2605 patients) provided data suitable for overall survival analysis. The pooled HR was 0.90 (95% CI, from 0.82 to 0.99; $p = 0.02$). When restricting the analyses to eight trials including only patients who received neoadjuvant cisplatin-based combination chemotherapy, the pooled HR was 0.87 (95% CI, from 0.78 to 0.96; $p = 0.006$); this translated into an absolute overall survival benefit of 6.5% (56.5% vs. 50%). Although results were mostly concordant with those for overall survival, available data on progression-free survival were insufficient to perform a meta-analysis. Finally, a major pathological response was associated with improved overall survival in four included trials.

Additional Randomized Controlled Trials

More recently, three small randomized controlled trials have been published but only negative results with regard to overall survival were reported by the investigators (Osman et al. 2014; Kitamura et al. 2014; Khaled et al. 2014). For example, the Japan Oncology Group (*JCOG0209*) analyzed 130 patients and found no significant difference in overall survival between those who received neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin plus radical cystectomy or radical cystectomy alone (Kitamura et al. 2014). However, this study closed early, as the slow accrual did not allow to reach the initially planned number of included patients. In addition, there was a trend toward better outcomes with neoadjuvant chemotherapy (HR = 0.65; multiplicity adjusted 99.99% CI, from 0.19 to 2.18, one-sided $p = 0.07$) and the rate of complete pathological response was greater in the neoadjuvant chemotherapy vs. radical cystectomy alone group (34% vs. 9%; $p < 0.01$). Accordingly, a very last meta-analysis of summary data published in 2016 showed a persistent overall survival benefit with neoadjuvant chemotherapy after including these negative trials (HR = 0.87; 95% CI, from 0.79 to 0.96), which was more pronounced when only considering patients who received cisplatin-based regimen (HR = 0.84; 95% CI, from 0.76 to 0.93) (Yin et al. 2016).

Long-Term Oncological Outcomes

In 2011, the International Collaboration of Trialists updated the results from the largest study analyzing the role of neoadjuvant chemotherapy and presented long-term outcomes (Sternberg et al. 2015). Interestingly, although the preliminary results were negative for overall survival in 1999, there was a significant benefit in patients who received neoadjuvant chemotherapy after a median follow-up of 8.0 years (5.7–10.2 years). Specifically, a 16% reduction in the risk of death from any cause was observed as compared to the local treatment alone group (HR = 0.84; 95%CI, from 0.72 to 0.99; $p = 0.037$); this corresponded to an increase in 10-year overall survival from 30% to 36%. It is noteworthy that almost all other oncological outcomes were also in favor of the use of neoadjuvant chemotherapy, as there was a 23% reduction in the risk of metastases

(HR = 0.77; 95% CI, from 0.66 to 0.90; $p = 0.001$) and 18% reduction in the risk of overall disease recurrence (HR = 0.82; 95% CI, from 0.70 to 0.95; $p = 0.008$). Only a nonsignificant trend favoring the neoadjuvant chemotherapy groups was observed for disease-specific survival (HR = 0;83; 95%CI, from 0.68 to 1.00; $p = 0.050$). Although the local treatment was not randomized in this study, exploratory analyses revealed that the treatment effect of neoadjuvant chemotherapy was more pronounced in patients who received radical cystectomy (HR = 0.74; 95% CI, from 0.57 to 0.96; $p = 0.02$) than radiation therapy (HR = 0.80; 95% CI, from 0.63 to 1.02; $p = 0.07$). However, the differences in baseline characteristics could largely limit the interpretation of such results. Table 1 summarizes the randomized controlled trials and meta-analyses testing the role of neoadjuvant chemotherapy prior to radical cystectomy.

Contemporary Retrospective Evidence

Several large retrospective reports have confirmed the benefit observed with the delivery of neoadjuvant chemotherapy in the "real-life" setting. For example, Zargar et al. analyzed pathological downstaging among 935 patients who received neoadjuvant chemotherapy followed by radical cystectomy. Interestingly, the rate of pT0N0 and ≤pT1N0 were 22.7% and 40.8%, respectively. Other observational studies focused on identifying the best candidates for neoadjuvant chemotherapy prior to radical cystectomy. For example, a risk-stratified approach initially proposed by Culp et al. (2014) has recently been validated. Specifically, patients were classified as high- or low-risk based on the presence of preoperative risk factors including lymphovascular invasion, ureterohydronephrosis on preoperative computerized tomography scan, aggressive variant histology (micropapillary, neuroendocrine, sarcomatoid, or plasmacytoid tumors), and/or cT3b-T4a disease. Overall, 153 (44.6%) low-risk and 190 (55.4%) high-risk patients were identified. Interestingly, 27.4% and 14.2% of low- and high-risk patients were downstaged at the time of radical cystectomy, respectively. Cancer-specific mortality-free rates at 5 years after radical cystectomy were 77.4% vs. 64.4% for low-risk and high-risk patients, respectively. As such, these results highlight the interest of selecting individuals who may have a greater likelihood to experience downstaging and benefit from neoadjuvant chemotherapy.

Biomarkers for Patient Selection

It is nowadays argued that the systematic delivery of neoadjuvant chemotherapy for muscle-invasive bladder cancer may result in significant overtreatment for a substantial subgroup of patients. In addition, this could lead to adverse oncological outcomes in chemoresistant individuals by unnecessarily delaying radical cystectomy. As such, to improve the patient selection and ultimately, the associated oncological outcomes, several biomarkers predicting the response to neoadjuvant chemotherapy have been explored over the past years.

Specifically, the classification of muscle-invasive bladder cancer into molecular subtypes provided an important framework for further study of the disease. Some reports developed similar molecular classifications between intrinsic basal and luminal subtypes associated with patient outcomes (Damrauer et al. 2014; Sjödahl et al. 2012). In addition, Choi et al. identified the p53-like subtype, mostly within luminal tumors, that was noted to be associated with a negligible response to neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin. This resistance pattern to neoadjuvant chemotherapy has also been subsequently reported for the gemcitabine plus cisplatin regimen. Interestingly, the p53-like subtype is characterized by a gene expression consistent with the activation of the p53 pathway and cellular death, but not p53 mutations. On the other hand, basal tumors were characterized by a high-proliferative index and were more responsive to neoadjuvant chemotherapy.

Furthermore, recent work with immunohistochemistry has identified other biomarkers associated with response to neoadjuvant chemotherapy or radiation therapy. For example, the bladder

Table 1 Clinical trials and meta-analyses testing the role of neoadjuvant chemotherapy

Studies	Number of patients			Population study	Median follow-up	Regimen	Duration	Oncological results
	Treatment	Control	Total					
EORTC (1999)	491	495	986	pT2/T3/T4 and N0 or Nx	4 years	Methotrexate Vinblastine Cisplatin	3 cycles	**Overall survival** HR = 0.85 95%IC 0.71–1.02 $P = 0.075$ **Metastasis-free survival** HR = 0.79; 95% CI, 0.66–0.93; $P = 0{\cdot}007$
EORTC (2011)	491	495	986	pT2/T3/T4 and N0 or Nx	8 years	Methotrexate Vinblastine Cisplatin	3 cycles	**Reduction in the risk of death** HR = 0.84; (95%CI, 0.72–0.99); $P = 0.037$ **Reduction in the risk of metastases or death** HR = 0.77; (95% CI, 0.66 to 0.90) $P = 0.001$ **Disease-specific survival** HR = 0;83; (95%CI,0.68–1.00); $P = 0.050$
Grossman et al. (2003)	153	154	317	pT2-T4a	8.7 years	Methotrexate Vinblastine Doxorubicin Cisplatin	3 cycles	**Median survival** 77 vs. 46 months; $P = 0.06$ **5-year survival** 57% vs. 43%; $P = 0.06$ **Cancer-specific death** HR = 1.66 (95%CI, 1.22–2.45); $P = 0.002$
Sherif et al. (2004)	306	314	620	pT1G3, T2–T4a	14.8 years	Cisplatin/ methotrexate or Cisplatin/ doxorubicin	2 cycles or 3 cycles	**Overall survival** HR = 0.80 (95%IC, 0.64–0.99); $P = 0.049$ **5-year overall survival** 56% vs. 48%

Kitamura et al. (2014)	64	66	130	pT2-4aN0	4.6 years	Methotrexate Vinblastine Doxorubicin Cisplatin	2 cycles	***(number of patients not reached)*** **Overall survival** HR = 0.65 (multiplicity adjusted 99.99% CI 0.19–2.1); $P = 0.07$ **5-year survival** 72.3% vs. 62.4% **Progression-free survival** HR = 0.64, (95% CI 0.37–1.11); $P = 0.054$ **5-year progression free survival** 67.9% vs. 56.4
Advanced Bladder Cancer Metananalysis collaboration (2003)	1344	1344	2688	–	6.2 years	Platinum-based combined chemotherapy	–	**5-year overall survival** HR = 0.87; (95%CI, 0.78–0.98); $P = 0.01$ **Absolute survival** 5% benefit (50% vs. 45%) **Disease-free survival** $P < 0.001$ **Locoregional DFS** $P = 0.012$ **Metastasis-free survival** $P = 0.001$
Advanced Bladder Cancer Metananalysis collaboration (2005)	–	–	3005	–		Platinum-based combined chemotherapy	–	**Overall survival** HR = 0.86, (95%ci, 0.77–0.95), $P = 0.003$ **Disease-free survival** HR = 0.78 (95%ci, 0.71–0.86), $P < 0.0001$

HR hazard ratio; *CI* confidence interval

expression of NrF2, a transcription factor causing resistance to cisplatin in vitro, correlates with worse overall survival in patients who received neoadjuvant chemotherapy. Similarly, the bladder overexpression of Bcl-2, an inhibitor of the apoptotic cascade, has been suggested as a marker to identify the nonresponders to neoadjuvant chemotherapy. The expression of GDPD3 and SPRED1 has also been shown to correlate with outcomes of neoadjuvant chemotherapy (Baras et al. 2015).

In addition, genomic assessment could provide interesting results for patient selection for neoadjuvant chemotherapy. Specifically, in vitro analyses showed that missense mutations of ERCC2 (a nucleotide excision repair gene) from exome sequencing predicted response to neoadjuvant cisplatin-based chemotherapy. Mutations in ERBB2/HER2 are also known to be associated with favorable response to neoadjuvant chemotherapy. More recently aberrations in DNA repair genes ATM, RB1, or FANCC were found to be predictors of pathological response to neoadjuvant chemotherapy and could be associated with an improved overall survival (Plimack et al. 2015).

All these studies taken together support the rationale for molecular analysis of muscle-invasive bladder cancer to identify biomarkers predictive of clinical response to neoadjuvant chemotherapy. However, only heterogeneous and small sample size studies are currently available and as such, none of the aforementioned biomarkers have been validated to date.

Toxicity Associated with the Delivery of Neoadjuvant Chemotherapy

Performing an overall analysis of the toxicity related to the delivery of neoadjuvant chemotherapy is challenging, given that there is a substantial heterogeneity in the regimens analyzed in the randomized controlled trials. Nonetheless, all clinical guidelines worldwide agree that neoadjuvant chemotherapy toxicity is acceptable.

Specifically, in the Southwest Oncology Group study published in 2003, 87% of patients in the neoadjuvant chemotherapy group received at least one cycle of MVAC, which was associated with grade 4 neutropenia in 33% of cases and grade 3 gastrointestinal toxicities in 17% of cases. However, no life-threatening toxicities or deaths from chemotherapy occurred and there was no increased risk of postoperative complications. No detailed information was available on dose reduction or treatment interruption.

In the International Collaboration of Trialists study, almost 80% of patients received all the cycles. However, dose reduction and/or cycle delay occurred in 25% of patients who received neoadjuvant chemotherapy (10% with vinblastine, 20% with methotrexate, and 60% with cisplatin). Only 1% of those patients experienced a fatal event related to the delivery of neoadjuvant (Sternberg et al. 2015).

In a more recent phase 2 trial evaluating accelerated methotrexate, vinblastine, doxorubicin, and cisplatin, no grade 3 or 4 renal toxicities and no toxicity-related deaths were observed. Grade 1 or 2 treatment-related toxicities occurred in 82% of patients (Plimack et al. 2014). In another similar study, grade 3 toxicities were observed in 10% of patients, with no neutropenic fevers or treatment-related death (Choueiri et al. 2014).

Finally, several retrospective studies have reported an increased risk of thromboembolic events with the use of neoadjuvant chemotherapy. For example, a recent multicentric international report on 761 patients showed that thromboembolic events occurred in 14% of them (Duivenvoorden et al. 2016). Such events were more likely to be observed before (58% of cases). Interestingly, older age and greater number of cycles of neoadjuvant chemotherapy were important predictors of experiencing thromboembolic events.

Surgical Outcomes After Neoadjuvant Chemotherapy

Concerns with regard to the tolerance of post-chemotherapy radical cystectomy have been raised by the urological community. Specifically, locoregional or bowel inflammatory as well as the risk of altered general condition after neoadjuvant chemotherapy may impact the outcomes of

radical cystectomy by notably delaying digestive recovery and increase the risk of fistula.

Nonetheless, although results on perioperative outcomes after radical cystectomy in the two largest randomized controlled trials were not comprehensively assessed, the investigators reported no increased risk of postoperative complications with the delivery of neoadjuvant chemotherapy. In addition, several retrospective studies have provided more granular information on perioperative outcomes of radical cystectomy after neoadjuvant chemotherapy. For example, Johnson et al. published in 2014 a study including 878 patients among whom, 12.1% received neoadjuvant chemotherapy. Overall, the rates of complications were 55.1% and 51.8% in patients who received neoadjuvant chemotherapy followed by radical cystectomy and radical cystectomy alone, respectively ($p = 0.58$). In multivariable analysis, neoadjuvant chemotherapy was not an independent predictor of postoperative complications ($p = 0.87$), reintervention ($p = 0.16$), wound infection ($p = 0.32$), or wound dehiscence ($p = 0.32$) (Johnson et al. 2014).

Comparison of Chemotherapy Regimens in the Neoadjuvant Setting

To date, no randomized controlled trial has compared the efficacy of the different neoadjuvant chemotherapy regimens available. Although it is well established that cisplatin is more active than carboplatin for urothelial carcinoma in general, no definitive conclusion can be drawn from the current literature with regard to the best cisplatin-based combination chemotherapy. Nonetheless, the methotrexate, vinblastine, doxorubicin, and cisplatin regimen could represent a better alternative than gemcitabine plus cisplatin, given the better response rate observed in the metastatic setting.

Only retrospective reports are available to assess the comparative effectiveness of cisplatin-based regimens for neoadjuvant chemotherapy. For example, Dash et al. compared the oncological outcomes observed after four cycles of gemcitabine plus cisplatin delivered over 12 weeks vs. four cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (Dash et al. 2008). The proportion of tumor downstaging and minimal or no residual disease at radical cystectomy was similar between the two treatment groups. In addition, there was no obvious difference in prolonged disease-free survival, although the patients who received gemcitabine plus cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin were not directly compared. Accordingly, a recent meta-analysis of all retrospective studies comparing these two regimens (including also individuals who received carboplatin instead of cisplatin in combination with gemcitabine) found no significant difference in pathological complete response (Yin et al. 2016). However, the investigators identified an overall survival benefit with gemcitabine plus cisplatin/carboplatin (HR = 1.26; 95% CI, from 1.01 to 1.57), which was no longer significant after excluding carboplatin patients (HR = 1.31; 95% CI, from 0.99 to 1.74). As such, these results should be interpreted with caution, especially given the biases related to the meta-analyses of retrospective data.

Different methotrexate, vinblastine, doxorubicin, and cisplatin regimens have also been described and compared in several phase 2 studies. For example, Plimack et al. evaluated the oncological outcomes obtained after three cycles of neoadjuvant accelerated vs. standard methotrexate, vinblastine, doxorubicin, and cisplatin regimen. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin were well tolerated and similar pT0 rates were observed between the two treatment groups (Plimack et al. 2014). An additional phase 2 trial of accelerated methotrexate, vinblastine, doxorubicin, and cisplatin with bevacizumab showed 5-year overall and disease-specific survival rates of 63% and 64%, respectively. Interestingly, pT0N0 and $\leq$ pT1N0 downstaging rates were 38% and 53%, respectively. Nonetheless, bevacizumab had no significant impact on survival outcomes. As such, accelerated methotrexate, vinblastine, doxorubicin, and cisplatin may represent the optimal regimen for neoadjuvant chemotherapy. Nonetheless, several ongoing randomized controlled trials such as VESPER (NCT01812369) are currently

comparing different cisplatin-based regimens in the neoadjuvant setting.

Adjuvant Chemotherapy

Rationale for the Use of Adjuvant Chemotherapy

Despite the high rate of pathological downstaging and the well-established survival benefit associated with the delivery of neoadjuvant chemotherapy prior to radical cystectomy (International Collaboration of Trialists et al. 2011), population-based studies have demonstrated that only 1% to 15% of patients with muscle-invasive bladder cancer receive such treatment strategy (David et al. 2007). More recent analyses suggest that this may be increasing (Reardon et al. 2015), but theoretical concerns such as delaying radical cystectomy while inducing unnecessary side effects in cisplatin-resistant patients represent a substantial limitation to the systematic infusion of neoadjuvant chemotherapy. Although multiple biomarkers predicting clinical and/or pathological response to cisplatin-based regimens have shown promising results (Plimack et al. 2015; McConkey et al. 2016), none of them can yet be routinely used to identify chemosensitive individuals with an adequate accuracy. As such, a significant proportion of patients with muscle-invasive bladder cancer remains currently chemotherapy naïve at the time of radical cystectomy; those with adverse postoperative features may be suitable for the delivery of adjuvant chemotherapy.

As opposed to a neoadjuvant strategy, the main advantages of an adjuvant strategy are that radical cystectomy is done immediately and the depth of infiltration of the bladder wall as well as lymph node status can be assessed from the definitive specimen to further guide treatment decision making. Indeed, pT and pN stages are the most established prognostic factors for progression and survival after radical cystectomy. Accordingly, 5-year overall survival is approximately 50% for patients with pT3/T4 and/or pN+ bladder cancer, but it can vary from 32% to 75% between those with and without lymph node involvement, respectively (Yafi et al. 2011).

Interestingly, Logothetis et al. first suggested in the late 1980s that patients with postoperative extravesical and/or pelvic lymph node-positive disease treated with cisplatin-based combination chemotherapy had greater 2-year disease-free survival than a historic control group of patients treated with observation after radical cystectomy (70% vs. 37%; $p < 0.001$) (Logothetis et al. 1988). As a result, multiple landmark randomized controlled trials have further explored the role of adjuvant chemotherapy in this population of high-risk individuals and several meta-analyses have been undertaken with the aim to overcome the associated limitations.

Oncological Outcomes

Meta-analyses of Randomized Controlled Trials

Skinner et al. were the first to report prospective evidence from a randomized controlled trial enrolling patients to receive either adjuvant chemotherapy or observation for advanced bladder cancer after radical cystectomy (Skinner et al. 1991); they were rapidly followed by others investigators. Unfortunately, there have been many methodological issues with the vast majority of these small sample size randomized controlled trials. Thus, the prospective evidence supporting the use of adjuvant chemotherapy is more contentious than that for the use of neoadjuvant chemotherapy. Specifically, in 2006, the investigators of the first meta-analysis relying on individual patient data raised significant concerns with regard to the impact of randomized controlled trials that stopped early and patients not receiving allocated treatments or salvage chemotherapy at the time of relapse (Advanced Bladder Cancer (ABC) Meta-analysis Collaboration 2006). Indeed, the corresponding systematic review of the literature initially identified 11 trials but individual patient data were available for only six of them (Skinner et al. 1991; Studer et al. 1994; Stöckle et al. 1995; Freiha et al. 1996; Mazeron et al. 2016; Otto et al. 2003), notably

because of poor accrual. Although such methodology led to the inclusion of 90% of the total patients randomized in adjuvant cisplatin-based combination trials, only 66% of the total patients randomized in all adjuvant chemotherapy trials were considered in this meta-analysis. In addition, only two of the selected randomized controlled trials completed the planned accrual (Mazeron et al. 2016; Otto et al. 2003) while, in two others, around a quarter of patients randomized to receive adjuvant chemotherapy did not receive it and many received regimens other than those described in the study protocol (Studer et al. 1994; Stöckle et al. 1995). Finally, four included trials did not specify the use of salvage chemotherapy for patients undergoing initial observation whose disease progressed or recurred (Skinner et al. 1991; Stöckle et al. 1995; Freiha et al. 1996), with a likely consequence of exaggerating the treatment estimate in favor of the adjuvant chemotherapy group.

In spite of the aforementioned limitations, this pioneering meta-analysis by the Cochrane collaboration found an overall survival benefit favoring the adjuvant chemotherapy vs. observation group (HR = 0.75; 95% CI, from 0.60 to 0.96; $p = 0.019$), which was more pronounced when only considering patients who received cisplatin-based combination chemotherapy (HR = 0.71; 95%, CI from 0.55 to 0.92; $p = 0.010$). This corresponded to an absolute improvement in 3-year overall survival of 9% (95% CI, from 1% to 16%), which extended to 11% (95% CI, from 3% to 18%) when using exclusively cisplatin-based combination chemotherapy. In addition, the delivery of adjuvant chemotherapy was associated with a disease-free survival benefit (HR = 0.68; 95% CI, from 0.53 to 0.89; $p = 0.004$), which was also more pronounced when only considering patients who received cisplatin-based combination chemotherapy (HR = 0.62; 95% CI, from 0.46 to 0.83; $p = 0.001$). This corresponded to an absolute improvement in 3-year disease-free survival of 12% (95% CI, from 4% to 19%) in the overall study population.

Contemporaneously, another meta-analysis of summary data from all published phase III randomized controlled trials was conducted by Ruggieri et al. (2006). The investigators found similar results than those reported in the Cochrane systematic review. Specifically, the delivery of adjuvant chemotherapy was associated with a 26% and 35% risk reduction in death from any cause (RR = 0.74; 95% CI, from 0.62 to 0.88; $p = 0.001$) and disease recurrence (RR = 0.65; 95% CI, from 0.54 to 0.78; $p < 0.001$), respectively. Logically, the same methodological issues than those previously described for the Cochrane systematic review were advocated to limit the clinical implications of these findings.

Nonetheless, further randomized controlled trials were undertaken and analyzed in an updated systematic review and meta-analysis of summary data published in 2013 (Leow et al. 2014). Leow et al. built on the 2005 Cochrane meta-analysis to include the Italian multicentric study, the Spanish Oncologic Genito-Urinary Group (SOGUG) study, and the US p53 Intergroup study in a more contemporary assessment of the adjuvant chemotherapy efficacy using random-effect and meta-regression models. In addition, the update of the 1994 Stöckle trial (Stöckle et al. 1995) published by Lehmann et al. in 2006 with a 10-year follow-up after radical cystectomy (Lehmann et al. 2006) was considered by the investigators, who found a 23% and 34% risk reduction in death from any cause (HR = 0.77; 95% CI, from 0.59 to 0.99; $p = 0.049$) and disease recurrence (HR = 0.66; 95% CI, from 0.45 to 0.91; $p = 0.014$), respectively. Mirroring the results from the Cochrane meta-analysis (Advanced Bladder Cancer (ABC) Meta-analysis Collaboration 2006), the treatment effect was more pronounced when using cisplatin-based combination chemotherapy rather than a single agent cisplatin regimen for both overall (HR = 0.74; 95% CI, from 0.58 to 0.94) and disease-free survival (HR = 0.62; 95% CI, from 0.45 to 0.87). That said, the specific gemcitabine-cisplatin combination demonstrated no significant efficacy, given that contradictory results were reported in the Italian and Spanish trials for both overall (HR = 1.29; 95% CI, from 0.84 to 1.99 and HR = 0.38; 95% CI, from 0.22 to 0.65, respectively) and disease-specific survival.

Although meta-regressions did not show any impact of gender or nodal status on the treatment effect for overall survival, the HR for disease-free survival associated with adjuvant cisplatin-based chemotherapy in studies with higher nodal involvement was 0.39 (95% CI, from 0.28 to 0.54), compared with an HR of 0.89 (95% CI, from 0.69 to 1.15) in studies with less nodal involvement. This updated meta-analysis remained limited in terms of sample size with only 945 included patients and suffered from the same methodological issues inherent to the inclusion of potentially biased randomized controlled trials. As such, the results from the European Organization for Research and Treatment of Cancer (EORTC) 30994 randomized controlled trial comparing adjuvant vs. deferred chemotherapy were awaited to potentially fill the gap of prospective evidence (Sternberg et al. 2015).

EORTC 30994 Randomized Controlled Trial

The EORTC 30994 is the largest phase III randomized controlled trial comparing adjuvant to deferred chemotherapy ever published (Sternberg et al. 2015). Nonetheless, the investigators were able to enroll only 284 (of the planned 660) patients with pT3/T4 and/or pN+ bladder cancer randomly assigned to receive either adjuvant ($n = 141$) or deferred ($n = 143$) chemotherapy. After a median follow-up of 7 years, 66 (47%) patients died in the adjuvant chemotherapy group, while 82 (57%) died in the deferred chemotherapy group. Although no significant improvement in overall survival was noted with the delivery of adjuvant chemotherapy (HR = 0.78; 95% CI, from 0.56 to 1.08; $p = 0.13$), such approach prolonged progression-free survival as compared to the delivery of chemotherapy at the time of relapse (HR = 0.54; 95% CI, from 0.40 to 0.73; $p < 0.001$). This corresponded to an absolute improvement in 5-year disease-free survival of approximately 16%. When performing post hoc exploratory analyses, Sternberg et al. found a significant interaction for overall survival only with pN stage (pN- vs. pN+; $p_{interaction} = 0.026$), while there was no significant interaction for progression-free survival. Specifically, the treatment effect of adjuvant chemotherapy on overall survival remained significant in patients without lymph node involvement at initial diagnosis (HR = 0.37; 95% CI, from 0.16 to 0.83; $p = 0.012$), while no difference was observed with the deferred chemotherapy group in those with pelvic lymph node-positive bladder cancer (HR = 0.94; 95% CI, from 0.65 to 1.34; $p < 0.72$). Finally, the investigators performed an updated meta-analysis building on the aforementioned Leow's report (Leow et al. 2014) and found an overall survival benefit (HR = 0.77; 95% CI, from 0.65 to 0.91; $p = 0.001$), which was borderline significant when restricting the inclusion to the Italian, Spanish, and EORTC studies (HR = 0.79; 95% CI, from 0.62 to 1.00; $p = 0.05$). Table 2 summarizes the randomized controlled trials and meta-analyses testing the role of adjuvant chemotherapy after radical cystectomy.

Contemporary Retrospective Evidence

Given that all randomized control trials comparing adjuvant chemotherapy vs. observation for advanced bladder cancer, including the EORTC 30994 study, share the common pattern of incomplete accrual with limited treatment protocol adherence, several contemporary retrospective reports have been published with the aim to overcome the underpowered prospective evidence. Unfortunately, other methodological limitations such as selection bias in the treatment allocation could substantially impact the corresponding findings. Nonetheless, a collaborative effort among 11 major centers has yielded an international cohort of 3947 off-trial patients treated with radical cystectomy and grouped into quintiles based on risk characteristics for relapse and death (Svatek et al. 2010). Of these, 932 (23.6%) received adjuvant chemotherapy, which independently correlated with improved cancer-specific survival (HR = 0.83; 95% CI, from 0.72% to 0.97%; $p = 0.017$). Interestingly, risk groups significantly predicted the survival impact of adjuvant chemotherapy; increasing benefit was observed with more aggressive disease. In fact, the cancer-specific survival benefit was only significant in the highest-risk quintile (HR = 0.75;

Table 2 Clinical trials and meta-analyses testing the role of adjuvant chemotherapy after radical cystectomy for pT3/T4 and/or pN+ bladder cancer

Studies	Number of patients			Population study	Median follow-up	Regimen	Duration	Treatment effect on overall survival			Complete accrual
	Treatment	Control	Total					HR/RR	95% CI	*P*-value	
Skinner et al. (1991)	50	52	102	pT3/T4 and/or pN+	14.5 years	Cisplatin Cyclophosphamide Doxorubicin	4×4-weekly cycles	0.75	0.48–1.19	–	No[a]
Studer et al. (1994)	46	45	91	pT1-T4	6.1 years	Cisplatin	2×4-weekly cycles	1.02	0.57–1.84	–	No[b]
Stökle et al. (1995)	26	23	49	pT3b/T4a	14.8 years	Cisplatin Methotrexate Vinblastine Doxorubicin	3 cycles	–	–	0.006	No[a]
Freiha et al. (1996)	27	28	55	pT3b/T4 and/or pN+	5.1 years	Cisplatin Methotrexate Vinblastine	4×3-weekly cycles	0.74	0.36–1.53	–	No[a]
Bono et al. (1997)	46	47	93	pT2-T4aN0	3.5 years	Cisplatin Methotrexate	4 cycles	0.65	0.34–1.25	–	Yes
Otto et al. (2003)	55	53	108	pT3N1/N2	3.6 years	Cisplatin Methotrexate Vinblastine Epirubicin	3×4-weekly cycles	0.82	0.48–1.38	–	Yes
Meta-analysis by Cochrane (2006)	246	245	491	–	5.2 years	–	–	0.75	0.60–0.96	0.019	–
Meta-analysis by Ruggieri et al. (2006)	167	183	350	–	–	–	–	0.74	0.62–0.88	0.001	–
Lehmann et al. (2006)	26	23	49	pT3/T4 and/or pN+	13.3 years	Cisplatin Methotrexate Vinblastine Doxorubicin	3 cycles	0.57	0.31–1.05	0.069	No[a]
Paz-Ares et al. (2010)	68	74	142	pT3/T4 and/or pN+	2.5 years	Paclitaxel Gemcitabine Cisplatin	4×21-day cycles	0.38	0.22–0.65	–	No

(*continued*)

Table 2 (continued)

Studies	Number of patients			Population study	Median follow-up	Regimen	Duration	Treatment effect on overall survival			Complete accrual
	Treatment	Control	Total					HR/RR	95% CI	*P*-value	
Stadler et al. (2011)	58	56	114	pT1/T2 N0	5.4 years	Methotrexate Vinblastine Doxorubicin Cisplatin	3 cycles	1.11	0.45–2.72	–	Yes
Cognetti et al. (2012)	102	92	194	pT2-T4 and/or pN1/N2	2.9 years	Gemcitabine Cisplatin	4×28-day cycles	1.29	0.84–1.99	0.24	No
Meta-analysis by Leow et al. (2014)	478	470	948	–	–	–	–	0.77	0.59–0.99	0.049	–
Sternberg et al. (2015)	141	143	284	pT3/T4 and/or pN+	7.0 years	Gemcitabine Cisplatin or Methotrexate Vinblastine Doxorubicin Cisplatin	4 cycles	0.78	0.56–1.08	0.13	No
Meta-analysis by Sternberg et al. (2015)	619	613	1284	–	–	–	–	0.77	0.65–0.91	0.002	–

HR hazard ratio; *RR* risk ratio; *CI* confidence interval

[a]Stopped early because interim analysis favored adjuvant chemotherapy

[b]Stopped early because interim analysis favored control group

95% CI, from 0.62 to 0.90; $p = 0.002$), which was characterized by the inclusion of approximately 90% of patients having both pT3/T4 and pN+ bladder cancer with an estimated 32.8% probability of cancer-specific survival at 5-year follow-up.

More recently, Galsky et al. reported a retrospective analysis of 5653 patients from the National Cancer Data Base who underwent radical cystectomy for pT3/T4 and/or pN+ bladder cancer (Galsky et al. 2016). This represents the largest series published to date, as almost 1300 participants received adjuvant chemotherapy. Analyses stratified by propensity score quintile showed that the delivery of adjuvant chemotherapy was associated with an overall survival benefit. Specifically, after adjusting for the baseline patient-, facility-, and disease-level characteristics, individuals who received adjuvant chemotherapy were 30% less likely to die following radical cystectomy as compared to their counterparts who received observation (HR = 0.70; 95% CI, from 0.64 to 0.76). This corresponded to an absolute increase in 5-year overall survival of approximately 8%. Exploratory analyses revealed that the benefit of adjuvant chemotherapy was significant in all subgroups considered such as pN0, pN+, or pNx patients, without any heterogeneity in treatment effect.

In addition, other sophisticated statistical approaches have been used to compare patients who received adjuvant chemotherapy vs. observation. For example, Vetterlein et al. performed a propensity-score weighted analysis with competing risk analysis showing that adjuvant chemotherapy vs. observation was associated with a decreased risk of cancer-specific mortality (subhazard ratio = 0.51, 95% CI, from 0.26 to 0.98; $p = 0.044$) without any increased risk of other-cause mortality (subhazard ratio = 0.48, 95% CI, from 0.14 to 1.60; $p = 0.233$).

It is noteworthy that retrospective evidence also identified that individuals benefiting the most from adjuvant chemotherapy may be those who have a low lymph node density and can receive at least four cycles of treatment. In addition, the lymph node dissection at the time of radical cystectomy has been reported to represent an important component of advanced bladder cancer management, which could certainly help with regard to indications for adjuvant chemotherapy.

Toxicity Associated with the Delivery of Adjuvant Chemotherapy

Overall, the toxicity of adjuvant chemotherapy was acceptable in the most contemporary randomized controlled trials. For example, Sternberg et al. reported hematological, renal, and hepatic toxicities consistent with those expected with cisplatin-based combination chemotherapy (Sternberg et al. 2015). In this study, gemcitabine plus cisplatin was the predominant regimen. Grade 3/4 myelosuppression occurred in 33 (26%) patients who received adjuvant chemotherapy vs. 24 (35%) patients who received deferred chemotherapy, respectively; neutropenia occurred in 49 (38%) vs. 36 (53%) patients, respectively; and thrombocytopenia in 36 (28%) vs. 26 (38%). In addition, only two patients died due to toxicity, one in each group.

Similar toxicity profiles of adjuvant gemcitabine plus cisplatin combination were reported in the Italian study, as both hematological and nonhematological toxicities were limited with a low incidence of grade 3/4 side effects (Cognetti et al. 2012). However, despite the quite acceptable incidence and severity of chemoinduced toxic effects, this randomized controlled trial found that the compliance of patients to chemotherapy after radical cystectomy was poor. Only 62% of patients could complete adjuvant chemotherapy as planned, and more than half of the patients required a dose reduction. These data suggest that the compliance to chemotherapy after radical cystectomy could decrease rapidly with a lower tolerance to drugs. The low compliance to adjuvant chemotherapy has been reported and could partly explain the negative results of most published randomized controlled trials. Nonetheless, the most recent data from the EORTC 30994 showed that only 14 (11%) of the 128 patients who received adjuvant chemotherapy stopped treatment because of toxicity, although 76 (59%) had at least one cycle of treatment postponed for a

maximum of 2 weeks because of adverse events (Sternberg et al. 2015).

In addition, Fléchon et al. confirmed the low toxicity profile of the gemcitabine plus cisplatin regimen in the adjuvant setting (Fléchon et al. 2006). In this prospective feasibility study, more than 70% of the patients were able to receive four cycles of adjuvant chemotherapy. The relative dose intensity of gemcitabine and cisplatin was 88% and 96%, respectively. The incidence of febrile neutropenia was moderate (10%), while 23.4% and 73.4% had grade 3/4 thrombopenia and neutropenia, respectively.

Comparison of Chemotherapy Regimens in the Adjuvant Setting

In general, the gemcitabine plus cisplatin regimen is preferentially used over the methotrexate, vinblastine, doxorubicine, and cisplatin combination for adjuvant chemotherapy. This is based on the randomized controlled trial by von der Maase showing no overall survival superiority of one regimen over the other for the treatment of advanced or metastatic bladder cancer, with a lower toxicity with gemcitabine plus cisplatin (von der Maase et al. 2000). Nonetheless, there is currently no prospective evidence comparing these regimens in the adjuvant setting. Only retrospective studies suggesting no significant difference in terms of recurrence and survival are available. As such, although carboplatin clearly represents a suboptimal systemic treatment for advanced urothelial disease in general, there is insufficient evidence to determine the optimal cisplatin-based chemotherapeutic regimen. Nonetheless, in the same manner than for neoadjuvant chemotherapy, several ongoing randomized controlled trials such as VESPER (NCT01812369) may provide additional guidance in the upcoming years.

Neoadjuvant Versus Adjuvant Chemotherapy

Although perioperative chemotherapy for bladder cancer treated with radical cystectomy is effective, the best treatment sequence (neoadjuvant or adjuvant) is yet to be determined, as there is limited comparative evidence. In fact, only a single randomized control trial has indirectly compared neoadjuvant to adjuvant chemotherapy (Millikan et al. 2001). In this study, planned treatment was five cycles of perioperative (methotrexate, vinblastine, doxorubicine, and cisplatin) plus radical cystectomy with pelvic lymph node dissection. Patients were randomly assigned to receive either two courses of neoadjuvant chemotherapy followed by surgery plus three additional cycles of chemotherapy or, alternatively, to undergo initial radical cystectomy followed by five cycles of adjuvant chemotherapy. After a median follow-up of almost 7 years, there was no significant difference in progression-free, cancer-specific, and overall survival between the two treatment groups. As such, the investigators concluded that the combination of multiagent chemotherapy and surgery can improve survival, without any preferred sequence.

In addition, an observational study recently compared patients who received neoadjuvant vs. adjuvant chemotherapy for muscle-invasive bladder cancer (Wosnitzer et al. 2012). Similarly, no difference was found in overall (HR = 1.08; 95% CI, from 0.67 to 1.73; $p = 0.76$) and disease-specific (HR = 1.24; 95% CI, from 0.70 to 2.18; $p = 0.46$) survival between neoadjuvant and adjuvant chemotherapy. However, the clinicopathological characteristics of included patients who received neoadjuvant and adjuvant chemotherapy were highly different with greater proportions of pN+ patients in the adjuvant group for example.

As such, the comparative effectiveness of neoadjuvant and adjuvant chemotherapy strategies remains mostly inconclusive in the current literature. Only a well-designed randomized controlled trial could adequately determine the most efficient approach. Nonetheless, the therapeutic landscape of advanced or metastatic muscle-invasive bladder cancer could dramatically change in a near future, given the recent advent of immune check-point inhibitors for metastatic disease, that may also find indications in the neoadjuvant or adjuvant setting.

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Metastatic Bladder Cancer Disease and Its Treatment

26

Anja Lorch and Günter Niegisch

Contents

Abstract

Approximately one third of patients present with muscle-invasive bladder cancer with 50% developing progression after radical cystectomy and up to 15% having metastatic disease upfront. Several independent clinical prognostic factors for first- and for second-line chemotherapy have been identified to predict survival. Since 1980 standard first-line treatment contains a platinum-based combination chemotherapy. In the second-line setting, no clearly established regimen with substantial prolonged survival existed for a long period of time. Quite recently, based on compelling phase II and phase III data with simultaneously favorable safety profiles, several checkpoint inhibitors (PD-1/ PD-L1) have been FDA and EMA approved not only for patients progressing after first-line chemotherapy but also for upfront therapy in platinum-unfit patients.

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Introduction

At the time of diagnosis, approximately one third of the patients present with muscle-invasive bladder cancer with 50% developing progression after radical cystectomy and up to 15% having metastatic disease upfront. Since 1980 standard first-line treatment contains platinum-based combination chemotherapy. For patients progressing after first-line treatment, no clearly established second-line regimen exists showing substantial prolonged survival. Several independent clinical prognostic factors for first- and for second-line chemotherapy have been identified to predict survival, but irrespective of these factors and the chosen regimen, outcome remains poor, and chemotherapy is only a palliative treatment option. Even with better understanding the biology of urothelial bladder cancer in the past, new developed targeted therapies failed to improve survival. Recently there appears to be hope with the use of immunotherapy. Promising results with significantly improved response rates using blocking antibodies targeting immune checkpoints (PD-1/PD-L1 blockade) were observed. Based on compelling phase II data with a simultaneously favorable safety profile, the PD-L1 antibody atezolizumab was the first FDA-approved drug for second-line therapy after platinum-containing chemotherapy in 2016.

This chapter will discuss current standards in chemotherapeutic treatment and new developments for urothelial bladder cancer in the first-line and subsequent setting. Furthermore, it should give the reader reasonable treatment choices for daily clinical practice.

Clinical Prognostic Factors

There are well-known clinical prognostic factors that are able to predict survival, both for chemotherapy-naïve patients and for patients refractory to or progressing after platinum-based upfront therapy.

Karnofsky performance status (KPS) of less than 80% and the presence of visceral metastatic sites represent independent factors of poor survival for patients treated with first-line cisplatin-based chemotherapy. A model of three groups, based on the presence or absence of these risk factors, was established in 1999. Both risk factors have been confirmed by others (von der Maase et al. 2005; Bellmunt et al. 2002). Patients with no risk factors appeared to have a median survival time of 33.0 months compared with 13.4 months for patients with one risk factor and 9.3 months for patients with two risk factors after 5 years (Bajorin et al. 1999).

In refractory patients or patients progressing after first-line treatment, three independent adverse prognostic factors could be identified such as hemoglobin less than 10 g/dl, ECOG performance status >0, and the presence or absence of liver metastases. According to these factors, four prognostic groups (risk 0, 1, 2, 3) have been established with median OS times for these groups of 14.2, 7.3, 3.8, and 1.7 months, respectively (Bellmunt et al. 2002; Niegisch et al. 2011). These risk factors could be confirmed as well by other groups (Shariat et al. 2013).

The knowledge of prognostic factors provide useful information for physicians and patients when considering prognosis and stratification for trial designs or comparing results of different trials (Figs. 1 and 2).

First-Line Treatment

Cisplatin-Combination Chemotherapy

Since over 30 years, standard first-line treatment in metastatic urothelial bladder cancer is a cisplatin-containing combination chemotherapy. The overall survival of patients increased from 8 to 9 months with single cisplatin up to 12–16 months with a combination regimen. In a phase III intergroup trial, 246 patients (pts) had been randomized, 120 pts to M-VAC and 126 to cisplatin alone. After a median follow-up of

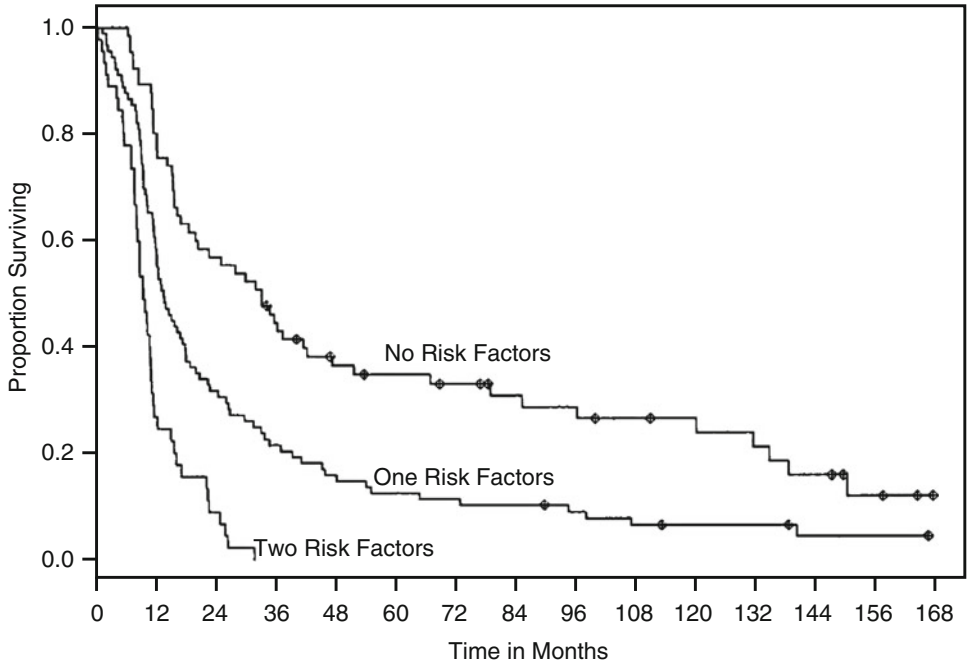

Fig. 1 Survival according risk factors first-line (Bajorin et al. 1999)

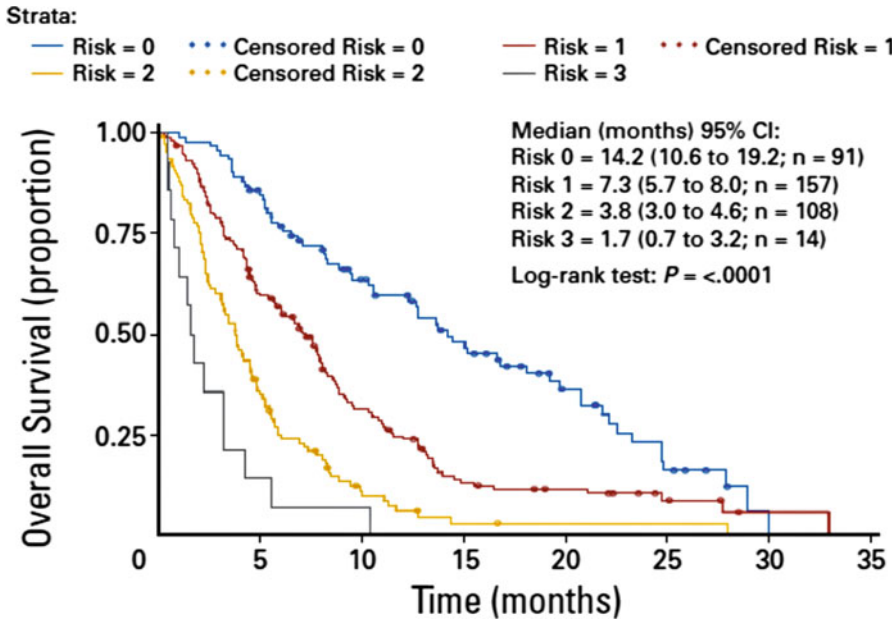

Fig. 2 Survival according risk factors second-line (Bellmunt et al. 2002)

nearly 20 months, a significantly prolonged survival of 12.5 months was observed with the combination of methotrexate, vinblastine, adriamycin, and cisplatin (M-VAC) compared to 8.2 months with cisplatin alone. Response rates in the M-VAC arm were 39% compared to single cisplatin with only 12%. As expected, grade 3 and 4 toxicity was higher in the combination arm. However, since these results M-VAC represented the new standard of care (Loehrer Sr et al. 1992). As a lot of patients with advanced or metastatic bladder cancer are old and often have severe comorbidities, the high toxicity profile of M-VAC led to the investigation of several other cisplatin-containing regimens. In a multicenter phase III randomized trial, the combination of gemcitabine and cisplatin (GC) was assessed against M-VAC. Overall, 405 patients had been randomized with 203 pts to GC and 202 pts to M-VAC. A total of six cycles every 4 weeks was administered in both arms. Response rates with 46% and 49% and median survival with 13.8 months for the GC arm compared to 14.8 months in the M-VAC arm were similar. Long-term survival results have confirmed the equivalence of these two regimens in terms of the response rate and survival. However, the toxicity profile was better for the GC combination with less hematologic toxicity, decreased infectious complications, and less mucositis. With comparable results in OS and the favorable toxicity profile, the GC regimen was recommended to be the new standard since then (von der Maase et al. 2000). To further decrease toxicity and simultaneously increase efficacy, dose-dense regimens have been tested. Within an EORTC prospective phase III trial, a dose-dense M-VAC (HD-M-VAC) in combination with G-CSF, given every 2 weeks, was evaluated against M-VAC, given every 4 weeks. A total number of 263 patients had been enrolled. As a result better response rates, a better 2-year progression-free survival (PFS), and less toxicity compared to M-VAC were achieved for HD-M-VAC. Though, there was no significant difference in median overall survival between the two regimens (Sternberg et al. 2001a).

Further attempts to increase efficacy by adding a third drug were performed but did not result in better survival outcome for these patients with often creating more toxicity. In a large randomized phase III trial, the addition of paclitaxel to cisplatin and gemcitabine (PCG) versus GC alone was evaluated. As a result, the response rate was significantly higher with the triple regimen (56% for PCG vs. 44% for GC), but merely a trend for prolonged OS improvement in the PCG population (15.8 vs.12.7 months) was observed (Bellmunt et al. 2012). Though adding paclitaxel to GC did not induce more severe side effects, it is recommended to use either M-VAC, HD M-VAC, or GC combination in the first-line setting for cisplatin-fit patients and avoid triple regimens (Table 1).

Table 1 Chemotherapy regimens first-line

M-VAC	Methotrexate	30 mg/m^2 day 1, 15, 22	Repeat day 29
	Vinblastine	3 mg/m^2 day 2, 15, 22	
	Doxorubicin	30 mg/m^2 day 2	
	Cisplatin	70 mg/m^2 day 2	
GC	Gemcitabine	1000 mg/m^2 day 1, 8, 15	Repeat day 29
	Cisplatin	70 mg/m^2 day 2	
Gem/Carbo	Gemcitabine	1000 mg/m^2 day 1, 8	Repeat day 22
	Carboplatin	AUC 4/5 day 1	
HD-M-VAC	Methotrexate	30 mg/m^2 day 1	Repeat day 15
	Vinblastine	3 mg/m^2 day 2	
	Doxorubicin	30 mg/m^2 day 2	
	Cisplatin	70 mg/m^2 day 2	
	G-CSF		

Definition "Fit" for Cisplatin

In all potential candidates for cisplatin-containing chemotherapy, renal function should be evaluated. In case of impaired renal function, all reversible causes should be identified and optimized before the application of chemotherapy. Patients can be divided into two groups of medically "fit" and "unfit" for cisplatin chemotherapy based on additional factors that potentially will increase the risks of toxicity. These criteria with at least one factor present have been published by a consensus working group in 2011 and are as follows: ECOG performance status of 2 or greater or Karnofsky performance status (KPS) of 60–70% or less, creatinine clearance less than 60 ml/min, hearing loss of 25 dB, grade 2 or greater peripheral neuropathy, and New York Heart Association (NYHA) class III or greater heart failure (Galsky et al. 2011). However, the presence of one of these criteria does not necessarily always exclude a patient from receiving ciplatinum-based combination therapy. Recent evidence suggests that also in patients with a creatinine clearance of 45–60 ml/min, cisplatin can safely be administered by according dose and schedule modifications (e.g., split-dose) (Hussain et al. 2012; Hussain et al. 2004).

Carboplatin-Combination Chemotherapy

Unfortunately, up to 50% of the generally elderly patient population is not fit enough to receive cisplatin-containing regimens due to the abovementioned severe comorbidities (Dash et al. 2006; Balducci and Yates 2000). For these patients carboplatin is a reasonable alternative even knowing that the efficacy of carboplatin is not equivalent. In randomized phase II trials comparing carboplatin with cisplatin chemotherapy, a lower response rate and a shorter OS for the carboplatin arm were demonstrated (Dogliotti et al. 2007; Dreicer et al. 2004). Moreover several trials with carboplatin-containing combinations focusing on patients with impaired renal function and/or a low performance status have been tested. In phase II trials, the combinations with, e.g., paclitaxel or gemcitabine were evaluated with comparable results concerning objective response rates in all trials. In an EORTC phase II/III trial, a combination of carboplatin and gemcitabine was assessed to carboplatin, methotrexate, and vinblastine (M-CAVI). Altogether 187 patients have been enrolled. Similar results regarding OS with 9.3 months for the doublet and 8.1 months for the triplet were observed with a significantly lower toxicity rate in the carboplatin/gemcitabine arm (13.6% versus 23%) (De Santis et al. 2012). Recent phase III data have confirmed these results. In these patients toxicity was managed by dose adjustment according to the patient's renal function. Of note is the greater risk of myelosuppression when using carboplatin. Carboplatin in combination with gemcitabine is considered standard of care in patients with renal impairment and or low performance status due to study results.

Non-platinum Combination Chemotherapy

Different combinations of gemcitabine and paclitaxel or docetaxel have been assessed as first- and second-line treatments. This combination is well tolerated. All the performed trials show large variations in response rates with numbers between 33% and 60%. Outcome and the results are difficult to interpret due to different doses and schedules used and a heterogeneous patient population included in the trials. In addition, non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomized trials. Therefore it should not be recommended for first-line use in cisplatin-fit patients (Sternberg et al. 2001b; Calabro et al. 2009; Fechner et al. 2006).

Combinations with Targeted Therapies

As overexpression of the epidermal growth factor receptor (EGFR) and overexpression of HER2 is very common in metastatic bladder cancer, several

trials have addressed the blockade of EGFR or HER2. In a phase II trial with gefitinib, a tyrosine-kinase inhibitor of EGFR in combination with cisplatin-based chemotherapy was conducted with a response rate of 43% and a median OS of 15 months (Philips et al. 2009). In a phase II trial, the combination of a carboplatin-based chemotherapy with trastuzumab, an anti-HER2 antibody, showed a response rate of 70% and a median OS of 15.8 months (Hussain et al. 2007). All trials failed to be superior over the chemotherapy combinations only. In another phase II trial, including 43 patients, the combination of the standard regimen cisplatin and gemcitabine with the vascular endothelial growth factor (VEGF) antibody bevacizumab was evaluated, showing significantly improved and encouraging results for response rate with 72% for all patients, a PFS of 8.2 months, and an OS of 19.1 months with a median follow-up of 27.2 months. Unfortunately the addition of bevacizumab resulted in significantly increased toxicity with a high rate of thromboembolic events (Hahn et al. 2011).

Second-Line Treatment

Chemotherapy

To date there is no Food and Drug Administration (FDA)-approved agent in the United States, whereas in Europe the third-generation vinca alkaloid vinflunine has been approved since 2009. This approval was based on a phase III randomized trial comparing vinflunine to best supportive care in patients progressing or relapsing after first-line cisplatin-containing chemotherapy. In this trial OS for patients treated with vinflunine was statistically significantly higher than with best supportive care (6.9 months versus 4.3 months) (Bellmunt et al. 2009). Similar OS results have also been observed with a combination of taxanes and gemcitabine which is considered as a reasonable alternative (Sternberg et al. 2001b; Albers et al. 2011; Sonpavde et al. 2016).

For most of the second-line treatment regimens, the majority of results arise from single-arm and some combination trials, often including a small sample size of patients and mostly designed as phase II trials. Limited efficacy for gemcitabine and taxanes (paclitaxel, docetaxel) as single drug or as part of a combination therapy was observed with showing better response rates and better PFS for the combination regimens compared to single-agent therapy but with no difference in OS between single and doublet regimens. Another chemotherapy agent that has been tested was pemetrexed, a multitargeted antifolate with an objective response rate of 28% and a median overall survival of 10 months in a phase II trial with 47 patients included. The toxicity profile was favorable (Sweeney et al. 2006). Unfortunately these results could not be confirmed. In other phase II trials, a response rate of only 8% was observed, and in one retrospective analysis of 123 patients, the response rate was only 5% with the use of pemetrexed (Galsky et al. 2007; Bambury et al. 2015). Nab-paclitaxel, the albumin-bound paclitaxel (nab-paclitaxel) with favorable tolerability, was demonstrating an objective response rate of almost 28% in a phase II trial (Ko et al. 2013). Although the prognosis and the efficacy of second-line therapies remain poor and the optimal treatment regimen is still not established, some patients may benefit of the described regimens. However, patients progressing after first-line therapy should be considered for clinical trials incorporating molecular analysis to identify genetic and epigenetic alterations. These molecular abnormalities are currently studied as potential prognostic and/or predictive markers, with the goal to help select treatment and to predict outcome. Though, none of these factors have been validated so far.

Immunotherapy

A lot of studies have been conducted in the past years to increase efficacy and to find new and active agents but have not been successful so far. Recently research into immunomodulatory therapies using checkpoint inhibition, particularly with antibodies directed against the programmed cell death-1 (PD-1) protein or its ligand (PD-L1), has offered new hope for patients with metastatic urothelial bladder cancer. With atezolizumab, the first PD-L1 inhibitor was approved by the US Food and Drug

Administration (FDA) in May 2016 for the treatment of advanced urothelial carcinoma that has progressed during or after previous platinum-based chemotherapy, either for upfront metastatic disease or for progressive disease less than 12 months after adjuvant or neoadjuvant cisplatin-based chemotherapy. Promising results had been firstly reported in a phase I study focusing on safety and treatment response of atezolizumab according to the expression level of PD-L1 on cancer and infiltrating immune cells (Powles et al. 2014). The results had been confirmed in a phase II two-cohort study including 310 evaluable patients with metastatic disease that had progressed during or after prior cisplatin-contained chemotherapy. For all 310 evaluable patients, the objective response rate was 15% independent of the expression of PD-L1. With a median follow-up of 11.7 months, PFS was 2.1 months for all patients, and OS was 7.9 months for the whole group. According to the expression level of PD-L1, the numbers for response rate, PFS, and OS were greater for patients with high expression than for those with low expression of PD-L1, but responses were seen also in patients with no expression of PD-L1. Toxicity profile of atezolizumab was favorable with no treatment-related deaths (Rosenberg et al. 2016). The results of the phase III trial (NCT02302807) comparing atezolizumab with second-line chemotherapy are still pending. Other checkpoint inhibitors have been assessed in phase II and III trials with also demonstrating activity, like the PD-1 inhibitors pembrolizumab and nivolumab and the PD-L1-inhibitor durvalumab (Sharma et al. 2016; Massard et al. 2016). Based on these data, pembrolizumab and nivolumab have now been approved in the United States and in Europe for second-line treatment in patients progressing after platinum-containing first-line chemotherapy.

Role of Post-chemotherapy Surgery in Metastatic Urothelial Bladder Cancer

The role of surgery after chemotherapy is still of debate. For patients with upfront limited metastatic disease having only lymph nodes involved, a good performance status, and only minor residual tumor left after chemotherapy, surgery can be evaluated for individual patients. This recommendation is based on low level of evidence and relies mainly on a retrospective analysis of 203 patients treated with M-VAC. Fifty patients were undergoing surgery of residual tumor after completion of chemotherapy. In 17 patients no viable tumor was found anymore. In another 30 patients, the residual tumor could be resected completely, and after 5 years 10 out of these 30 patients were still alive (Dodd et al. 1999).

Summary

Outcome remains poor for patients with metastatic urothelial bladder cancer despite the use of chemotherapy. For patients with a good performance status, an adequate renal function, and no severe comorbidities, standard of care for first-line still is a cisplatin-based combination chemotherapy. For cisplatin-unfit patients, carboplatin-based regimens or a non-platinum-containing chemotherapy or immunotherapy can be evaluated. For those patients who will relapse after first-line treatment, single-agent chemotherapy or combination chemotherapies or best supportive care may be reasonable options. However, as checkpoint inhibition has shown very good clinical activity in several phase II and III studies, it has become the new standard of care for second-line therapy. Whenever possible, enrolment in clinical trials is strongly recommended.

Conflicts of Interest Anja Lorch: advisory role: BMS, Novartis, Ipsen, AstraZeneca
Günter Niegisch: travel expenses: Roche Pharma AG, Pfizer Pharma AG; advisory role: Roche Pharma AG, BMS Health; reserach grant: 4SC AG

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Rare Subentities of Urothelial Bladder Carcinoma

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Bastian Keck and Simone Bertz

Contents

Abstract

Urothelial carcinomas harbor a propensity to divergent histologic differentiation with different clinical behavior and prognosis of the different histologic subtypes. The WHO classification therefore described a variety of distinct histologic variants of infiltrating urothelial carcinomas in 2016. Plasmacytoid urothelial carcinoma is characterized by a single-cell growth pattern that might be caused by loss of cell adhesion due to the lack of E-cadherin. Its clinical course is very aggressive with a high proportion of locally advanced disease and peritoneal spread. Micropapillary carcinomas respond poorly to intravesical BCG and progress rapidly to muscle invasive and metastatic disease, so that radical cystectomy with urinary diversion is regarded as the therapy of choice in this subtype. Nested-type and large nested urothelial carcinomas present tumor cells whose nuclei show only little or no atypia and are arranged in small nests. Treatment options do not differ from conventional urothelial carcinomas. Microcystic urothelial carcinoma shows round to oval microcysts and is a very rare and aggressive variant with hardly no survival of the cases described so far. Giant cell urothelial

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carcinoma is an extreme form of dedifferentiation with a bizarre and anaplastic appearance and frequent typical or atypical mitotic figures. Sarcomatoid urothelial carcinoma is characterized by spindle cells and has a very bad prognosis; however, it accounts only for a few cases. Lymphoepithelioma-like urothelial carcinoma which harbors a distinct lymphoid infiltrate including T and B lymphocytes, plasma cells, and differential diagnosis to exclude lymphoproliferative diseases is therefore very important in the clinical management.

Introduction

Since the WHO classification 2004, which described several histologic variants of urothelial carcinomas, increasing interest has been developed describing their distinct histologic and molecular features and impact on clinical decision-making or prognosis. Beside urothelial carcinomas with divergent histologic differentiation, i.e., glandular or squamous differentiation, different histologic variants like micropapillary, nested-type, or plasmacytoid urothelial carcinomas harbor distinct molecular and clinical features. These molecular and clinical features might offer the patients the opportunity to individualize therapies in the future.

In the following chapter, the most relevant histologic variants of urothelial carcinoma, their histopathologic and molecular features, as well as their clinical behavior are displayed in a comprehensive manner.

Classification of Urothelial Carcinomas

Urothelial carcinomas represent about 90% of bladder cancer, whereas other types like squamous cell neoplasms or adenocarcinomas and others like urachal carcinoma or neuroendocrine tumors are much less common. Urothelial carcinomas are classified in non-infiltrating and infiltrating urothelial carcinomas. Whereas infiltrating tumors are characterized by a propensity to divergent differentiation, noninvasive tumors account for the majority of urothelial bladder neoplasms and are further separated in flat and papillary lesions. Further their risk of recurrence or progression is determined by several clinical and histopathologic factors like growth pattern, grade, size, multifocality, or time to recurrence. These factors have been incorporated in all clinical guidelines to classify these tumors in low-, intermediate-, or high-risk tumors by the EORTC risk calculator (Sylvester et al. 2006).

Regarding infiltrating urothelial carcinomas, their ability to present divergent histologic differentiation led to the definition of histologic variants according to the fourth WHO classification of 2016 (Moch et al. 2016).

An overview of these variants is given in Table 1.

Since the description of these variants, an increasing interest in their pathologic, molecular, and clinical behavior has been evolved. In the following a summary of their features are displayed in a comprehensive manner.

Plasmacytoid Urothelial Carcinoma (PUC)

PUC is a highly aneuploidy tumor that is characterized by small- to medium-sized tumor cells with eosinophilic cytoplasm that harbor round-to-oval hyperchromatic and eccentrically located nuclei, which may be accompanied by nucleoli. Typically the tumor cells of PUC present a

Table 1 Histologic variants of infiltrating urothelial carcinoma according to the fourth WHO classification of 2016 (Moch et al. 2016)

Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid/signet-ring cell/diffuse
Sarcomatoid
Giant cell
Poorly differentiated
Lipid-rich
Clear cell

discohesive growth pattern, often arranged in an Indian-file pattern or small nests (Fig. 1) (Keck et al. 2011; Lopez-Beltran et al. 2009a). Loss of membranous E-cadherin expression and its nuclear accumulation is described as a specific molecular feature of PUC that is seen in up to 76.2% and 46.5% of the cases, respectively (Keck et al. 2013a). The characteristic single-cell growth pattern might be caused by loss of cell adhesion due to the lack of E-cadherin like it is observed in lobular breast cancer and the diffuse type of gastric cancer (Keck et al. 2011). Beside the loss of membranous E-cadherin, its nuclear accumulation is associated with plasmacytoid differentiation in bladder cancer and serves as a prognostic factor (Keck et al. 2013a). Moreover PUCs usually are positive for different cytokines like PAN-CK, CK7, CK20 or 34ßE12, p63, GATA 3, or uroplakins II and III (Keck et al. 2011; Lopez-Beltran et al. 2009a; Li et al. 2014). Their morphologic similarity to lymphoid carcinomas makes differential diagnosis essential. Usually immunohistochemistry for lymphoid markers like MUM-1 are negative, but PUCs are usually positive for CD138, so that this marker is not suitable for differential diagnosis (Keck et al. 2011; Goto 2016). The vast majority of PUCs presents in advanced clinical stage including local and distant metastases (Cockerill et al. 2016). Peritoneal spread is an often-observed phenomenon, and a high risk for positive surgical margins is described (Ricardo-Gonzalez et al. 2012). Due to these clinical features at presentation and despite systemic cisplatin-based chemotherapy, survival seems to be very limited; however, some single cases of complete response have been reported; adjuvant or neoadjuvant chemotherapy should be advised due to the high risk of recurrence and metastatic disease (Dayyani et al. 2013; Keck et al. 2013b).

Micropapillary Carcinoma

Micropapillary carcinomas of the bladder usually present with medium-sized tumor cells and abundant eosinophil cytoplasm and peripherally located nuclei that often show mitoses and sometimes nuclear pleomorphism (Comperat et al. 2010). The tumor cells often arrange in small nests that gather in lacunae (Fig. 2). Superficial parts of micropapillary carcinomas show slender filiforme processes without fibrovascular cores. Lymphovascular invasion is also a common feature of MPC, and the tumors usually are high-grade tumors. In order to do not overdiagnose LVI, it is important to be aware that the lacunae of MPC may mimic lymphovascular invasion. Micropapillary tumors are described to respond poorly to intravesical instillations with BCG, so that radical cystectomy with urinary diversion is the therapy of choice in muscle-invasive and the

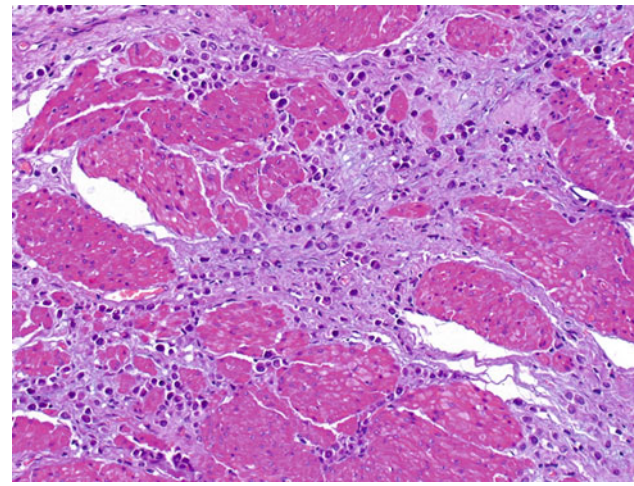

Fig. 1 Histologic specimen of a plasmacytoid urothelial carcinoma of the bladder stained with hematoxylin and eosin (200×)

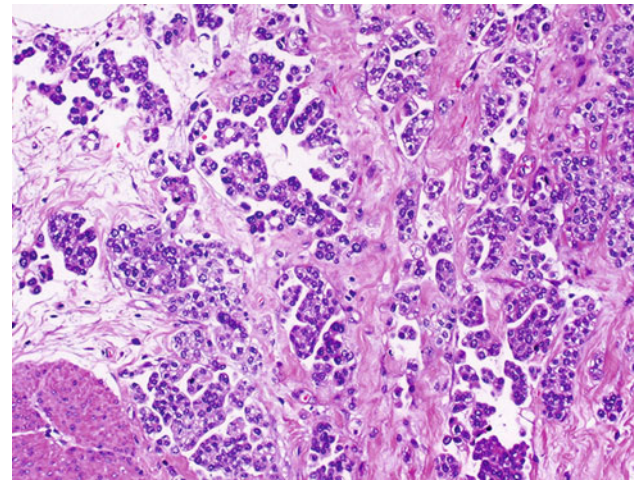

Fig. 2 Histologic specimen of a micropapillary carcinoma of the bladder stained with hematoxylin and eosin (200×)

majority of nonmuscle-invasive tumors, because of their ability of fast progression (Kamat et al. 2007). As an alternative to BCG and radical cystectomy, combined radiochemotherapy has evolved as an established organ-sparing therapy approach in MIBC with considerable long-term outcomes in well-selected patients (Krause et al. 2011; James et al. 2012; Ploussard et al. 2014). However first data shows that urothelial carcinoma with extensive micropapillary morphology (>30%) seem to indicate a patient population with poor prognosis after combined TURBT and radiochemotherapy (Bertz et al. 2016). Like in other histologic variants, clinical outcomes of micropapillary urothelial carcinoma treated with radical cystectomy and adjuvant or neoadjuvant chemotherapy are limited; however, a comparative study showed that cisplatin-based adjuvant chemotherapy seems to be similarly effective if compared to conventional UC regarding overall survival (Keck et al. 2013b). Nevertheless micropapillary carcinoma was associated with higher recurrence rates after radical cystectomy and platinum-based adjuvant chemotherapy than that with pure urothelial tumors, but no association between micropapillary carcinoma and cancer-specific mortality is described in this setting (Masson-Lecomte et al. 2015). Regarding specific molecular alterations, activating mutations and amplifications of Her2 are associated with micropapillary urothelial carcinomas and moreover seem to define patients with poor prognosis (Schneider et al. 2014). As Her2 has the potential to serve as a therapeutic target, micropapillary urothelial carcinomas may be candidates for a Her2-targeted therapy. However clinical experience in this setting is still lacking.

Nested-Type/Large Nested

The nested variant of urothelial carcinoma is also usually diagnosed in advanced pathologic stage that leads to a worse overall prognosis if compared to conventional urothelial carcinomas (Drew et al. 1996; Beltran et al. 2014). Histomorphologically, they present themselves as tumor cells whose nuclei show only little or no atypia (Drew et al. 1996; Beltran et al. 2014). Tumor cells are arranged in small (sometimes large) nests beneath the urothelium, sometime also showing tubules or microcystic features. Typical is also the confluence of small nests and the infiltration at the base of the lesion. Nested urothelial carcinomas can be accompanied by conventional urothelial carcinomas, but often they present themselves purely. As the expression profile of immunohistochemistry is similar to that of conventional urothelial carcinomas, it is not a very helpful diagnostic tool (Paner et al. 2014). Because of their appearance, differential diagnosis of Von Brunn nests and other benign lesions has to be taken into consideration as well in order to not to delay definite therapy (Murphy and

Deana 1992). In this context the diagnosis of telomerase reverse transcriptase.

TERT promoter mutation is a useful tool to distinguish nested variants of urothelial carcinoma from its benign mimickers (Zhong et al. 2015). Treatment recommendations do not differ to conventional urothelial carcinoma as clinical experience with this histologic variant is rare (Fig. 3).

Microcystic Urothelial Carcinoma

Only few cases of microcystic urothelial carcinoma have been reported so far. Despite this very limited information on its clinical course, it is regarded as a very aggressive variant of urothelial carcinoma as hardly any of the reported patients survived. Its histologic pattern shows round-to-oval microcysts that give the variant its name. These microcysts are usually lined by urothelium. Their lumina can be empty or contain secretions and calcifications. During microscopic examination differential diagnosis of cystitis glandularis cystica has to be performed. The presented cysts may be infiltrative and can invade the detrusor muscle. They can express CK20 and CK7 as well as GATA3, S 100P, or p63. Uroplakin III or thrombomodulin are expressed to a lower extent. As only a handful of cases have been reported so far, there is no individualized therapy recommendation, so all microcystic variants should be treated as conventional UC, unless more experience about their clinical course has been reported (Paner et al. 2014; Venyo 2013; Paz et al. 1997).

Giant Cell Urothelial Carcinoma

Pleomorphic giant cell carcinoma is a very rare and aggressive histologic variant of urothelial carcinoma (Samaratunga and Delahunt 2012). The reported cases are associated with a poor clinical prognosis, and it is usually presented at an advanced clinical stage. It is regarded as an extreme form of dedifferentiation that leads to giant cells with a bizarre and anaplastic appearance with frequent typical or atypical mitotic figures (Samaratunga et al. 2016). The pleomorphic giant cell urothelial carcinoma can constitute 20–100% of the tumor. Differential diagnosis to trophoblastic or osteoclast-like tumors has to be performed. Immunohistochemistry can show positivity for CK 8/18 and AE1/AE3, CK7, CK20, or uroplakin III and GATA3 (Samaratunga et al. 2016; Lopez-Beltran et al. 2009b).

Clear Cell Urothelial Carcinoma

Clear cell urothelial carcinoma is named by its large tumor cells that present a glycogen-rich

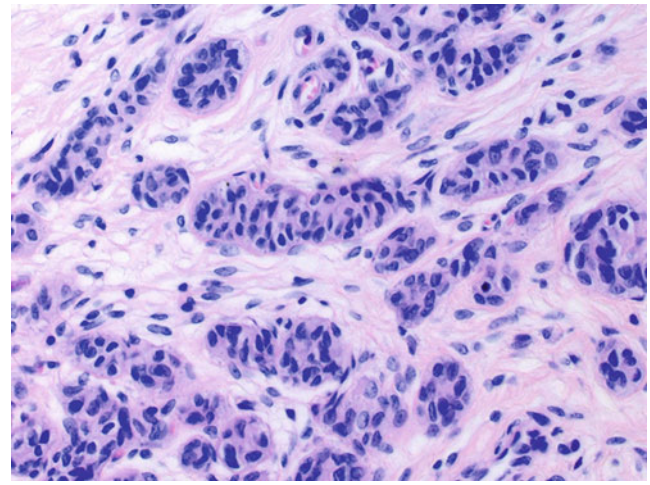

Fig. 3 Histologic specimen of a nested-type urothelial carcinoma of the bladder stained with hematoxylin and eosin (400×)

cytoplasm. This confers a clarity that reminds to clear cell renal cell carcinoma (Fig. 4). It is usually accompanied by conventional urothelial carcinoma or papillary componands, and it is usually high grade. The immunohistochemical profile is characteristic to conventional urothelial carcinoma. They can show positive expression of GATA 3, S 100P, p63, PAX8, CK5 or CK20, and CK7 (Mai et al. 2016; Yamashita et al. 2006; Kotliar et al. 1995). Only very few cases have been reported so far, so that the prognostic impact of this variant is still not clear, because experience of large clinical case series is lacking.

Sarcomatoid Urothelial Carcinoma

Sarcomatoid urothelial carcinoma is characterized by its spindle cell and epithelial elements. It shows usually high-grade histomorphology, and heterologous differentiation can contain elements of osteo-, chondro-, or rhabdomyosarcoma, but also lipo- or angiosarcoma may be present in different proportions of the tumor, and additionally conventional urothelial carcinoma and squamous or glandular componands can be present as well (Fig. 5). The incidence of sarcomatoid urothelial carcinoma is reported to be as low as 0.6% of all

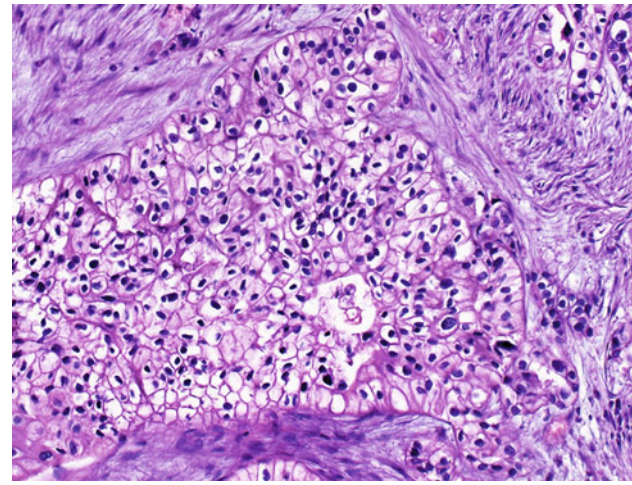

Fig. 4 Histologic specimen of a clear cell urothelial carcinoma stained with hemtoxilin and eosin (200×)

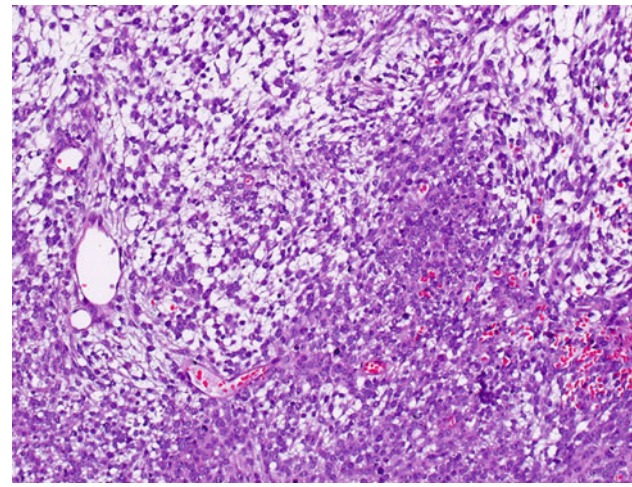

Fig. 5 Histologic specimen of a sarcomatoid urothelial carcinoma stained with hematoxylin and eosin (200×)

bladder tumors, and the mean patient age is 66 years with a male to female ratio of 3:1 (Reuter 1993; Amin 2009). Prognosis is reported to be very limited with a 5-year cancer-specific survival after radical cystectomy of 20% (Wang et al. 2010). EMT markers like Vimentin is expressed in about 80% of the epithelial cells, but also FoxC2, snail, or ZEB1 are described to be expressed in 100%, 88.5%, and 69.2%, respectively (Sanfrancesco et al. 2016). Immunoreactivity of the sarcomatous componands includes pancytokeratin and high-molecular-weight cytokeratins CK5/6 and p63 as well as GATA3 (Fatima and Osunkoya 2014; Ikegami et al. 2000; Lopez-Beltran et al. 1996, 1998). Benign (i.e., pseudosarcomatous myofibroblastic proliferations) and other malignant lesions like urothelial carcinomas with osseous or chondroid differentiation have to be ruled out in differential diagnosis.

Lymphoepithelioma-like Urothelial Carcinoma

Lymphoepithelioma-like carcinoma is also usually diagnosed in advanced pathologic stage showing haematuria as the most common clinical sign at diagnosis (Tamas et al. 2007; Amin et al. 1994). Beside the urinary bladder, lymphoepithelioma-like carcinomas are also described in the upper urinary tract (ureter and renal pelvis) as well as in the urethra. Histologically it resembles lymphoepithelioma of the nasopharynx with undifferentiated cells showing large nuclei with prominent nucleoli that are arranged in nests, sheets, or cords and show ill-defined cytoplasmic borders (Amin et al. 1994). Characteristically the tumor harbors a distinct lymphoid infiltrate including T and B lymphocytes, plasma cells, and others. Therefore differential diagnosis to exclude lymphoproliferative diseases is important, and cytokeratin staining is a useful tool to classify the tumor correctly. The epithelial cells of the tumor are described to express p63 and GATA3, but also other cytokeratins like CK7 or CK8 are frequently detected (Tamas et al. 2007; Lopez-Beltran et al. 2001). Unlike in nasopharyngeal carcinomas, Epstein-Barr virus is not found in lymphoepithelioma-like carcinomas of the bladder (Lopez-Beltran et al. 2001; Fukunaga and Ushigome 1998; Gulley et al. 1995). Lymphoepithelioma-like carcinomas can present themselves purely or only focally, but the prognostic impact of the lymphoepithelioma-like component is not clear, but it seems to behave similarly to conventional urothelial carcinomas if treated with radical cystectomy (Tamas et al. 2007; Amin et al. 1994; Holmang et al. 1998).

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Risk Stratification and Prognostication of Bladder Cancer

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Abstract

Bladder cancer (BC) is divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). The majority of NMIBCs are treated conservatively and primary prognostic outcomes are progression and recurrence. The strongest prognostic factors for progression are T-classification, presence of carcinoma in situ (CIS), and tumor grade, while recurrence is associated with tumor multifocality, size, and prior recurrence rate. The European Organisation for Research and Treatment of Cancer (EORTC) and Club Urológico Español de Tratamiento Oncológico (CUETO) have independently created prognostic models for NMIBC, based on different populations. Despite their prognostic value in NMIBC in general, T1 BC remains perilous disease for which adequate risk stratification is lacking.

Nonmetastatic MIBC usually requires a radical cystectomy (RC), preferably combined with neoadjuvant chemotherapy (NAC). The most important prognosticators for survival are pT- and pN-classification and lymphovascular invasion (LVI). Additional poor prognostic factors found in individual studies are progression from NMIBC, variant histology, hydronephrosis, positive surgical margins at RC, and tumor localization in the bladder trigone. A few clinical risk models for MIBC have been created, but not validated, in order to identify patients who might benefit from NAC. NAC has a positive impact on survival, especially if a complete response is observed at RC. Research aimed at predicting NAC response has mainly focused on molecular markers in TUR specimens by means of immunohistochemistry and genome signatures. Recently, the distinctive subtypes basal and luminal BC have been discriminated. These subtypes appear to be both prognostic and predictive of NAC response but require further validation.

Introduction

Bladder cancer (BC) can be divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Prognosis and treatment differ greatly between both entities. NMIBC, formally known as superficial BC, has a relatively good prognosis. Most NMIBCs can be treated conservatively with transurethral resection and intravesical instillation(s) of chemotherapy (mitomycin) or bacille Calmette-Guerin (BCG). The associated cancer-specific mortality is low (Babjuk et al. 2017). However, NMIBC patients have a lifetime risk of recurrence and progression. Moreover, if progression occurs, 5-year CSS rates drop to 35% (van den Bosch and Witjes 2011). Therefore, careful cystoscopic follow-up is indicated, and if new suspicious lesions are seen, repeated transurethral resections (TUR) and/or fulguration is indicated. In high-risk NMIBC, urinary cytology and computed tomography (CT) imaging are added to the follow-up scheme. Prognosticators for progression and recurrence are essential to decide on continuing conservative treatment and follow-up. Furthermore, in a small subset of patients (T1 and/or G3, CIS), progression risk can be estimated to be so high that more aggressive treatment by means of cystectomy is considered.

MIBC is a perilous disease. Classically, treatment in absence of metastasis (cN0M0) consisted of a cystoprostatectomy and bilateral lymph node dissection (radical cystectomy – RC). However, the associated 5-year overall survival is dismal at 45–66% (Dalbagni et al. 2001; Stein et al. 2001). Over the years, attempts to improve survival have principally aimed at refining and extending the treatment around surgery. So far, the most important breakthrough was the introduction of

cisplatin-based neoadjuvant chemotherapy (NAC). The purpose of NAC administration is to eliminate occult metastases before surgery. Combined NAC and RC improve absolute 5-year survival rates with 5–8% compared to RC alone (Advanced Bladder Cancer (ABC) Meta-analysis Collaboration 2005; Grossman et al. 2003). However, despite the introduction of NAC, survival of BC patients has only marginally improved over the past three decades. A possible explanation is that urologists are hesitant in administering NAC because of toxicity, especially for patients who might not benefit from this combination therapy. Indeed, more than half of MIBCs turn out to be chemo resistant (ABC Meta-analysis Collaboration 2005; Grossman et al. 2003). Therefore, the focus of research in MIBC has been twofold: first, to stratify risk of occult metastases and therefore a poor prognosis and, second, to predict response to NAC.

In this chapter, prognostic and predictive factors for NMIBC and MIBC are discussed. For NMIBC, primary outcomes are recurrence and progression, whereas risk stratification in MIBC is focused on survival. In both entities, prognostic and predictive factors are identified based on cystoscopy, histological examination of TUR and RC specimens, and imaging, which are standard components of work-up.

Work-up for NMIBC and MIBC: Cystoscopy, TUR, and Imaging

Cystoscopy, computed tomography (CT) imaging, and TUR are standard diagnostic procedures for BC. The primary tumor is visualized by white light cystoscopy and CT. Cystoscopy should describe all macroscopic features of the tumor, including site, size, number and appearance (solid or papillary), and mucosal abnormalities (Babjuk et al. 2017; Chang et al. 2016). In addition, voided urine cytology is advised as an adjunct to cystoscopy to detect high-grade cancer and carcinoma in situ (CIS) (Babjuk et al. 2017). Urine cytology has >90% specificity for detecting BC but a low sensitivity, especially for low-grade tumors (Babjuk et al. 2017). Additionally, new technologies have been developed to visualize lesions that are easily missed with conventional white light cystoscopy, including photodynamic diagnosis (fluorescence cystoscopy) and narrowband imaging. CT urography (CT-IVU) can be used to evaluate the presence of upper urinary tract tumors (Babjuk et al. 2017). According to the American Urological Association (AUA) guidelines, this is indicated in all BCs (Chang et al. 2016), and according to the European Association for Urology (EAU) guidelines, only in selected cases (e.g., tumors located in the trigone, multiple tumors or high-risk tumors) (Babjuk et al. 2017). For MIBC, pelvic contrast-enhanced CT or MRI is used to determine the extent of local tumor invasion, and contrast-enhanced CT of the abdomen and chest to evaluate possible tumor spread to lymph nodes and to other organs (Witjes et al. 2017). Ultimately, the primary diagnosis of BC depends on histological evaluation of TUR specimens. The TUR procedure itself is both a prognostic and therapeutic procedure, and a complete and correct TUR is essential to achieve a good prognosis in NMIBC (Babjuk et al. 2017). Therefore, all visible lesions should be removed completely, and the detrusor muscle should be present in the resected specimens in order to reduce the risk of residual disease and understaging.

Non-muscle-Invasive Bladder Cancer

The majority (>70%) of BCs are non-muscle-invasive at initial diagnosis (Kirkali et al. 2005). Of all NMIBCs, 30–80% recur within 5 years and 1–45% progress to MIBC (van Rhijn et al. 2009). This wide variance in recurrence and progression rates has led to extensive research on prognostic variables. The strongest prognosticators for progression are T-classification, the presence of CIS, and tumor grade. The most important predictors for recurrence are tumor multiplicity, size, and prior recurrences.

Prognosticators of Progression

TNM Classification and CIS

The most often used staging system for BC is the tumor, node, metastasis (TNM) classification (Table 1, TNM 2016) (Sobin et al. 2016). The TNM classification divides NMIBC into papillary

Table 1 TNM classification for bladder cancer (Year 2016) (Sobin et al. 2016)

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Ta		Noninvasive papillary tumor
Tis		Carcinoma in situ: "flat tumor"
T1		Tumor invades subepithelial connective tissue
T2		Tumor invades muscularis propria
	a	Tumor invades superficial muscularis propria (inner half)
	b	Tumor invades deep muscularis propria (outer half)
T3		Tumor invades perivesical tissue
	a	Microscopically
	b	Macroscopically (extravesical mass)
T4		Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
	a	Tumor invades prostatic stroma, uterus, vagina
	b	Tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N) Regional lymph nodes include both primary and secondary drainage regions. All other nodes above de aortic bifurcation are considered distant lymph nodes.		
Nx		Lymph nodes cannot be assessed
N0		No lymph node metastasis
N1		Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2		Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3		Lymph node metastasis to the common iliac lymph nodes
Distant metastasis (M)		
M0		No distant metastasis
M1		Distant metastasis

tumors confined to the mucosa (Ta and CIS) and tumors invading the lamina propria (T1). Approximately 70% of NMIBC patients present with Ta, 20% with T1, and 10% with CIS lesions (van Rhijn et al. 2009). CIS is a flat, high-grade, noninvasive urothelial carcinoma. It has been defined as a distinctive malignancy with a high risk for recurrence and progression (Sylvester et al. 2006). If left untreated, CIS will progress to MIBC in 54% of cases (Babjuk et al. 2017). The pathophysiology of CIS is discussed in another chapter of this book. Ta-LG tumors have a low risk of progression and are therefore primarily conservatively treated with TUR alone or TUR combined with mitomycin or BCG instillations.

Tumors that invade the lamina propria are staged T1. Approximately two-thirds of T1 tumors recur and one-third progresses to MIBC. However, progression rates reported in the literature vary between 21 and 50% (Martin-Doyle et al. 2015). This wide variability creates a therapeutic dilemma. As progressive disease is potentially life-threatening, some experts advise to perform an immediate cystectomy for all T1 BCs (van Rhijn et al. 2009). However, immediate RC would be overtreatment for many nonprogressive tumors. Hence, most physicians opt for conservative treatment.

One of the reasons for the wide range in T1 BC progression rates could be high interobserver variability in staging. Histopathological evaluation of TUR specimens is challenging because of thermal artifacts, tangential sectioning, and desmoplastic reactions. Also, the ability to differentiate between T1 and T2 disease depends on the completeness of the resection and the presence of muscularis propria of the specimens (Babjuk et al. 2017). As a result, stage and grade are consistent among pathologists in only half of the T1 NMIBCs (Babjuk et al. 2017). In order to improve these results, two important recommendations have been adapted by international guidelines: All patients with T1 BC should undergo a second TUR, and if the muscularis propria is absent in the TUR specimens, a second TUR is indicated for all NMIBCs (Babjuk et al. 2017; Chang et al. 2016). The main reason for recommending a second TUR for T1 BC is that this results in upstaging to MIBC in up to 30% of patients, depending on the presence of detrusor muscle in the specimen (Herr and Donat 2008). Despite improvements in T1 BC staging accuracy, its heterogeneous prognosis remains an issue.

Retrospective studies have therefore aimed to identify specific prognostic factors in T1 BC. The most important prognostic factors identified in BCG-treated T1G3 tumors are female sex, concurrent CIS, CIS in the prostatic urethra, age, and tumor size (Palou et al. 2012; van Rhijn et al. 2009). In T1G2 BC, treated with TUR only, recurrence at 3 months was the most important prognosticator for progression (Palou et al. 2009). Current research is focused on further T1 BC risk stratification by creating T1 substage classifications. These substages are based on tumor depth and extent of lamina propria invasion (metric substage) or on invasion of a distinct layer of smooth muscle fibers within the lamina propria, the muscularis mucosae. The prognostic value of these systems for progression has been demonstrated in several retrospective studies (Roupret et al. 2013; van Rhijn et al. 2012). However, the reproducibility of T1 substages has not yet been established. Currently, the EAU guidelines state that the depth and extent of invasion into the lamina propria can be evaluated, although it is not yet recommended in the WHO classification (Babjuk 2017).

Histological WHO Grade

Tumor grade is based on several histomorphologic criteria, including nuclear size, shape, polarity, chromatin distributions, and the presence of nucleoli and mitotic figures. The World Health Organisation (WHO) adopted the first BC grading classification in 1973, dividing urothelial cell carcinomas in grade 1 to grade 3 (G1-3) (Table 2) (Mostofi 1973). Despite its strong prognostic value in NMIBC, the 1973 grading system was replaced by a new classification in 2004 (Eble et al. 2004). The main reasons for replacing the 1973 classification were lack of clear definitions for each grade category, high interobserver variability among pathologists, and a high amount of NMIBCs that were categorized as Grade 2, also known as the default diagnosis. The WHO 2004 classification comprises papillary urothelial neoplasm of low malignant potential (LMP), low-grade papillary urothelial carcinoma (LG), and high-grade urothelial carcinoma (HG) (Table 2). With this new classification, G2 BCs were reclassified as LG or HG, whereas all G3 BCs were HG. The 2004 WHO classification aimed to provide better defined histologic criteria and therefore improve the pathologists' consensus. However, several retrospective studies failed to establish a benefit of the 2004 grading system over the 1973 classification (van Rhijn et al. 2012). In fact, in T1 NMIBC, the 2004 classification appears to lose its prognostic value as a result of a very low number of LG-T1 BCs (van Rhijn et al. 2012). The WHO 2016 classification continues to recommend the 2004 grading system, although the WHO committee states that admittedly, controversy remains (Humphrey et al. 2016). Currently, the EAU guidelines advise to simultaneously use the 1973 and 2004 WHO grading classifications (Babjuk et al. 2017). The AUA guidelines describe the WHO 2004 grading system as the most widely accepted and utilized system in the United States (Chang et al. 2016).

Table 2 WHO classification systems for tumor grade published in 1973 and 2004 (Mostofi 1973; Eble et al. 2004)

WHO 1973
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
WHO 2004
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

Other Prognosticators and Risk Nomograms for Progression

Two prognostic models have been created to stratify risk of NMIBC progression. One model was created by the European Organisation for Research and Treatment of Cancer (EORTC). Their risk model was based on research of a population from seven prospective trials, which compared intravesical

treatments after TUR (Sylvester et al. 2006). Apart from tumor stage, WHO 1973 grade, and CIS, the model includes tumor multiplicity, tumor size ≥3cm, and recurrence ≤1 year as poor prognostic factors. WHO 2004 grade was not investigated. The weighted scores of the prognostic factors are displayed in Table 3, and the associated probability of progression in Table 4. Important limitations are that the study population did not receive maintenance BCG and that patients did not undergo a second TUR, which is now the standard recommended treatment for T1BC and for all HG/G3 tumors (Sylvester et al. 2006). The EORTC updated their model based on a study on intermediate- and high-risk patients treated with BCG for 1 to 3 years (Cambier et al. 2016). In this study, patients with CIS were not included. Factors associated with progression in this population were tumor stage and grade. Another prognostic model was created by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Fernandez-Gomez et al. 2009). Unlike the original EORTC population, the CUETO study population principally consisted of high-risk patients treated with BCG instillations. Prognostic factors for progression were stage, WHO 1973 grade 3, recurrence at first cystoscopy, and prior tumors (Fernandez-Gomez et al. 2009). Again, WHO 2004 grade was not investigated. The weighted scores and associated probabilities of progression are displayed in Tables 5 and 6. Unlike in the first EORTC study, CIS was associated with progression on univariable analysis, but not in the multivariable analysis of the CUETO model. This could be explained by the differences in study populations or more effective BCG treatment for CIS in the CUETO study. As the EORTC and CUETO models provide complementary information, both are recommended in international guidelines (Babjuk et al. 2017; Chang et al. 2016). The EAU recommends the EORTC risk tables for prediction of the short-term and long-term risks after TUR, whereas the CUETO tables are preferred in patients treated with BCG (Babjuk et al. 2017). Additionally, the AUA and EAU guidelines have both translated these risk models into three risk groups (low-, intermediate-, and high-risk tumors), which are displayed in Table 7a and b. The risk groups are also based on novel parameters that have been associated with a worse prognosis. These parameters are the presence of lymphovascular invasion (LVI) and variant

Table 3 Weighting of prognostic factors included in the European Organisation for Research and Treatment of Cancer (EORTC) model to predict recurrence and progression (Sylvester et al. 2006)

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2–7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/year	2	2
>1 recurrence/year	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
1	0	0
2	1	0
3	2	5
Total score	0-17	0-23

Table 4 Probability of recurrence and progression according to total EORTC risk score (Sylvester et al. 2006)

Recurrence score	**Probability of recurrence 1 year % (95% CI)**	**Probability of recurrence 5 years (95% CI)**
0	15 (10–19)	31 (24–37)
1–4	24 (21–26)	46 (42–49)
5–9	38 (35–41)	62 (58–65)
10–17	61 (55–67)	78 (73–84)
Progression score	**Probability of progression 1 year % (95% CI)**	**Probability of progression 5 years % (95% CI)**
0	0.2 (0–0.7)	0.8 (0–1.7)
2–6	1.0 (0.4–1.6)	6 (5–8)
7–13	5 (4–7)	17 (14–20)
14–23	17 (10–24)	45 (35–55)

Table 5 Risk of recurrence and progression according to the total score by the Club Urológico Español de Tratamiento Oncológico (CUETO) model (Fernandez-Gomez et al. 2009)

Factor	Recurrence	Progression
Gender		
Male	0	0
Female	3	0
Age		
Less than 60	0	0
60–70	1	0
Greater than 70	2	2
Recurrent tumor		
No	0	0
Yes	4	2
No. of tumors		
3 or less	0	0
Greater than 3	2	1
T Category		
Ta	0	0
T1	0	2
Associated CIS		
No	0	0
Yes	2	1
Grade		
1	0	0
2	1	2
3	3	6
Total score	0–16	0–14

Table 6 Probability of recurrence and progression according to total CUETO score (Fernandez-Gomez et al. 2009)

Recurrence score	**Probability of recurrence 1 year % (95% CI)**	**Probability of recurrence 5 years (95% CI)**
0–4	8 (6–11)	21 (17–25)
5–6	12 (8–16)	36 (29–42)
7–9	25 (20–31)	48 (41–55)
10 or greater	42 (28–56)	68 (54–82)
Progression score	**Probability of progression 1 year % (95% CI)**	**Probability of progression 5 years % (95% CI)**
0–4	1.2 (0.2–2.2)	4 (2–6)
5–6	3 (0.8–5.2)	12 (8–16)
7–9	6 (3–8)	21 (16–27)
10 or greater	14 (7–21)	34 (23–44)

histology. Over 90% of BCs originate from urothelial cells and are therefore defined as urothelial cell carcinomas. Squamous cell carcinomas comprise 5% of BCs and <2% are adenocarcinomas. Especially, rare histology variants such as micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, and microcystic differentiations have a poor prognosis (Babjuk et al. 2017). LVI is defined as tumor invasion of blood vessels and/or lymphatics. LVI in NMIBC in general has been associated with an increased risk of pathological upstaging and metastasis (Lotan et al. 2005). LVI in T1BC is associated with a poor prognosis (Babjuk et al. 2017).

Molecular Markers to Predict Progression

Retrospective studies have aimed at identifying molecular markers from TUR specimens to predict NMIBC progression. Promising markers in immunohistochemistry studies were expression of p53, Ki-67, and a combination of cell cycle regulators (p53, pRB, p21, and p27) (van Rhijn et al. 2014; Shariat et al. 2007). Altered expression of these markers was associated with an increased risk of progression. However, these markers have not been confirmed in other studies, which might reflect the limitations of immunohistochemistry as a diagnostic technique in molecular research. In several independent studies on tumor DNA status, *FGFR3* mutations were associated with a low risk of progression to MIBC. This led to the hypothesis that *FGFR3* mutations are responsible for a favorable pathway in bladder cancer (van Rhijn et al. 2014). International guidelines have not yet adopted molecular markers as NMIBC prognosticators, because further validation is warranted (Babjuk et al. 2017; Chang et al. 2016; Witjes et al. 2017).

Prognosticators and Risk Models for Recurrence

The most important prognostic factors for NMIBC recurrence are tumor multiplicity, tumor size, and prior recurrence (van Rhijn et al. 2009). The

Table 7 Risk group stratification provided by the European Association of Urology (EAU, a) and the American Urological Association (AUA, b) based on the EORTC and CUETO models (Babjuk et al. 2016; Chang et al. 2016)

Risk group	Characteristics	
	According to EAU	*According to AUA*
Low risk	Primary, solitary, Ta, G1 (PUNLMP or LG), <3 cm, no CIS	LG solitary Ta and ≤3 cm
Intermediate risk	All tumors not defined in the low-risk or high-risk categories	Any of the following Recurrence ≤1 year, LG Ta Solitary LG Ta, >3 cm LG Ta, multifocal HG Ta, ≤3 cm LG T1
High risk	Any of the following T1 Grade 3 (HG) CIS Multiple and/or recurrent and/or large (>3 cm) Ta grade 1–2 tumors (all conditions must be presented)	Any of the following HG T1 Any recurrent HG Ta HG Ta, >3 cm or multifocal Any CIS Any BCG failure in HG patients Any variant histology Any LVI Any HG prostatic urethral involvement
	Subgroup of highest-risk tumors[a]	
	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, unusual histology of urothelial carcinoma, LVI	
	BCG failures	

LG, low grade (a mixture of grade 1 and grade 2); HG, high grade (a mixture of some grade 2 and all grade 3 tumors); CIS, carcinoma in situ; PUNLMP, papillary urothelial neoplasm of low malignant potential; LVI, lymphovascular invasion
[a]For these tumors, radical cystectomy should be considered in those who refuse intravesical full-dose BCG instillations for 1–3 years. For BCG failures, radical cystectomy is recommended

EORTC study additionally found T1 stage, concomitant CIS, and WHO 1973 tumor grade to be associated with recurrence (Sylvester et al. 2006; Cambier et al. 2016). The CUETO included sex, age, tumor grade, prior tumors, multiplicity, and CIS in their model to predict recurrence (Fernandez-Gomez et al. 2009). Notably, female sex has also been identified as a poor prognostic factor in a selected study on T1G3 BC, both for recurrence and progression (Palou et al. 2012). A possible explanation is a less common urinary immunological response to intravesical BCG instillations in women than in men (Palou et al. 2012). Likewise, aging might have a negative impact on intravesical immunotherapy response (Joudi et al. 2006). The weighed scores for these factors and the associated probabilities of recurrent disease in the EORTC and CUETO models are displayed in Tables 3 and 4 for the EORTC model and in Tables 5 and 6 for the CUETO model.

Molecular Markers to Predict Recurrence

Several molecular markers have been investigated as prognosticators for NMIBC recurrence. However, thus far results have been conflicting (van Rhijn et al. 2014). Also, little is known of the pathophysiology behind tumor multiplicity, which limits the role of molecular markers for recurrence prediction.

Muscle-Invasive Bladder Cancer

A minority of BCs (approximately 20% - 25%) is muscle-invasive at first diagnosis. Additionally, 1–50% of NMIBCs progress to MIBC (van Rhijn et al. 2009). MIBC staging, treatment, and prognosis rely on a close cooperation between urologists, pathologists, radiologists, medical

oncologists, and radiation oncologists. The most important prognosticators for MIBC are primary tumor stage (T-stage) and nodal classification (N-stage). Tumor grade has limited prognostic value in MIBC, because most cases of MIBC are G3 according to the WHO 1973 classification and nearly all are HG according to the WHO 2004 classification (Humphrey et al. 2016).

Local Tumor Extent: cT-Stage

If muscle invasion is present in TUR BC specimens, clinical stage is at least cT2, and further clinical TNM classification is based on CT and/or MR imaging (TNM 2016) (Sobin et al. 2016). The images should be evaluated for the following staging parameters: extent of local tumor invasion and suspicion of tumor spread to lymph nodes and other distant organs (Witjes et al. 2017). Clinical T-stage differentiates tumors only invading the muscularis propria (cT2), tumors growing through the bladder wall into perivesical fat (cT3), and tumors invading adjacent organs (cT4a) and the pelvic or abdominal wall (cT4b) (Table 1). An increase in T-stage is associated with a higher probability of lymph node metastases, distant metastases, and therefore a decrease in survival. Perivesical fat tissue invasion can be microscopic (T3a) or macroscopic (T3b) (TNM 2016) (Sobin et al. 2016).

CT and MRI can be used to suggest macroscopic invasion of perivesical fat tissue (cT3b) or adjacent organs (cT4). Microscopic perivesical invasion cannot be detected using current imaging modalities (Witjes et al. 2017). Furthermore, imaging is often performed after TUR of the primary tumor. The TUR itself can cause an inflammatory reaction of surrounding tissues, which is difficult to differentiate from local tumor invasion. MRI provides better contrast between different soft tissues (e.g., bladder wall from fat) than CT. Therefore, MRI initially provided a superior cT staging accuracy. However, over the years, the introduction of new techniques has improved CT resolution. Currently, the additive value of conventional MRI over CT is unclear (Witjes et al. 2017).

Lymph Node Metastases (cN-Stage) and Distant Metastases (M-Stage)

BC metastases can be categorized into pelvic lymph node metastases (local, N1-3) and distant lymph node and/or visceral metastases (M1, Table 1). Common sites of distant visceral metastases are the liver, lungs, bones, peritoneum, pleura, and adrenal glands (Witjes et al. 2017). If distant visceral metastases are present, treatment is considered palliative. Patients with metastatic disease have a median survival of up to 14 months, if treated with cisplatin-based chemotherapy (Witjes et al. 2017). An increase in median survival for future patients may be achieved, as promising immunotherapeutic agents (PD1 and PDL1 inhibitors) have recently been developed and tested in the second-line metastatic setting (Powles 2015).

Curatively intended cisplatin-based neoadjuvant chemotherapy followed by RC is only recommended for cT2-4aN0M0 BC in international guidelines (Witjes et al. 2017). In the clinical practice, induction chemotherapy with curative intent is regularly offered to BC patients with limited pelvic lymph node metastases, followed by RC if a good response to induction chemotherapy is observed. However, induction chemotherapy is applied without sufficient evidence from RCTs compared to NAC. Nevertheless, retrospective studies on selected cN+ patients have shown a complete pathologic response to chemotherapy in up to one-third of patients with a corresponding 5-year overall survival of 41–79% after RC (Hermans et al. 2016; Herr et al. 2001). However, nonresponders still have a poor prognosis, and pathologic response cannot be accurately predicted (Witjes et al. 2017). New effective treatments are urgently needed in this patient group.

CT is of low diagnostic value for cN stage, because it cannot detect lymph node metastases in normal-sized lymph nodes (Witjes et al. 2017). Understaging is therefore an important issue. MRI has similar results compared to CT for detecting lymph node metastases (Witjes et al. 2017). With both imaging modalities, pelvic nodes >8mm and abdominal nodes >10mm in maximum short-axis

diameter should be regarded as pathologically enlarged (Barentsz et al. 1996, 1999). If no lymph node or distant metastases are detected on CT and/or MRI (cT2-4N0M0), still approximately half of the patients die within 5 years following RC (Witjes et al. 2017). Furthermore, it has recently been shown in a large population-based cohort that cN1- and cN2–3-staged patients were associated with a 31% and 19% pN0 rate at RC (Hermans et al. 2016). Taken together, the high probability of both false-positive and false-negative results indicates that CT and MRI cannot accurately detect BC metastases, especially in case of higher cT-stages (Witjes et al. 2017).

A relatively new imaging modality is 18F-fluorodeoxyglucose (FDG) PET/CT (FDG-PET/CT). FDG consist of sugar (glucose), combined with a radioactive label (18F). A positron emission tomography (PET) scan can visualize the radioactive label and therefore the sugar uptake in different tissues. Because cancer cells have an increased metabolism, FDG preferably accumulates in tumor tissue. The PET images are combined with CT images for anatomical correlation. Small prospective studies have shown promising results for detecting local lymph node and distant metastases with FDG-PET/CT (Kibel et al. 2009; Lu et al. 2012). However, routine use of PET/CT is not yet advised by MIBC guidelines as more evidence of its additive value is being awaited (Witjes et al. 2017).

Other Prognostic and Predictive Factors

Prognostic and Predictive Clinical Factors

As in NMIBC, presence of LVI and variant histology in TUR or RC specimens are poor prognostic factors in MIBC (Lotan et al. 2005). Variant histology includes squamous cell and/or glandular differentiation, micropapillary and microcystic urothelial cell carcinoma, nested variants, lymphoepithelioma, plasmacytoid, giant cell, undifferentiated, trophoblastic differentiation, small-cell carcinoma, and sarcomatoid carcinoma (Witjes et al. 2017). On CT imaging, the presence of unilateral or bilateral hydronephrosis is associated with a high risk of pathological upstaging and a poor survival following RC (Mitra et al. 2013). Additionally, tumors that were initially non-muscle-invasive and progressed to MIBC may have a poorer prognosis than tumors that were muscle-invasive at initial diagnosis (Babjuk et al. 2017). This could be the result of a more aggressive nature of progressive NMIBC. Another explanation is that NMIBCs are often understaged (35–62%), which causes a delay in appropriate staging and treatment (Witjes et al. 2017). Finally, the tumor location within the bladder could be a prognostic factor. An observational cohort study has shown that tumors in the bladder trigone have a greater risk of lymph node metastases and a decreased cancer-specific survival (Svatek et al. 2014).

Combining prognostic clinical factors has created some predictive risk models for MIBC in order to identify patients who will benefit from NAC. Common factors in these models are cT-stage, presence of hydronephrosis, and LVI (Mitra et al. 2013; Culp et al. 2014). Additional factors included in individual models were variant histology (micropapillary or neuroendocrine features) and tumor growth pattern (Mitra et al. 2013; Culp et al. 2014). However, none of these predictive models have been validated or compared to each other.

Prognostic Factors at RC

Additional prognostic factors at RC for worse clinical outcome are the presence of tumor tissue in surgical margins, the presence of (occult) lymph node metastases, and extranodal extension of lymph node metastases (Witjes et al. 2017). Retrospective research has shown that positive surgical margins of perivesical fat tissue (soft tissue margins) also decrease cancer-specific survival for BC without lymph node or distant metastases (pN0M0) (Neuzillet et al. 2013).

Pelvic lymph node dissection (PLND) is a standard procedure when performing RC (Witjes et al. 2017). Because current imaging modalities (contrast-enhanced CT and MRI) poorly detect lymph node metastases (see above), PLND is the most important and reliable nodal staging instrument. Moreover, resection of affected lymph

nodes might have a therapeutic effect as well. In retrospective studies, patients who underwent PLND had better oncologic outcomes than patients who had not undergone PLND (Bruins et al. 2014). However, based on the literature thus far, the therapeutic value of PLND cannot be distinguished from the consequences of improved disease staging (Bruins et al. 2014). A standard PLND comprises resection of all lymphatic tissue within the external iliac arteries, the presacral, obturator and internal iliac fossa, up to the common iliac bifurcation, with the ureter as the medial border (Witjes et al. 2017). Some retrospective studies report that extension of the dissection template improves recurrence-free survival (Bruins et al. 2014). However, thus far the optimal LND extent has not been defined. Others have found a positive prognostic value for the number of lymph nodes removed (lymph node count, LNC) (Herr et al. 2003). It is suggested that a minimum of 10 lymph nodes is sufficient for adequate nodal staging. However, LNC is influenced by many factors that these studies did not account for. Moreover, both the anatomical LND extent and LNC are subject to a selection bias.

Prognostic Molecular Markers

Recently, extensive research has focused on potentially prognostic molecular markers. Frequently reported prognostic immunohistochemistry (IHC) markers in retrospective studies are p53, Ki-67, and a combination of cell-cycle and proliferation-related markers (Malats et al. 2005; Margulis et al. 2009; Shariat et al. 2014). These are the same markers that were identified as prognostic for progression in NMIBC. Again, these results are likely compromised by the limitations of IHC as the method of marker identification. P53 is the most extensively explored IHC marker. International guidelines do not recommend the standard use of p53 in high-risk MIBC, because of insufficient evidence to adjust individual patient treatment (Witjes et al. 2017).

Predictive Molecular Markers to Assess NAC Response

Tumor markers associated with a poor prognosis may serve to select patients for NAC. The first reason for this theory is the poor prognosis of these tumors without NAC; the second reason is that more aggressive tumors (tumors with a high proliferation rate) appear to be more susceptible to chemotherapy. Tumor downstaging following NAC, especially a complete pathologic response (pCR, ypT0N0), is associated with a major survival improvement (Rosenblatt et al. 2012). Although several efforts have been made by means of imaging prior to RC to assess response to NAC, thus far, no tools can accurately predict pathologic response to NAC (Witjes et al. 2017). Recent research has focused on genome signatures and mutational profiling from TUR specimens to predict NAC response. Recent findings suggest at least two distinctive subtypes: basal and luminal MIBC (Choi et al. 2014a, b). These are similar to basal and luminal profiles found in breast cancer. Basal MIBCs have squamous and sarcomatoid features and portent a poor prognosis. Of note, these tumors appeared highly sensitive to cisplatin-based chemotherapy. Luminal MIBCs are less aggressive than basal tumors. They could be further subdivided into luminal and p53-like subtypes. P53-like luminal MIBCs show a poor response to chemotherapy and worse clinical outcome compared to luminal MIBC (Choi et al. 2014a, b).

Some studies have identified individual DNA mutations associated with chemo-response. These include ERBB2 and ERCC2 mutations (Groenendijk et al. 2016; Allen et al. 2014). Although genomic markers are promising NAC selection tools for the future, further research is warranted to confirm their predictive value.

Conclusions

In NMIBC, the main prognostic factors for progression are T-classification, presence of CIS, and tumor grade. The main prognosticators for recurrence are tumor multiplicity, size, and prior recurrences. The EORTC provides short-term and long-term progression and recurrence risk calculation for NMIBC, while the CUETO risk tables are preferred for NMIBC treated with BCG. Information from both models are implemented in

AUA and EAU risk group stratification. T1 BC has a high risk of progression. Adequate tools for T1 risk stratification are currently lacking.

In MIBC, the pT- and pN-classifications are next to LVI the most important prognosticators for survival. Although multiple additional prognostic factors have been identified, currently no validated risk stratification models for MIBC exist. A complete pathologic response to NAC has a significant positive impact on survival. Genome signatures and some specific mutations analyzed in TUR specimens show promising results as prognosticators and predictors of NAC response. However, their prognostic and predictive value still has to be validated.

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Qualified Rehabilitation After Radical Treatment for Bladder Cancer

29

Michael Zellner, David Ridderskamp, and Mohamed Fawzy

Contents

Abstract

Urological tumor diseases and consecutive invasive therapy with temporary or permanent impairments of health are a biographical break. During the early phase after radical intervention, a professional specific urological care should be carried out to deal with subjective as well as objective problems (e.g., incontinence, erectile dysfunction, stoma care, and metabolic disturbances). Usually, the hospitals that undertake the acute postoperative care would be underequipped and have personal and administrative limitations to carry out the postoperative rehabilitation. Nevertheless, urology outpatient clinics have much less resources to meet the necessary requirements for a qualified rehabilitation. Through an immediate post-interventional, specific urological rehabilitation, negative consequences of the disease and/or invasive therapy procedures can be markedly reduced and the viability or self-employment and reintegration into the social environment of the patient concerned possible. By the time, the urological rehabilitation has developed into a sophisticated, scientifically oriented subdiscipline

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within urology with further improvement of the rehabilitation potential. It is important to diagnose the somatic, mental, and social impairments. However, a prerequisite for a quality-oriented implementation is the exclusive support in adequately staffed and infrastructure-oriented treatment facilities under the supervision of qualified and experienced main occupational rehabilitation urologists (specific to the urological rehabilitation center). For the "overall outcome" of invasively treated urological tumor patients, this topic must be given a further and growing place in urological education. It is not permissible (again) to make the mistake of leaving this important urological subdiscipline to other specialist groups from unconsidered and/or lack of interest.

Introduction

A urological tumor disease often represents a considerable caesura for a patient's life. According to the definition of the WHO, health is the state of complete physical, mental, emotional, and social well-being. Diagnosis and consecutive therapy may be a significant impairment to one or more of these entities of health. With the least suspicion of a malignant disease, a group of diagnostic tests and maybe invasive interventions might take place to ensure the diagnosis. In a case of confirmed diagnosis of a malignant disease, the standard procedures will follow: determination of tumor stage followed by suggestion of a suitable treatment plan (curative, palliative, conservative, or radically curative).

From the perspective of evidence-based and quality-oriented urological medicine, this approach is a professional routine. With statistical aids, treatment results, consequences, and complications can be quantified. By increasingly advanced treatment and surgical procedures, the consequences and complications are diminishing. In spite of the fact that a real cure for the urological tumor diseases can be often achieved, it must not be overlooked that, in the early phase after a radical intervention, more or less pronounced consequences must exist.

Table 1 Typical consequences after radical urological tumor interventions

Disturbed bladder emptying
Incontinence
Reduced libido
Erectile dysfunction
Weakness
Depression
Loss of appetite
Metabolic disorders
Bowel function disorders
Disturbance in lymphatic drainage
Disturbance of wound healing
Others

These consequences from an objective and a subjective point of view may lead to impairment of health (Table 1). Not to mention the recent regulations and protocols that led to remarkable shortening of the postoperative hospital stay (e.g., diagnosis related groups system). Tightness of resources in the field of outpatient care limits the options for optimal postinterventional care. The regular hospitals are usually not well prepared infrastructurally and administratively for long-term postoperative care. Nevertheless, there is no actual budget for providing the needed resources to optimum qualified post interventional care.

Through the introduction of a urology-specific rehabilitation, the consequences of a tumor disease as well as an invasive therapy can be reduced. Nevertheless, the ability to work, independence, and reintegration of patient in his social life can be largely achieved. The somatic, emotional, and social impairments can be dealt with through interdisciplinary cooperation. The tumor follow-up can be later achieved though outpatient urology clinics.

The transformation in the structure of healthcare demands also a rethink about the requirements of a qualified rehabilitation. Until now patients are required to fulfill certain physical and psychological requirements to be accepted in a rehabilitation program, for instance, status of wound healing, incontinence, absence of urinary diversion, or confidence in handling stomata. A modern professional urological rehabilitation is required to cover the patients' needs in these different cases. The qualified urology-specific

Table 2 Structural requirements for modern urological rehabilitation centers

Independent urological department/clinic with at least 30 beds
At least two full-time, rehabilitative specialists for urology
Adequate diagnostic/therapeutic infrastructure Laboratory for blood and urine testing (including blood-gas analysis and urine cytology) Urosonography including color Doppler and duplex sonography Urological endoscopy (video!) Uroradiology unit (digital) Uroflowmetry and a large urodynamic measuring station Option for simple acute interventions
Experienced physiotherapists (continence training!)
Experienced psychoanalysts

Table 3 Rehabilitation goals after invasive tumor interventions

Learning a multimodal continence training
Optimization of the existing supplies
Learning the independent stoma care
Sexual medical consultation, possibly in the presence of the sexual partner/partner
Learning and applying treatment options for erectile dysfunction independently
Increased overall performance and endurance
Screening of previously unknown risk factors
Influencing existing risk factors
Psychological stabilization after cancer diagnosis and invasive therapy
Sociomedical screening and, where appropriate, assistance with professional rehabilitation

rehabilitation aims at achieving rapid social, family, and job integration.

A prerequisite for a follow-up treatment and rehabilitation, which meets the modern needs and urological findings, is the fulfillment of the minimum structure and processing quality standards as published by the Research Group on Rehabilitation of Urological and Nephrological Diseases of the Academy of German Urologists (Arbeitskreis Rehabilitation urologischer und nephrologischer Erkrankungen der Deutschen Gesellschaft für Urologie) (Vahlensieck et al. 2005) (Table 2). The specialization within the subject requires the guidance of a full-time specialist for urology to carry out a specific urological rehabilitation. Such specific urological department requires at least 30 urological beds and adequate diagnostic and therapeutic urological facilities to ensure adequate care. Only a urologist can be familiar with all aspects of urological diseases, in particular therapies and complications as well as their course. This requires at the same time a simultaneous, full-time employment of at least two urologists with proper experience in the treatment, follow-up, and rehabilitation of urological diseases (Vahlensieck et al. 2005). This includes disorders of the bladder and sexual function, urinary diversion after cystectomy, and specific questions concerning surgery, stage-oriented adjuvant therapies, prognosis, stoma care, supply, etc. The quality-oriented implementation of a goal- and symptom-oriented treatment also requires the cooperation of numerous different professional groups (e.g., psychologists, internists, neurologists, orthopaedists, stoma- and physiotherapists, nursing experts, etc.).

The health disorders after invasive uro-oncological therapy can be arranged in three categories: medical, psychooncological, and sociomedical disorders (Table 1). From these typical somatic, psychosocial consequences, complications, and consecutive impairments, clearly formulated rehabilitation goals can result (Table 3). These rehabilitation goals should be discussed and made clear by the rehabilitant. The focus is on individual impairment, disability, social position, or the role of the person concerned to participate in social life in the sense of social impairment (handicap) (Schmid et al. 2003). This is done according to the WHO "International Classification of Functioning, Disability and Health"(ICF) (WHO 2001).

The rehabilitation of patients with urogenital tumors pursues three objectives which should be offered depending on the underlying tumor:

1. Medical rehabilitation
   Through information, guidance, training, and specific therapeutic procedures
2. Psychooncological rehabilitation
   Taking into account specific stress factors and interventions
3. Social medical counseling and, if necessary, professional rehabilitation

Medical Rehabilitation

Urinary Incontinence

Radical pelvic surgery (e.g., radical prostatectomy, radical cystectomy) is usually followed by unavoidable disturbances in bladder function. Incidence of postoperative incontinence 1 year after radical prostatectomy is between 6% and 68%. Consequently, different definitions for urinary incontinence as well as different subjective methods of assessment are used (Ahmadi et al. 2013; Jemtzik et al. 2012). Nevertheless, controversial discussions are taking place about the value of nerve protection and its effect on postoperative urinary incontinence (Abrams et al. 2002). Functional defects in the external sphincter and pelvic floor muscles, detrusor hyperactivity, as well as neobladder peristaltic movements reduced bladder capacity, and neurovascular lesions are also possible causes to be considered. The transmission concept of continence has proved to be the key factor in understanding the functional background of loading incontinence.

The external sphincter muscle tone can withstand a pressure of approximately 50–80 cm H_2O, which is essential for continence under resting conditions (e.g., moving and lying still) (Fig. 1). Urodynamic detectable correlate for this is the urethral pressure profile under resting conditions (Fig. 2a).

While continence at rest is ensured by the tone of the external urethral sphincter (50–80 cmH_2O), continence under physiological conditions of increased intra-abdominal pressure is achieved by passively compensating this pressure transmitted to the urethra through the prostate and pelvic floor (pelvic floor muscles and connective tissue supporting structures). In men, the major part of this transmitted pressure is compensated by the prostate. In both genders, active reflex contraction of pelvic floor muscles augments this pressure transmission (Fig. 3).

As similar to women, loading incontinence post radical prostatectomy is aggravated due to commonly associated pelvic floor muscle insufficiency (coordination, power, and endurance). This is usually demonstrated with heavy physical activity, lack of body awareness, overweight, and connective tissue weakness. In loading situations the intra-abdominal and intravesical pressure overcome the passive and active closure mechanism of the prostate and pelvic floor muscles successively leading eventually to involuntary urine leakage (Fig. 2b).

This mechanism can be supported by clinical observation of patients after prostatectomy. The minority of patients experience involuntary urine leakage under resting condition (controlled by external urethral sphincter tone), and incontinence is usually aggravated by increased intra-abdominal pressure, e.g., coughing or change in position (Fig. 4).

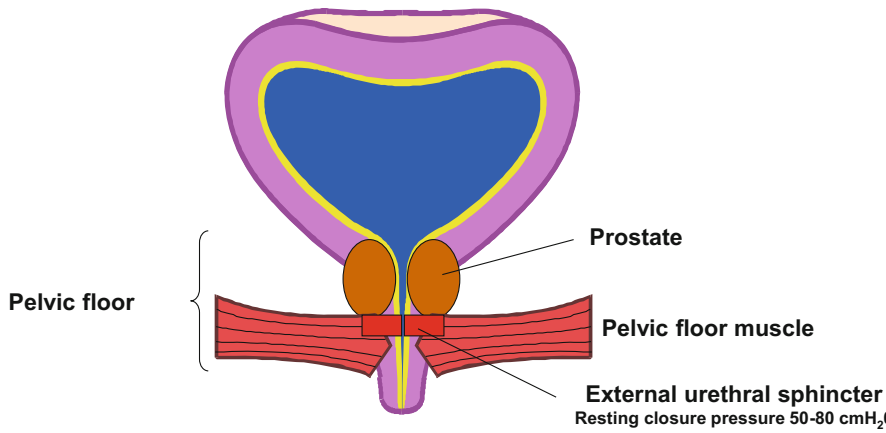

Fig. 1 Physiology of continence under resting conditions

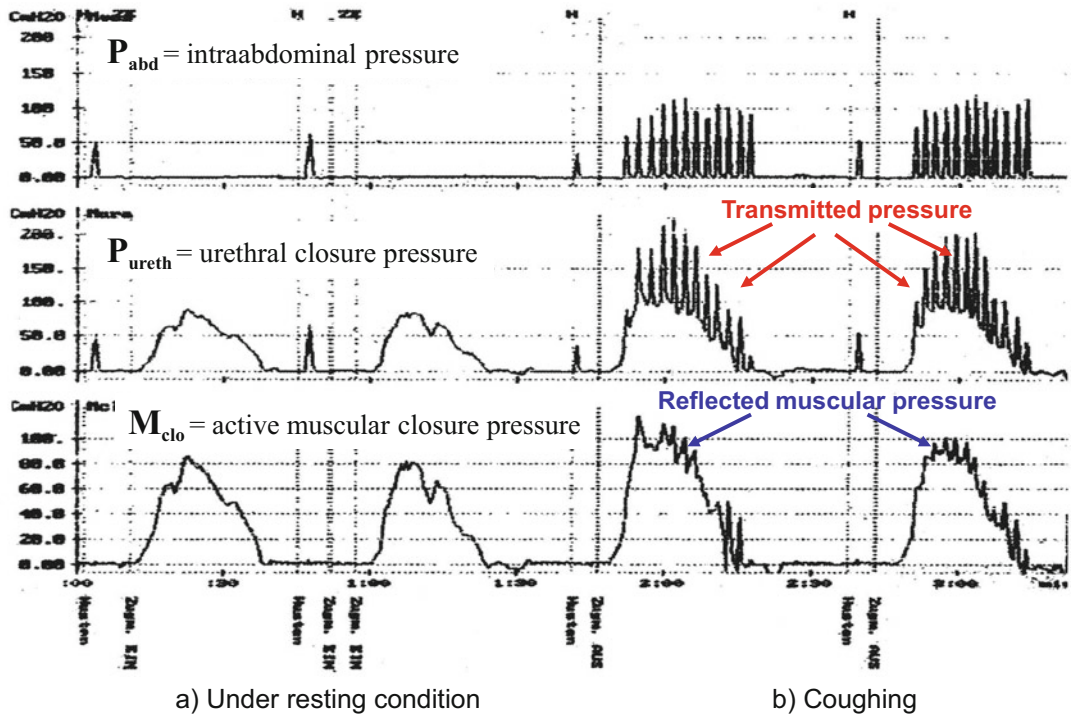

Fig. 2 Urethra pressure profile. (**a**) Under resting conditions. (**b**) Under stress, e.g., coughing

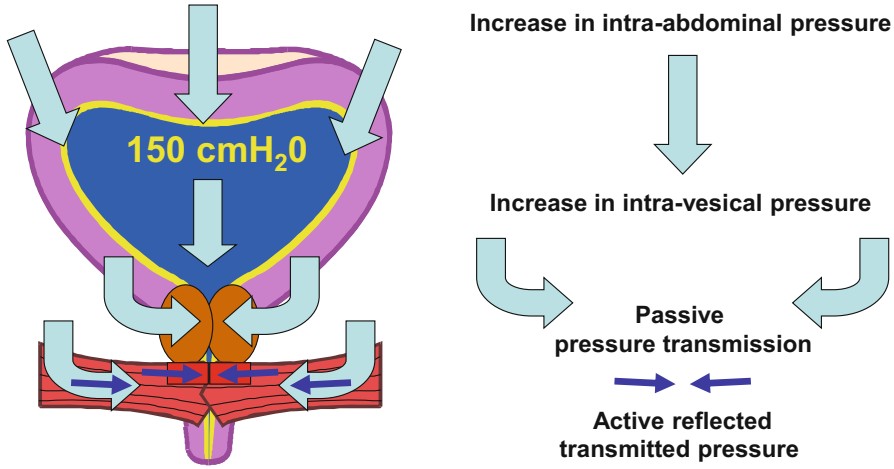

Fig. 3 Physiology of continence under stress

Supplies

During the early postoperative phase, attempts should be done to minimize the effect of this newly disabling situation. Padding and urinary condoms can be possible initial supplies introduced to patients. The use of these supplies should not interfere with any of the casual therapies or replace them. The use of diapers is found to be annoying and discriminating by many patients. This can be explained by the psychological phenomenon of regression, in which there is a reset to the care level of a small child. Therefore, a great

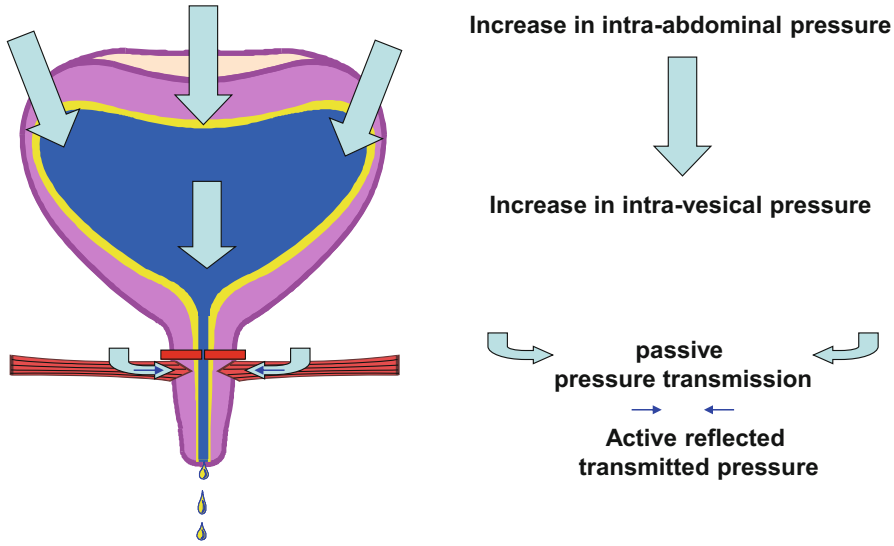

Fig. 4 Stress incontinence due to insufficient pelvic floor in men (postoperative) and female

attention is paid to a dynamic supply that is adapted to the degree of continence in terms of size, quality (especially absorbency due to gel-forming core and anti-wetting surface, profiling for rapid discharge when large amounts of urine flow), fit, and comfort wear. Unit sizes and pulp diapers from the roll should be exonerated from the supply repertoire. Decisive for the supply is also the instructions for a proper handling and a training of the regular handling. The use of the recommended supplies provided during the rehabilitation will help avoiding unnecessary complications as moisture-induced skin irritations, intertriginous eczema, and microbial infections that can be unpleasant.

Qualified Multimodal Continence Training

Principles of Biofeedback Training

For the assessment of the spontaneous continence, a postoperative latency of one to one and a half years is estimated in the literature. Through a qualified, multimodal continence training (a combination of qualified physiotherapy, apparatus training, such as electrostimulation, biofeedback, whole-body vibration, transpelvic magnetic stimulation, and applied training under everyday circumstances), this estimated time can be reduced to a few weeks to months. By consistent training, the insufficient pelvic floor muscle can, on the one hand, coordinate and, on the other hand, gain more strength.

A prerequisite for a successful conservative continence training is the ability to contract the pelvic floor correctly, selectively, and intentionally. However, only a small proportion of patients have adequate body awareness. Most of them cannot contract their pelvic floor, even after careful verbal instruction. Most of the patients (unspecified) use unsuitable (irrelevant) muscle groups (abdominal, gluteal, and thigh muscles) and often forget to breathe. As a result, the training is perceived as not only a very exhausting one but also ineffective in an overwhelming number of cases. By applying the principles of biofeedback, the therapeutic result can be optimized.

Biofeedback is a method that enables conscious control of these functions, e.g., the regular use of pelvic floor muscles under load, by the simultaneous feedback of normally unconscious physical functions.

Physiological afferents (e.g., muscle, tendon, and spindles) continuously transmit the current

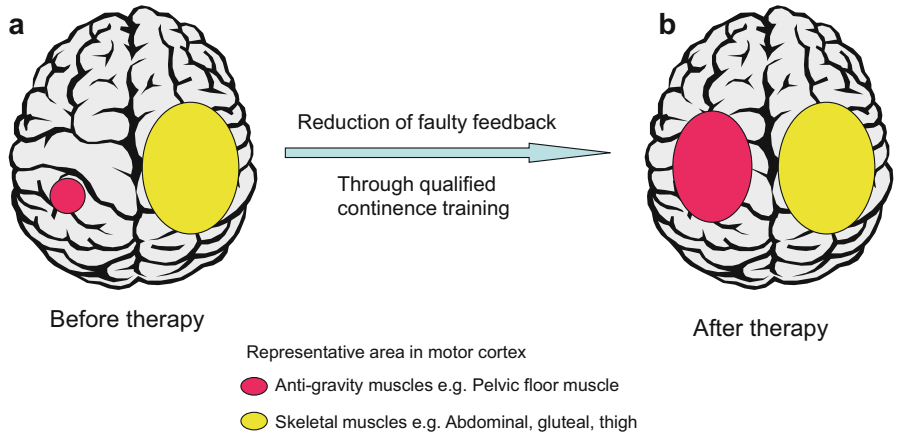

Fig. 5 Role of CNS incontinence biofeedback trainings

functional state of the muscle to the central nervous system (CNS), for example, the motor cortex. Biofeedback processes activate additional afferents (optically, acoustically, or tactilely). As a result, the trained musculature is perceived more intensively while at the same time optimizing neuronal control circuits with subsequent improvement of the central nervous control (Basmaijan 1989).

Above all, the current social lifestyle with predominantly sedentary activity and lack of exercise has led to the fact that mainly the representation areas of gravitationally effective muscle groups (e.g., the normal tone of the back and pelvic floor muscles) within the motor cortex compared to those of the skeletal musculature (e.g., abdominal, gluteal, and thigh musculature) are comparatively low (Fig. 5a).

However, since the intensity of the proprioceptively mediated feedback is dependent on the relative strength of a muscle contraction, an insufficient voluntary control of the pelvic floor muscles results in a masking of the sensory basal floor signals, which are already weak, in addition to the "compensatory" contraction of skeletal muscle (abdominal, gluteal, and thigh muscles). Inevitably, this results in an increased contraction of the artificially and continually inactive muscle groups ("faulty feedback") in the CNS. In addition, this increases the pressure on the bladder and the closure device with consecutive reinforcement of stress incontinence (Tries 1990).

The aim of a multimodal continence training is the relative enlargement of the central representational areas of the pelvic floor muscle in comparison to the rest of the skeletal muscles (Fig. 5b). The commonly recommended "pinch the buttocks together until a piece of coin loses the coinage" supports only this "faulty feedback." It should be therefore finally eliminated from the so-called recommendations for pelvic floor gymnastics.

Personal Biofeedback: Physiotherapy

A prerequisite for a successful continence training is the mediation of basic anatomical and physiological knowledge. The visualization of the anatomical conditions in the area of the small pelvis and the tactile accompaniment of the patient (palpation of the patient's own pelvic floor and continuous correction by the therapist during the active exercise) are decisive for a targeted reduction of "faulty feedback."

Under qualified therapeutic guidance, the patient continuously trains his pelvic floor muscles under stress, e.g., coughing, lifting, standing up, jumping, climbing stairs, etc. (coordination optimization). This results in a noticeable improvement of the continence under everyday conditions after only a few days of consistent training. Characteristically, during this early training phase, patients report an improvement especially in the morning hours, whereas in the afternoons and even after long walks, a marked

worsening would occur again. In addition to the rapidly achievable coordination improvement (competent use of pelvic floor muscles without accompanying auxiliary muscles during stress phases), the importance of an adequate training lasting several weeks to months to increase endurance and strength of pelvic floor muscles (neural adaptation by increasing the excitation frequency and the number of recruited motor units through the training) manifest (DiNubile 1991).

During the early postoperative phase, there is usually a relative tissue acidity of the pelvic floor muscle leading to inadequate pelvic floor control. In such case, initial relaxing procedures are indicated by the physiotherapist. Any form of tonic or force training, including apparatus procedures (especially electrostimulation!), would be counterproductive in this situation as they would contribute to a further overburden of the muscles. However, after the initial survey of the pelvic floor status, it is also possible to indicate a good biofeedback for relaxing the pelvic floor.

Although the prerequisite for a successful therapy is to accompany the patient through a qualified continence therapist, training in German physiotherapy schools for this indication is presumably still not considered to be satisfactory (Wiedemann and Zumbé 1999). Only very few schools have integrated a concept of education that promises success in terms of time and content in their curriculum. It is still largely unknown that digital guidance (rectal/vaginal palpation) must be regarded as indispensable for the mediation of a purposeful continence training. Intensive post-training and further qualification by correspondingly experienced centers and physiotherapy associations should help to narrow this gap. In particular the training technique of the manual examination of the pelvic floor and the digital control of the training must be intensively advanced.

Training under Everyday Conditions

Decisive for a lasting treatment success is the integration of the learned pelvic floor coordination in everyday situations. The concentration on simple realistic movements, instead of hopping on balls and ground exercises, is necessary to prevent the unwanted loss of urine under stress conditions of everyday life, e.g., climbing stairs, lifting objects, or exercising. Through appropriate accompaniment of the person concerned, he learns to transfer this behavior less and less consciously than in a reflexive way into everyday life.

Biofeedback Training Devices

As soon as the patient has learned (and not sooner!) to contract his pelvic floor safely and selectively in stressful situations, continence training can be supported by apparative biofeedback. Surface electrodes, rectally or vaginally inserted probes, can derive the EMG activity or a pressure change in pelvic floor contraction and relaxation and convert it into optical and/or acoustic signals. In this case, either an increasing number of illuminating signal lamps or a higher-frequency sound signal indicates the increasing pelvic floor contraction. As a result, the patient receives a simultaneous feedback on the functional state of his pelvic floor and learns to control this safely.

A prerequisite for an optimal result of the biofeedback training is also the ability of the patient to selectively contract the pelvic floor without the use of artificial muscle groups. Otherwise, a "faulty feedback" strengthens the use of continual muscle groups and puts the therapeutic result into question. An unconditional prerequisite for the regulation of an apparatus for biofeedback training, for example, with small, handy mobile devices, which are also suitable for use under domestic conditions, is the guidance to a safe selective pelvic floor contraction by an experienced therapist. The habit of instructing the patient only about the device functions without the initial pelvic floor training and to rely on acoustic or optical signals is a major cause for the often criticized (usually from unexperienced users in this technique) failure of this therapy form. Optimal for the training are multichannel devices. In addition to the pelvic floor signal, the signals of one or more artificial muscle groups are simultaneously derived. The goal of the training is to achieve the highest possible signal intensity for the pelvic floor

with the lowest possible signals for the derived artificial muscle groups. This can be used in both inpatient and outpatient setting (Figs. 6 and 7).

In consistent training, the conscious, coordinated use of the pelvic floor increases the speed, strength, and endurance of muscle contraction in everyday situations. Due to the optimized reflex contraction performance of the pelvic floor in stress situations with any increase in intra-abdominal pressure, the stress incontinence can be significantly improved or full continence can be recovered.

If consistent continuous training is not achieved within approximately 10–14 days, an intensification of the therapy by optical biofeedback has proven to be successful. The external sphincter is set by videoendoscopy with a flexible endoscope. In most cases, a fear of an intraoperative sphincter lesion, which is latent in many patients, can be eliminated abruptly because the patient recognizes the toning over the entire circumference and realizes the possibility of arbitrary amplification. By retracting the instrument for a short distance, the voluntary contraction of the pelvic floor can be visually perceived additionally. The reason for a persistent incontinence is the lack of coordination of external sphincter and pelvic floor with any increase in intra-abdominal pressure in the predominant number of cases. The result is not the contraction required for continence, but the relaxation of the occlusion apparatus (external sphincter and pelvic floor), which is evident to the person concerned, with consecutive urine output. Under vision, it is subsequently trained until the coordinated bladder closure is successfully achieved. In most cases, a single session of this kind is sufficient to achieve a (significant) improvement in muscle coordination and thus continence. Endoscopically, there are also other pathological changes which may be the cause of a prolonged continence disorder, e.g., wound healing, anastomotic leakage, etc.

Transrectal sonography (TRUS) can be performed with the same objective with significantly lower methodological outlay. In case of light filling, the bladder and pelvic floor are adjusted longitudinally. Usually, a gap in the region of the bladder neck is shown, with a proximal, slightly opened, and distally closed urethra as an evidence of the regular sphincter function (Fig. 8a). When exposed to stress (e.g., cough) without coordinated muscle contraction, proximal urethra and sphincter open at the same time as unwanted (noticeable) urine loss. Conversely, in the case of coordinated muscle contraction during exercise (e.g., coughing), both the pelvic floor contraction and the concluding occlusion of the urethra and thus the increase in the functional urethral length (= transmission range) become apparent to the patient (Fig. 8b).

In cases of a sudden deterioration of an already improved continence, differential diagnosis of acute urinary tract infections, residual urine formation, and mucous retention should be excluded (Hautmann et al. 2013).

Electroneurostimulation

The intermittent anal, vaginal, or superficial cutaneous electrostimulation of the pudendal nerve leads to repeated contraction of the pelvic floor muscles. These contractions can be consciously perceived by the patients and can be trained as a result of the isolated use of the pelvic floor. In addition, electrostimulation serves a targeted forceful training. Under physiological conditions, the motor units (= muscle fibers innervated by the same motor neuron) of a muscle are activated asynchronously by nerve pulses from CNS and thus contract at different times. Contraction and relaxation of different motor units allow for a uniform contraction and powerful distribution in the muscle, while the non-contracting elements can recover. This allows continuous contraction. An increase in strength can be achieved by additionally recruiting motor units or increasing the nerve pulse frequency. Physiological muscle work is performed at low to medium pulse frequencies (<< 50 Hz). As a result, predominantly motor type I fibers (slow-twitch fibers: contract less rapidly and vigorously, fatigue slowly, supplied by thin axon fibers, therefore higher stimulus threshold). In the case of high force or continuous power, additional types of fibers (almost fast twitch fibers: contract rapidly and strongly, fatigue rapidly, fed by thick axon fibers, therefore lower stimulus threshold) are also included by

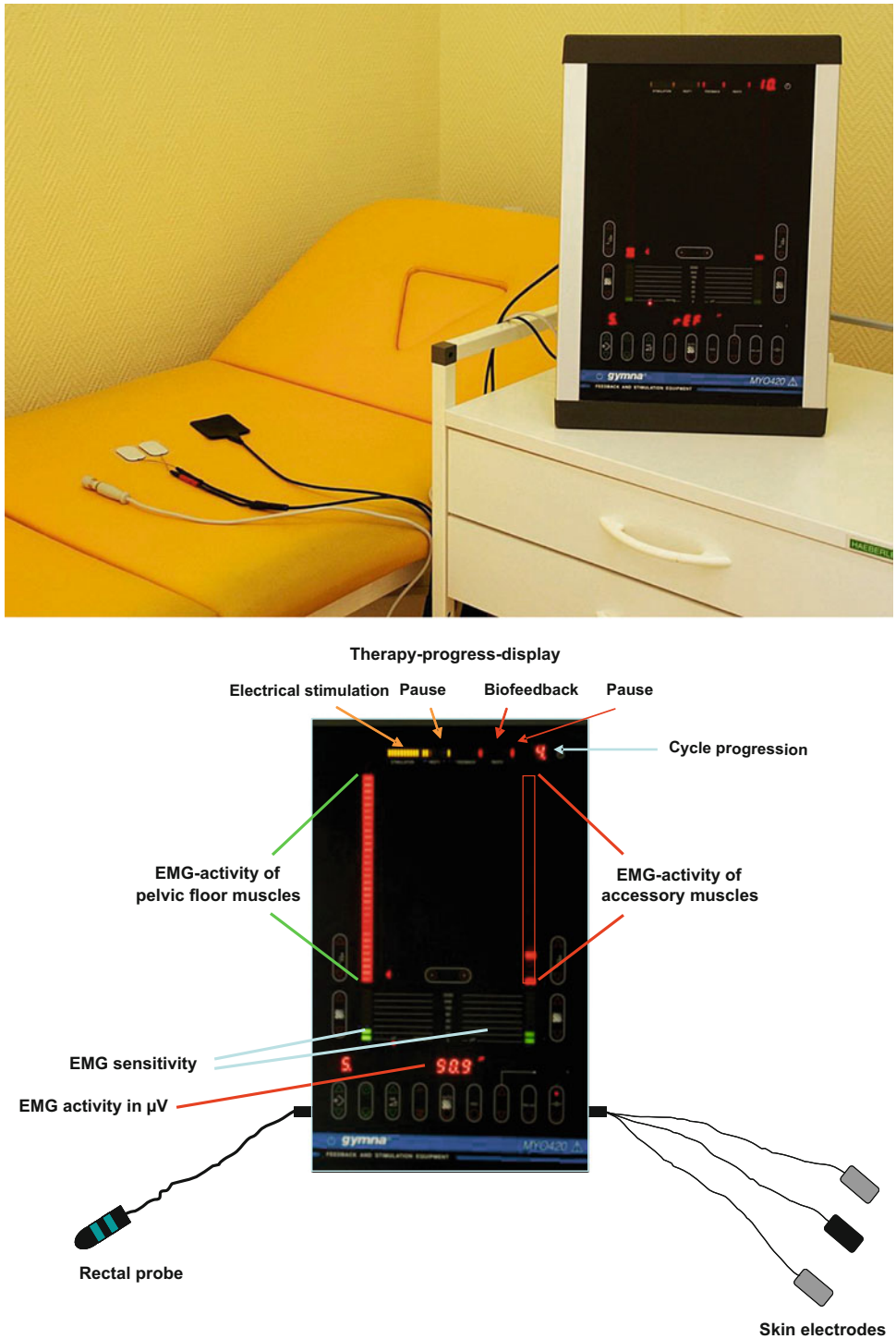

Fig. 6 Multichannel device for combined electrostimulation and biofeedback training of pelvic floor muscle

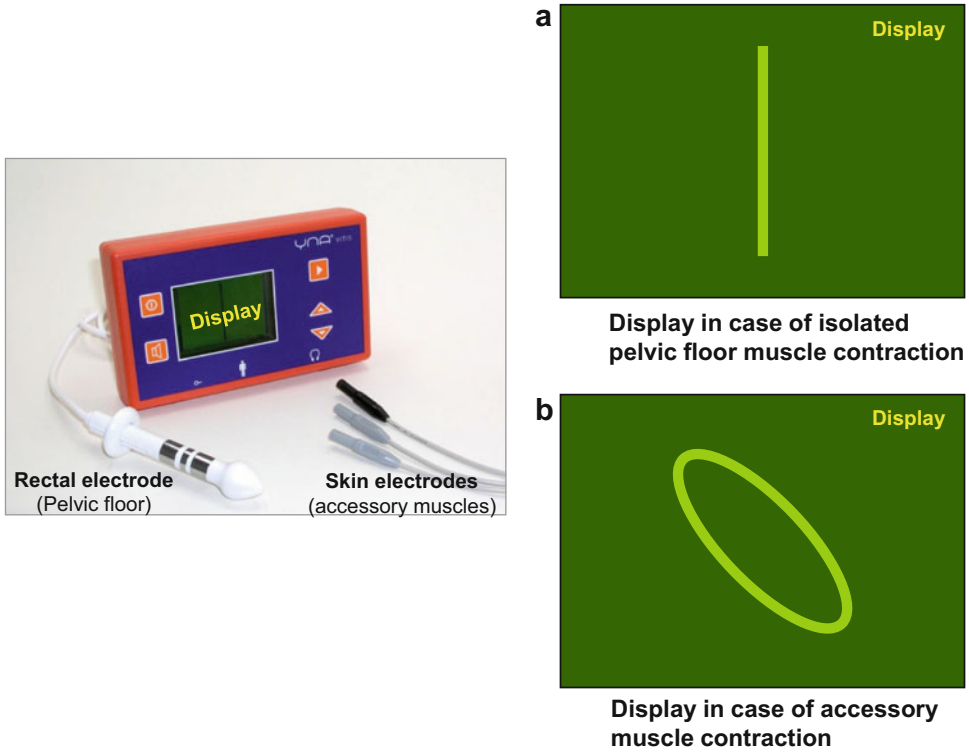

Fig. 7 Two-channel biofeedback home device for continence training

higher pulse frequencies (50 Hz). By stimulation with faradic current, the physiological conditions for muscle activation can be reversed. Due to the lower stimulus threshold, type II fibers are first to be addressed, but only if the stimulus frequency and intensity are correspondingly increased, type I fibers are also addressed. If the stimulation intensity (current intensity) is high enough and if the stimulation frequency is more than 50 Hz, all muscle fibers can be reached and a tetanic contraction can be triggered in the stimulated area. A maximal, exhausting contraction followed by a sufficiently long recovery phase is necessary to strengthen the pelvic floor muscles. Only in this way can the intramuscular energy stores be refilled and the function of the motor end plate be restored. A (physiological) stimulation frequency around 50 Hz is considered to be sufficient. Higher frequencies lead to faster fatigue. To trigger a depolarization and thus a contraction, the pulse duration and intensity must exceed a minimum value. Increasing one or both parameters enhances muscle contraction. Depending on the formation of the under-skin fatty tissue (insulation!), motor units are addressed with current intensities of about 100 mA. If the current is still higher, the force will not increase significantly (Cabric and Appell 1987).

Apparative Continence Training: Innovative Approaches

For the purpose of optimizing consciousness, coordination, endurance, and strength, a randomized prospective controlled trial has proven the efficacy of medical whole-body vibration training in various body postures (Zellner 2011) (Fig. 9). Also promising results of transpelvic magnetic stimulation (TPM) (Fig. 10) with minimum use of at least 10–15 sessions of 20 min each were shown in prospective field study (data in press).

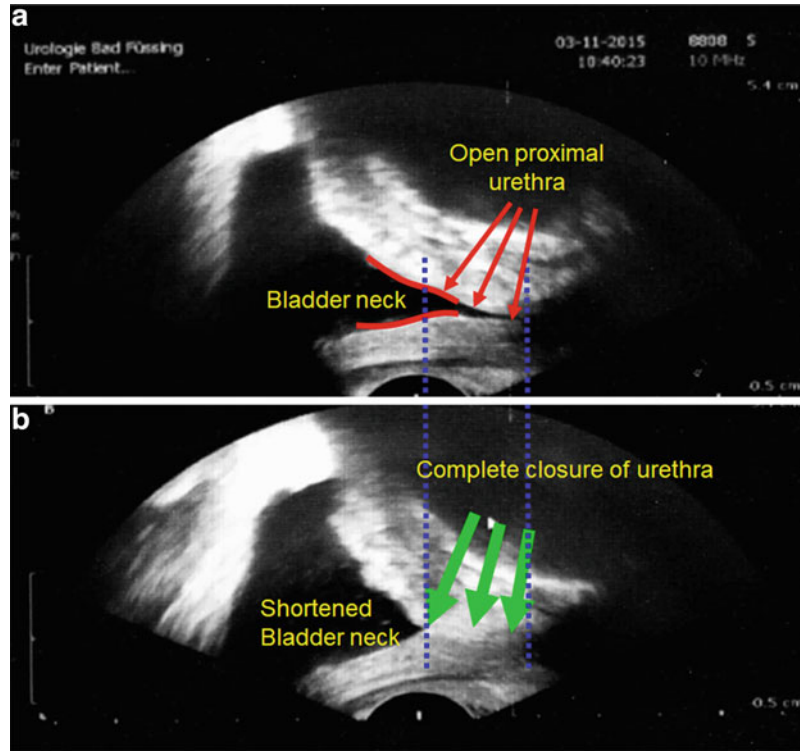

Fig. 8 Transrectal ultrasonography for pelvic floor muscle training

Change in Lifestyle: High Priority for Incontinence Treatment

Changing the stressful lifestyle is of major importance for the success of conservative continence therapy. With increasing body mass index (and life age), not only the probability for the occurrence of urinary incontinence (OR to 3.59) rises but also the deficiency of vital nutrient supply (Calton 2010) and consecutive insufficiently stable collagen biosynthesis with inadequate (pelvic) muscle buildup. Likewise, in chronic constipation (OR to 2.9) and diabetes mellitus (Abdel-Fattah and Rizk 2012), the risk of continence disorder rises considerably. Therefore, individual dietary therapy, weight optimization, and indicated orthomolecular substitution should be an integral part of a purposeful continence training program as well as effective support for smoking cessation.

Instrumental Urinary Diversion and Urostomy (Stoma Care)

Continent Urinary Diversion: Ileal Pouch and Orthotopic Neobladder

In cases of continent stomata (bladder pouch) as well as pathological residual urine formation in neobladder (in nearly 9% of men (Ahmadi et al. 2013) and 58% of women (Jemtzik et al. 2012), the intermittent catheterization should be performed in adequate sterility and sufficient frequency. In contrast to the postoperative situation in men, in women up to 50% of cases experience a so-called hypercontinence, which then might depend on intermittent catheterization for bladder emptying (Bartsch et al. 2014). With the trial of various catheter systems (tip, coating, lubricant application, etc.), the user should determine the most suitable system for him by trial and error.

Fig. 9 Continence training using whole-body vibration

Nocturnal Urinary Incontinence in Orthotopic Neobladder

After the formation of an orthotopic neobladder, good daytime continence can be achieved quickly by a qualified multimodal continence training. A strongly irritating nighttime incontinence emerges as a result of the lack of sensory feedback of the filling state and the nocturnal relaxation of the occlusive muscles. In addition, due to the increased secretion of free water through the mucous membrane of the urine reservoir, there is sometimes a considerable overload on the neobladder. The widespread practice of achieving night dryness by awakening in 1- to 2-h intervals ("alarm clock") leads to a severe impairment of the physiological sleep behavior. Daytime fatigue with reduced cognitive functions by reduced performance and increased risk of accidents are recognized consequences. In addition, an increased risk of malignancy is discussed in the long term (chronodisruption).

Therapeutically, the use of a urinary condom catheter is recommended for men at night. With increasing pelvic floor competency and daytime continence within the framework of multimodal continence training, the nighttime continence is often also improved. As a rule, the use of the condom catheter can soon be dispensable. So far no negative influence on the daily training has not been yet established in the majority of cases. Unfortunately, there is no adequate alternative for female use till now.

Stoma Care

A proper rehabilitation program should provide the patient with the important information about his stoma. For a patient with an incontinent urinary diversion, learning proper care of his stoma and troubleshooting of all the aspects of his urostomy bag would be of utmost importance. A successful rehabilitation program would provide a competent stoma nurse, different materials used during stoma care, and psychological reassurance of the patient, life partners, family members, etc. This is the best way to achieve and ensure a better quality of life. Whether it is a ureterocutaneous diversion or ileum conduit, the same principles apply. The goal is to achieve a constantly dry patient with healthy skin at the site of application of the urostomy bag.

It is not often enough to emphasize that proper marking and selection of the site of the diversion on the abdominal wall preoperatively is extremely important. In addition the preoperative mental preparation of the patient would also help in the psychological recovery postoperative. Demonstrative videos and photos and attending a session of group therapy for bladder cancer patients helps the patient to get better after the operation.

Patient should be taught that stoma care is a clean, not a sterile, process. The patient should be

Fig. 10 Continence training using transpelvic magnetic stimulation

also encouraged to be able to perform the whole process independently. A continuous feedback from the stoma nurse is essential to monitor his or her progress.

Particularly after the end of the early postoperative phase, the quality of life of the patient is markedly compromised. Social embarrassing and fear of leakage from the stoma gradually withdraw the patient from participation in social life. The modern advances in manufacturing the needed material can achieve an acceptable level of stoma care, e.g., stoma belts which are made of highly elastic material can achieve a wrinkle-free sitting position and support to the abdominal wall without causing atrophy of abdominal wall muscles, fixing the stoma securely and also protecting the stoma from hernia.

We should inform the male patients that there is no need to avoid swimming from medical point of view, but they can cover their stoma with a special swimming suit to overcome the feeling of being ashamed of having the abdomen exposed. A recent advance is the availability of stoma belts made of neopren and include a pocket to store the urostomy bag rendering it water proof (Fig. 11). If additional weights in water gymnastics are carried over the stomabandage, the bandage is thought to be a training tool for water gymnastics.

Disturbances of Sexual Function

Sexual activity is an important factor for quality of life, and it has been included in the WHO criteria of health since 2006. Sexually active patients live longer and healthier. This observation can be attributed to the endocrinal process that occurs during orgasm, e.g., the release of oxytocin, dopamine, endorphins, cortisol, and immunoglobulins with positive effects on psychological status, pain relief, and immune system (Bayerle-Eder 2015).

Erectile Dysfunction

Not only the impairment of continence but also a disturbed sexual function after radical tumor intervention is considered by many patients a strong factor affecting quality of life (Heathcote et al. 1998). With the increasingly improving intervention methods (e.g., bilateral preservation of relevant neurovascular structures), spontaneous

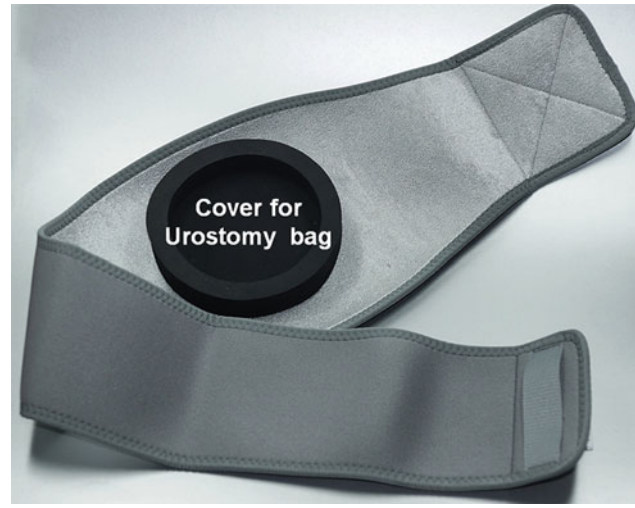

Fig. 11 Stoma care belly band for bathing and swimming

erectile ability can be obtained in an increasing proportion of subjects. Nevertheless, it must not be overlooked that this spontaneous erection capacity cannot be expected in every case shortly after the radical operation. Sometimes a delay of 1 year or longer can be expected (Sivarajan et al. 2014). In order to prevent degenerative changes of the erectile tissues with increasing fibrosis, adequate postoperative rehabilitation of erectile tissues should start as soon as possible through repeated trials to stimulate the penis mechanically and chemically, e.g., by phosphodiesterase-5 (PDE-5) inhibitors (Stadler et al. 2008).

Although the treatment options in recent years have undergone a significant improvement, especially after the introduction of PDE-5 inhibitors, there is still no optimal therapy. The treating physician should rather try to help the patient choose the most appropriate option from the available possibilities (PDE-5 inhibitors, vacuum erection device (VED), intracavernous autoinjection therapy (ICI), medicated urethral system for erection (MUSE), and penile prosthetics). It is important to avoid the possibility of projecting your own prejudices and evaluations to the patient regarding the indication for the treatment and the different options. Most men accept a probable loss of erectile ability after the diagnosis of a malignant disease. However, the loss of erectile potency may also lead to a psychosocial impairment (Althof 2002). About two thirds of men experience the "loss of masculinity" with reduced self-confidence. The partnership is impaired in about one third of cases and is terminated in about one fifth due to the potency disturbance. It is also not uncommon that the patient describes alterations in the everyday relations with friends and colleagues (Tomlinson and Wright 2004).

In the early postoperative phase, a normal sexual intercourse is not yet experienced by the majority of patients. In most cases, the desire for curative therapy is the priority, while a more or less pronounced continence disorder is the most important impairment for quality of life. After the ablation of these acute stresses associated with diagnosis and invasive therapy, the topic of erectile dysfunction becomes increasingly important and the sexual interest returns to preoperative levels.

Informing the patients about the potential effects of prolonged postoperative absence of erections on penile tissue (fibrosis) is also essential. The need for consultation is immense. In a consecutive treatment series of 1584 patients (mean age 64.7 [37–82] years) after radical prostatectomy, 97.3% of patients, regardless of age, degree of continence, tumor stage, and nerve-sparing procedure, have voluntarily accepted counseling about possible treatment options. 1112 patients (72.2%) have subsequently agreed on one or more treatment options (with PDE-5 inhibitors, VED, MUSE or ICI). 472 patients

(29.8%) refused further treatment (Zellner and Riedl 2008). A 69-year-old patient after radical prostatectomy gave a possible reason for this high consultation need: ". . . Actually, it should not be a big loss that I can not get an erection after the operation because I rarely sleep with my wife. But the feeling that I could if I wanted was always very important to me" (Zettl and Hartlapp 2008).

Phosphodiesterase-5 Inhibitors

Without any doubt, with the introduction of the PDE-5 inhibitors, a milestone for the treatment of erectile dysfunction was set. However, there is still a proportion of patients who did not respond to the treatment, had coexistent contraindications to the treatment, or could not afford it, even after introduction of generic active ingredients. Almost all insurance companies ignore the legal and the medical regulations for medical treatment of erectile dysfunction (with the exception of one-time medication used for diagnostic purposes and VED in Germany). Despite the remarkable improvement in the surgical techniques of nerve-sparing procedures, a latency of the effectiveness of the PDE-5 inhibitors must be considered from weeks to months, even though regularly administered. For many nonresponders of PDE-5 inhibition, especially after invasive tumor therapy in the area of the small pelvis, the question is raised about an effective alternative. Both partners should be informed about the available alternatives in a comfortable and relaxing atmosphere. The possibility of practical testing and the safe handling is also important for acceptance of the offered alternatives.

Intracavernous (Auto)injection Therapy

The indication for obtaining a penile erection is not only for the demonstration of the procedure but also for the simultaneous evaluation of the penile perfusion as a secondary preventive approach in case of coincident risk factors. Apart from the appreciation of urologists to this method, the acceptance of patient to this kind of treatment as a permanent treatment form should be carefully assessed. From a randomly selected group of 1584 men after radical prostatectomy, 100 (6%) had undergone a consultation for ICI for diagnostic purpose 44 (44%) out of the 100 investigated patients reached an efficient erection (E4 or E5). 19 patients (19%) had no complaints during the process or follow-up. 12 users (12%) experienced minor discomfort. 36 (36%) considered it unpleasant or painful, while 15 patients (15%) considered it strongly painful. 22 patients (22% of the patients tested, 2.0% of all patients with a treatment request) have subsequently decided for therapeutic ICI. The main reason not to decide for this method was pain (in spite of education about the discomfort and pain during process) (Zellner and Riedl 2008).

Medicated Urethral System for Erection (MUSE)

Despite the theoretically simple application of alprostadil, the acceptance of the system (MUSE) (Fig. 12) in the meantime is also not particularly high. 117 patients (7.4%) have tried the application of a MUSE. Nearly 50% of them reported a sufficient rigidity. Characteristic side effects were urethral pain and mild bleeding (Zellner et al. 2008).

Vacuum Erection Device (VED)

Contrary to Germany, where ICI was used for many years financed by the health insurance system, treatment in the USA had to be financed independently. As a cost-effective, low-impact, and effective therapy, vacuum pumps have quickly spread in the USA. In Europe, their use is still relatively low.

The cause for this was certainly also hemodynamic examinations. The erection achieved by vacuum systems was accompanied by hypoxemia and prolonged acidosis hence considered to be nonphysiological. In the meantime, however, it has been shown that an improvement in spontaneous erection ability can also be achieved by vacuum therapy. This supports the assumption that not only pharmacologically but also by means of a postoperative penile training, using vacuum therapy can promote an improvement in the ability to erect (Bosshardt et al. 1994).

For a satisfying sexual life, emotional acceptance and safe handling are elementary for the VED. It is also not uncommon that patients are

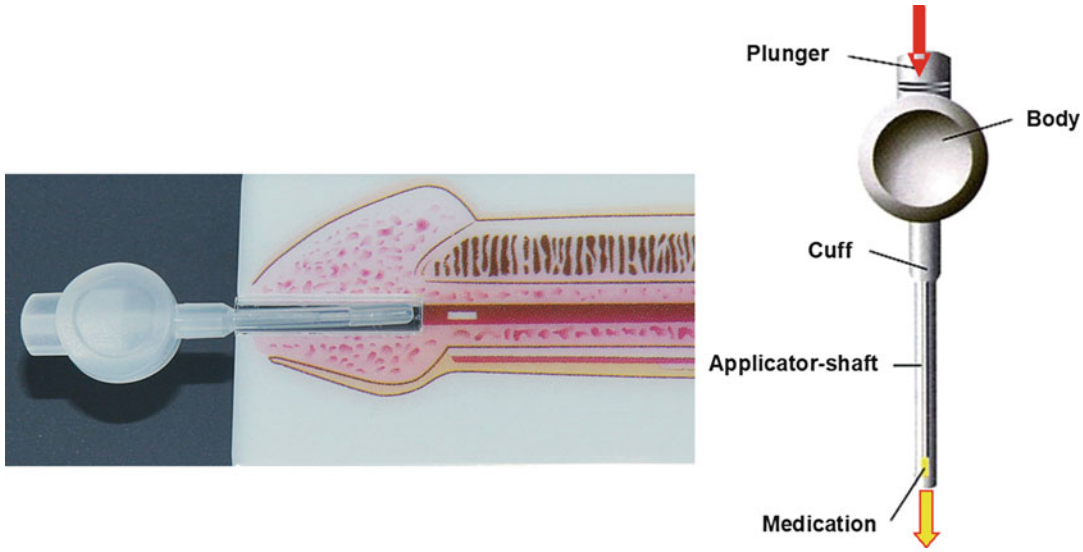

Fig. 12 *M*edicated *U*rethral *S*ystem for *E*rection (MUSE)

unsatisfied with VED despite having successful erections. If the system is brought along to discuss the application again, an unused, originally packaged system is often presented, which cannot be assembled by the patients. At the beginning the medicine product is often rejected, whereas after consultation and training, it can be easily accepted by both partners as a "sex toy" (Zellner et al. 2008).

The handling should be tried with the patient, usually together with the partner. The VED is usually disassembled in a standby bag with complete accessories (Fig. 13). It consists of a transparent plastic cylinder (Fig. 13-1), sealing rings (Fig. 13-2), a manually or electrically operated pump (Fig. 13-3), a selection of constriction rings (Fig. 13-4), a cone (Fig. 13-5) for applying the constriction rings, and a lubricant (Fig. 13-6).

First, a constriction ring (to be selected individually) is applied to the cylinder over the cone (Fig. 13-7). It can be easily applied using lubricant gel. The cone is removed and a sealing rubber ring is fitted (Fig. 14). In order to achieve a good tightness over the pubic hair area, the rubber ring is also coated with lubricating gel. The pump head is placed on the opposite side. Then the penis is inserted into the cylinder. To avoid a (painful) gluing of the penile skin with the cylinder, some lubricant should be applied to the inside of the cylinder. In order to achieve a good seal on the abdominal wall, the cylinder is pressed well against the abdominal skin and the vacuum is generated mechanically or electrically with the pump. This results in a mechanical passive venous penile filling. The constriction ring, which is stripped from the cylinder to the penis root, ensures erection, and the pumping system is removed. To avoid ischemic tissue changes, the constriction ring should not be left after a maximum of 30 min. The rate of successful erections is indicated by about 60%. From the 38% of patients with a VED application, almost 21% decided to adopt a home-based system (Zellner et al. 2008).

The most common side effect of vacuum therapy after radical procedures is a painful erection. The primary induction of erection by the vacuum system was found to be less painful than the application of the constriction ring. Almost exclusively, patients who found it a painful procedure failed to achieve a successful erection using the vacuum system. Three patients with primarily insufficient erection (E1, E2) and ten patients with tolerably sufficient erection (E3) asked for the VED just as a way of regular penile training. Apart from one case (E1), only patients who experienced a painless first time

Fig. 13 Electrically operated vacuum system (Components)

Fig. 14 Electrically operated vacuum system (Assembled Unit)

application asked for the prescription of a VED. Other side effects in descending order included petechiae/hematomas, cold feeling, sensory disturbances in the penis, and scrotal skin suction. In individual cases paraphimoses, skin necrosis, and hyperpigmentation of the penis skin were found. Patients on anticoagulation did not have relevant complications. Overall, vacuum therapy can be considered as a very low-side-effect and low-complication treatment (Zellner et al. 2008).

In general, there are still a large number of misjudgments of the affected persons and their partners in sexual counseling after invasive tumor therapy. The prescription of a PDE-5 inhibitor (especially for the first approved product Viagra®) still holds a considerable resentment, since not only patients often consider the medication harmful and dangerous. The use of the PDE-5 inhibitors, which is very safe when the contraindications are observed, has not yet reached the broad population's conscience.

Sometimes the main reasons for the rejection of an erection treatment are not from the patient but from his partner. The decision whether and which therapy in many cases is not only made by the patient himself but also his partner. Especially the suggestion of an ICI is often rejected by the partners as "unpleasant for the man."

Sexuality of Women After Invasive Tumor Therapy

Unlike the male erectile dysfunction, there are no obvious organic restriction of sexuality and no "organic" therapeutic approach. That is to say sexual medical care and rehabilitation of female patients after invasive interventions are not yet carried out to an optimum extent. In women too, the causes of sexual function disorders after oncological diseases are multifactorial: psychological impact caused by an abdominal scar or a visible stoma but also and hormonal changes after oophorectomy in terms of anterior pelvic exenteration or accelerated menopause following chemo- and/or radiotherapy. Consequent symptoms include reduced or loss of libido, vaginal atrophy, and dyspareunia resulting from vaginal atrophy and/or following anterior vaginal wall resection (Hanjalic-Beck et al. 2012).

The libido reduction as observed in healthy postmenopausal women should in no way lead the treating physicians to the assumption that in female patients who underwent cystectomy at an average age of 66 years, there is no need for sexual advice (May et al. 2011).

The observation that 60-year-old females with a stable relationship can have more sexual contact than 30-year-old female singles is alone encouraging for undertaking counseling and discussing of possible treatment options, e.g., hormone replacement therapy. This should be an essential part of rehabilitation in order to maintain quality of partnership and (sexual) health of both partners (Bayerle-Eder 2015). However, the fact remains out of the 80% of women after invasive oncological intervention, who were interested in getting information about sexuality, only 25% actively articulate this desire in a medical conversation (Bergant and Marth 2009).

For example, a consultation can be following the model "PLISSIT" (permission, limited information, specific suggestions, intensive therapy). A confirmation that the patient wishes to undertake the counseling about sexuality is followed by listing of difficulties and problems of the couple, finally leading to suggested solutions and offered treatment options. Frequently, mental blockages and maladjustments can be eliminated, especially when due to insufficient information about disease, therapies, and the assumed (not always real) effects on sexual activity. Concrete solutions can be used, e.g., the use of lubricating gel or a local estrogen treatment in the case of lubrication disorders, vibrators with reduced vaginal sensitivity, or vaginal dilatators in vaginal stenoses. In addition, various aids can help to compensate for disturbances in body image perception, e.g., attractive special pants with pouch for covering urostomy bag.

As a part of the intensive therapy, further measures from the field of sexual or behavioral therapy can be initiated and a potential accompanying depression can be detected and treated (Bayerle-Eder 2015; Bergant and Marth 2009; Hanjalic-Beck et al. 2012).

Also in women with little interest in genital sexuality, sexual advice is useful. Just after the diagnosis of a serious illness and invasive therapy, despite the lack of desire for penetrating sexual intercourse, there is often an increased need for tenderness and body contact. Counseling can help to identify these needs with the patient and provide help to mediate with the partner (Bergant and Marth 2009).

Urinary Tract Infection after Cystectomy

Due to the microbial colonization of the intestine, urinary diversion using intestinal segments predisposes to urinary tract infections mainly within the first postoperative months. In 797 urine cultures of 47 patients, 74.5% showed initially positive cultural growth. Without antimicrobial therapy, a decline to 6.7% was observed within 18 months, indicating a high spontaneous clearance (Abdel-Latif et al. 2005).

However, urinary tract infections are the most common complication after cystectomy with urinary diversion via intestinal segments. Despite perioperative antibiotic prophylaxis, approximately 40% of the patients experience symptomatic urinary tract infections following a neobladder (Shigemura et al. 2012). In a section study, 86% showed signs of previous infections of the upper urinary tract after an ileum conduit compared to only 28% in bladder cancer patients without urinary diversion (Bergman and Knutson 1978).

A clear distinction must be made between an asymptomatic bacteriuria and/or pyuria, which does not require any treatment, and a symptomatic urinary tract infection with clinical and/or laboratory chemical infection signs (ascending infection). Only symptomatic urinary tract infection is the indication for rapid, test-appropriate, possibly parenteral, antibiotic treatment (Suriano et al. 2008). A broad spectrum antibiotic should be given till the availability of the culture and sensitivity tests, preferably taking into account the locally different bacterial spectrum and resistance (consultation with the operating hospital, possibly obtaining antibiotic sensitivity tests available there). Because of the postoperative almost regular intensive medical care, the presence of hospital-acquired infections should be also considered, e.g., *Proteus*, *Pseudomonas*, and *Serratia* as well as multiresistant strains (Wagenlehner et al. 2014).

Additionally, a urinary catheter should be applied in cases of continent urinary diversion to achieve a low pressure system: This prevents the further reflux of contaminated urine and guarantees an optimal urine drainage. If there is an insufficient therapy and ectasia of the upper urinary tract, the indication for a drainage by nephrostomy should be made without hesitation (Heyns 2012).

Urinary tract infections are caused by stress-induced reduction of immunity as a result of anesthesia, surgery, and malnutrition (Herwig et al. 2003). In addition, reflux of contaminated urine, especially in dilated ureters and kidneys, as in case of obstruction, prolonged catheterization in pouch system or ureterointestinal or neovesicourethral anastomotic stricture (Heyns 2012).

Metabolic Changes Following Cystectomy and Urinary Diversion

In addition to impaired bladder and sexual function, further specific problems may occur after radical cystectomy. Special surgical techniques as well as the use of more or less long bowel segments for urinary diversion can lead to altered pressure conditions in the urinary tract. In particular, it is important to protect the upper urinary tract from typical following complications (especially infections, reflux, urinary congestion, congestive nephropathy, gradual renal insufficiency).

Disturbances in the Acid-Base Balance

The altered physiological conditions caused by the use of intestinal segments for urinary diversion can lead to serious metabolic changes. In particular, marked changes in the acid-base balance can be seen. They are primarily dependent on the size of the intestinal segment, the contact time of urine with the intestinal mucosa, and the composition of urine (also depending on the nature of the neoreservoirs, the renal function, and the dietary habits). In addition, the changed physical requirements in the early phase of convalescence (increasing physical resilience, dynamic changes in catabolism, wound healing, extent of urinary incontinence, etc.) can lead to severe fluctuations. Metabolic acidosis is associated with ileal neobladder in the early postoperative period in more than 50% of patients and declines after 1 year to almost 20% and after 2 years to only 7% (Kim et al. 2016). There is an active, energy-consuming reabsorption of chloride ions from the urine through the intestinal mucosa of neobladders and pouches, while to a lesser extent in conduits. Protons are absorbed and/or bicarbonate is secreted to maintain electroneutrality (Fig. 15). The base excess in the context of hyperchloremic acidosis can sometimes show considerable alteration. A regular (at least weekly) blood-gas analysis should be mandatory.

A venous bicarbonate concentration below 21 mmol/l and/or a base excess of ≤ -2 mmol/l is an indication for a base substitution, e.g., with sodium bicarbonate at a dose of about one gram per mmol/l base excess. The most important side

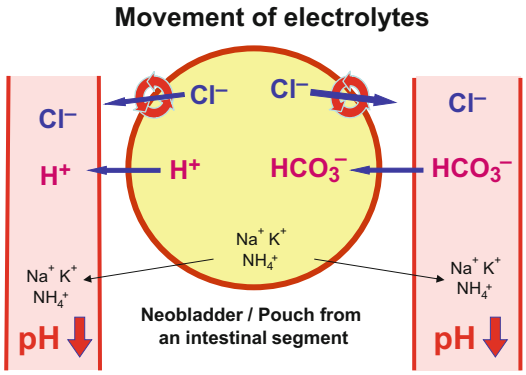

Fig. 15 Hyperchloraemic metabolic acidosis in urinary diversion using intestinal segments

effect of this base substitution is disturbing flatulence especially in higher doses. As an effective alternative, sodium citrate is available in a dose of one to three grams four times a day, and despite the poor taste, it has a good patient adherence. If a high sodium intake is to be avoided (e.g., in the case of cardiac and/or renal comorbidity), retarded nicotinic acid (500–2000 mg twice daily) or chlorpromazine (25–50 mg four times daily) must be prescribed as alternatives. The inhibition of cAMP-dependent chloride ion transport cannot compensate for a stronger form of acidosis but reduces the need for alkalizing substances. In the case of severe acidosis, compensatory hyperkalemia is also to be expected (Koch and McDougal 1985).

Malabsorption and Malnutrition

Depending on the intestinal segment which has been used for the urinary diversion, a depletion of vitamins (A, D, E, K, B12, folic acid) and electrolyte disturbances can occur during the further postoperative course. This can lead to further metabolic disorders (including vitamin deficiency, osteoporosis, renal and gallstone disorders). Actually, there is still a lack of long-term experience and comprehensive studies that deal with such questions qualitatively. Nevertheless, it should not be assumed that the necessary preoperative care about diet and sufficiently filled body stores at the time of an invasive intervention were efficiently done, and a frequently required substitution treatment should not be delayed.

Theoretically, the knowledge of the essential meaning of a "healthy way of life and nutrition" can certainly be assumed. During times of increased work pressure and occupational and private stress, industrial food production and predominant consumption of junk foods is not a health-promoting way of life with potential shortage of vital substances essential for metabolism (vitamins, minerals, trace elements, phytochemicals, essential amino, and fatty acids) together with an expected overload of carbohydrates and saturated fats. This is accompanied by an increased demand for vital nutrients within the framework of the post-aggression metabolism.

In Europe almost 30% of admitted patients have malnutrition-related disease with a range of 20–60% (Dewys et al. 1980; Norman et al. 2008; Sullivan et al. 1999). The German Hospital Malnutrition Study confirms a moderate to severe lack of nutrition in 25% of the treated cases with the highest prevalence among oncological and geriatric patients (Pirlich et al. 2006). Till now, only few data exist on the prevalence of malnutrition patients with urological diseases. A prospective analysis held by the NRS 2002 (Nutritional Risk Screening) on 897 patients with benign (49%) and malignant (51%) diseases in a urology department of a university hospital confirms a mild to moderate risk of malnutrition in 79% and a high risk in 16% of all admitted patients. Significant risk factors included age, malignancy, and type of procedure (each $p < 0.001$) (Karl et al. 2009).

The postoperative catabolic phase is characterized by release of numerous hormones and cytokines with consecutive insulin resistance of tissues and muscles. The energy supply for cell metabolism is then carried out via the degradation of body substance. Muscle proteins are degraded to amino acids and used for gluconeogenesis and synthesis of essential visceral proteins. This persistent post-aggression metabolism has a long-lasting effect up to 6 months after cystectomy, and only 63% of protein loss is compensated (Mathur et al. 2008). A moderate to high malnutrition with reduction of body cell mass and cell quality as a parameter for protein deficiency was confirmed by bioimpedance vector analysis in 63% of patients after radical cystectomy

(n = 50). A postoperatively prolonged loss of appetite leads to the risk of prolonged convalescence. The introduction of high-quality amino acids in liquid form consisting mainly of essential amino acids (the intake in liquid form is more acceptable by the patients) can lead to a significant reduction in postoperative protein loss while optimizing the body composition in obese patients (Zellner et al. 2014).

Vitamin B12 Deficiency

For the assessment of the vitamin B12 status, the determination of the total vitamin B12 concentration has only a limited meaning. Symptoms of a vitamin B12 deficiency can already be found at values within the reference range. If the methylmalonic acid is elevated at the same time, this may be a metabolic sign of an intracellular B12 deficiency which has already occurred. However, a lower methylmalonic acid level is also possible at a lower B12 concentration (Herrmann 2008).

Holo-transcobalamin as a metabolically active vitamin B12 fraction correlates well with methylmalonic acid. Within the reference range, vitamin B12 correlates well with holo-transcobalamin but less in low concentrations. For detection of a vitamin B12 deficiency, methylmalonic acid and holo-transcobalamin are more suitable, with the holo-transcobalamin being the earliest marker of a deficiency (Herrmann 2008).

With coexistent impairment of renal function, a methylmalonic acid concentration above 300 nmol/l at a holo-transcobalamin concentration below 40 pmol/l indicates a vitamin B12 deficiency, when a normalization or significant reduction of methylmalonic acid can be achieved by the substitution.

In general, the vitamin B12 deficiency develops over different stages. Hyperhomocysteinemia is known to be a risk factor for atherosclerosis, but its existence with vitamin B12 deficiency is also a sign of impaired metabolism (hypomethylation). This can be demonstrated in the molecular biology, e.g., DNA and RNA synthesis in nerve cells (myelin, phospholipids, and neurotransmitters) with consecutive development of neurological sequelae (neuropathies), e.g., funicular spinal disease (myelosis) as well as psychiatric and neurological disorders, e.g., cognitive disorders and depression. Dementia can precede the hematological anomalies for a long time (months to years).

Morphological changes in blood and bone marrow cells are among the main signs of vitamin B12 deficiency. Due to its high cell turnover rate, hematopoiesis reacts quickly and sensitively to the blocked nucleic acid metabolism. A megaloblastic anemia due to vitamin B12 deficiency develops secondary to disturbed DNA synthesis and a resulting nuclear maturation disorder, whereas the development of the cytoplasm (other cell components) is normal (Herrmann 2008).

Vitamin D Deficiency

Vitamin D deficiency results in insufficient resorption and renal reabsorption of calcium and phosphate, followed by a decrease in the serum levels of calcium and phosphate together with an increase in alkaline phosphatase. A hyperparathyroidism develops in a compensatory manner. Clinically, deficiency is manifested by characteristic symptoms of the bone (e.g., osteomalacia) and nervous system (e.g., latent or manifest tetany, frightiness, increased irritability, and nerve excitability).

Electrolyte Imbalance

Using intestinal segments for urinary diversion may lead to disorders of the electrolyte balance, especially hypokalemia, hypocalcemia, and rarely hypomagnesaemia. Hypokalemia can occur due to mucous secretion through the mucous membrane of the intestinal segment used for urinary diversion in addition to renal losses.

Chronic metabolic acidosis is continually buffered by the release of carbonates from the bone with subsequent release of bony calcium. The resulting calcium excess in the blood is compensated by increased renal excretion. Simultaneously, acidosis and sulfates lead to reduced calcium resorption. This results in the progressive development of hypocalcemia with consecutive

formation of secondary hyperparathyroidism (Kurtz 2007).

The essential biochemical functions of minerals and trace elements are predominantly on a cellular level. Therefore, what can be measured in the serum does not necessarily allow for conclusions on cellular compartments. If the distribution between blood cells and plasma is considered, potassium, magnesium, iron, zinc, and selenium are predominantly concentrated in the blood cells. Thus, for example, in the sole analysis of zinc in serum, the result represents only 10% of the total body zinc, because 90% is intracellular. In general, the assessment of a (postoperative) deficiency situation has to consider the analysis in whole blood, especially if the serum levels are in the low normal range.

Bone Metabolism After Cystectomy

The major change in bone metabolism in urinary diversions using intestinal segments is demineralization through various metabolic pathways. The chronic hyperchloremic acidosis leads to an increased activity of osteoclasts with consecutive release of minerals (calcium, carbonates, sodium) from bone buffering acidosis. In addition, acidosis leads to an increased renal activation of vitamin D, which is indispensable for regular bone mineralization.

In addition, the elimination of the resorbing function of bowel components used for urinary diversion leads to a restricted absorption of calcium and vitamin D. Patients with renal insufficiency are more susceptible to these pathological mechanisms.

Renal Function and Stone Formation After Cystectomy

The incidence of kidney stones increases in patients with intestinal urinary diversion. Compared to continent urinary diversions (neobladder and pouch), the risk of stone formation in the upper urinary tract after the formation of an intestinal conduit (ileum or colon) appears to be higher and is stated to be between 11% and 20%. After a follow-up of 20 years, kidney stones can be detected in up to 20% of patients with ileal conduit (Turk et al. 1999). At the metabolic level, hyperchloremic metabolic acidosis leads to calcium phosphate and/or calcium oxalate stones. In addition, alkaline urine with elevated concentrations of phosphate, sulfate, and magnesium, as well as low levels of citrate, can predispose to stone formation. A chronic bacterial colonization or infection, especially with urease-producing germs, can lead to the formation of struvite and/or apatite carbonate stones. The (additional) presence of foreign bodies, e.g., seam or staple material, can act as a nucleus for stone formation. Moreover, the intestinal mucus can act as a nidus for stone formation. Besides, it can be a cause for chronic infections (Van der Aa et al. 2011).

In addition to a statistically significant increase of kidney stones after ileum conduit, the follow-up shows significantly more frequent ureteral obstruction, acute and chronic pyelonephritis, and a worsening of the renal function (about 60 months postoperatively). There is no relevant difference between the colonic and the ileal conduit. Moreover, as independent risk factors of renal insufficiency postoperatively, higher age and arterial hypertension were detected (Naganuma et al. 2012).

Altered Pharmacokinetics

Numerous substances are secreted and excreted normally and unchanged into urine. In the case of intestinal urinary diversion, reabsorption of these substances carries a potential risks such as overdosis or poisoning, e.g., methotrexate poisoning in patients with ileal conduit after normal therapeutic dosage. Also other drugs such as antibiotics, phenytoin, theophylline, and lithium are known to be reabsorbed from urine through the intestinal segments. The general clinical significance of these processes is also difficult to be determined due to the individually different absorption characteristics of the ileum. However, in individual cases, the indication of a dose adjustment should always be checked, especially for drugs with a low therapeutic range and potentially toxic substances. Particularly in urine reservoirs, a permanent urinary catheter should be indicated whenever chemotherapy is required (Van der Aa et al. 2011).

Disturbances of Intestinal Function After Cystectomy

Short Bowel Syndrome

Recurrent diarrhea after urinary diversions should be assessed to exclude short bowel syndrome. This can be due to a number of pathomechanisms. Reabsorption of bile acids takes place mainly in the terminal ileum. The larger the length of the intestinal segment used, the more nonabsorbed bile acids can pass into the intestine and produce a secretory diarrhea. In addition, an accelerated intestinal transit time can lead to an incomplete absorption of nutrients, which can bind water and lead to osmotic diarrhea.

The decreased absorption of electrolytes and water in the ileum can also play a role in developing diarrhea (secretory diarrhea).

Bile acids are used for fat digestion and absorption. They are synthesized in liver and reabsorbed up to 85–95% in the terminal ileum (enterohepatic circulation). Non-resorbed bile acids are excreted. Following a resection of about 60 cm of ileum, a bile acid loss syndrome may occur. If this loss could not be compensated for by liver synthesis, a malabsorption of fats with consecutive steatorrhoea occurs. Direct irritation of the colon can also induce irritative diarrhea.

As a further consequence, the lithogenicity of the biliary fluid for cholesterol stones increases. Therapeutic success can be achieved with the use of bile acid-binding substances, e.g., cholestyramine in a dose individually adjusted (maximum 12 g daily) and, whenever appropriate, intestinal motility-reducing drugs, e.g., loperamide.

It should be kept in mind that in addition to the loss of the reabsorbing surface of the intestine, a long-term and/or higher dosage of cholestyramine can trigger or amplify deficiency of fat-soluble vitamins (A, D, E, K).

If you lose Bauhin's valve, the risk of diarrhea increases. In addition, an overgrowth of anaerobic organisms of the small intestine can occur, which can disrupt the lipid solubility and contribute to a bacterial malabsorption syndrome by deconjugating bile salts and metabolizing them via a disturbed micelle formation. In the case of a massive bacterial colonization, the binding of the vitamin B12-intrinsic factor complex will further disrupt the vitamin B12 reabsorption.

Intestinal Hypomotility and Paralytic Ileus

It is not uncommon to experience disturbances in the intestinal motility during the first few weeks postoperatively secondary to cystectomy and interruption of intestinal continuity. By intensive manual colonic massage, which should be initiated in the rehabilitation phase, symptoms of subileus or ileus can usually be safely avoided. If necessary, after the exclusion of a mechanical cause, administration of cholinergic stimulants, e.g., 2 mg neostigmine s.c., can achieve a rapid relief. Expected cholinergic side effects are mainly abdominal pain or cramps and hypersalivation. Bradycardia and syncope are rarely observed (antidote atropine) and can be avoided by bed rest for a few hours after application.

Mucous Formation Within Intestinal Reservoirs

In case of excessive mucous formation and recurrent retention especially with neobladder or pouch, regular wash should be indicated using sterile saline solution (strictly sterile, low pressure to avoid reflux of contaminated urine), possibly with 20% N-acetylcysteine solution. The oral administration of acetylcysteine is rendered ineffective (N'Dow et al. 2001). Through the intramuscular administration of 20 mg of long-acting octreoid (a synthetic somatostatin analogue) preoperatively for 4 weeks and on the day of surgery, postoperative mucous production could be dramatically reduced (Khorrami et al. 2017). Experiences about the efficacy in the long-term application and on dosage intervals are not yet available.

Osmolarity Equilibrium in Intestinal Urinary Reservoirs

The pathophysiologic characteristics of intestinal urine reservoirs also influence osmolarity equilibrium of concentrated urine.

In intestinal lumen and therefore in neobladder or pouch lumen, there cannot be an osmolarity of more than approx. 380 mOsmol/l in comparison

to serum (approx. 280 mOsm/l), because the intestinal wall is not able to withstand an osmolarity gradient of more than 100 mOsmol/l. Due to urine concentrations of more than 1000 mOsmol/l, there is secretion of free water through the mucous membrane of the urine reservoir. Especially in elderly people with reduced sensation of thirst, there is a risk of dehydration due to the increased liquid excretion. Therefore, training to achieve a balanced fluid balance during urinary diversion after radical cystectomy is mandatory.

Disturbance of Lymphatic Flow after Pelvic Lymphadenectomy

Due to frequent lymphadenectomy in the area of the small pelvis in bladder tumor operations, an interruption of continuity of lymphatic system is inevitable. Consequences include disturbed lymph drainage and lymphedema of the lower extremities as well as lymphocele in the area of the resected lymph nodes with potential restriction to venous drainage and increased risk of thromboembolism.

Lymph is a capillary ultrafiltrate and has essential transport tasks, e.g., transport of interstitially formed proteins derived from the degradation of body cells and microorganisms. The circulation of immunologically active cells between the blood and interstitium and via lymph system back into the bloodstream is one of the fundamental immunological processes in the human body. A smaller part of the lymphocytic cell load is caused by pathogens and cancer cells, which in the lymph nodes lead to the activation of the immune response and, in the best case, to their elimination.

Regarding the physiological importance of the lymphatic system, consistent prophylaxis of disturbed lymph drainage is of utmost importance to maintain normal tissue function and avoid chronic tissue damage.

Lymphoedema Following Pelvic Lymphadenectomy

Interruption of the continuity of lymphatics in lymphadenectomy is the most frequent cause of a secondary (acquired) lymphedema in the western world. Clinical appearance of lymphatic drainage disorder can be classified to a latency stage (disturbances without morphologically visible changes, reversible), stage I (stasis without morphological tissue alteration, reversible), and stage II and stage III (progressive signs of chronic congestion such as fibrosclerosis and papillomatosis, potentially reversible with therapy (stage II) or irreversible (stage III)). The latency stage is most common after pelvic lymphadenectomy, followed by the completely reversible stage I. The primary goal of the therapeutic lymphatic drainage treatment is to prevent manifest edema or the transition to chronic, irreversible forms.

The backbone of the therapy (collectively referred to as complex physical decongestive therapy) includes manual and apparatus lymphatic drainage, physical exercises, respiratory therapy, compression therapy, as well as skin and foot care to avoid complicating infections (e.g., erysipelas) (Kovnerystyy et al. 2006).

Manual Lymphatic Drainage

Manual lymph drainage uses, for example, dorsal grip techniques on the lower limb from the distal to the proximal or the thigh back to the presacral lymph nodes, deep abdominal as well as the lateral abdominal and thoracic wall in the direction of the axilla (Fig. 16).

Device-Assisted Lymphatic Drainage with Positive Pressure

In this form of lymphatic drainage of the legs, trouser-like, cramped leg cuffs including the pelvic region are used. The cuffs are recurrently filled from distal to proximal by a compressor, thus mechanically enhancing lymphatic drainage from distal to proximal (Fig. 17).

Device-Assisted Lymphatic Drainage with Intermittent Negative Pressure

By applying intermittent negative pressure in a vacuum chamber, not only the arterial and venous flow but also the lymphatic effusion can be optimized. In the case of intermittent vacuum therapy (IVT), the lower body till a point slightly above the umbilicus is located in a vacuum chamber

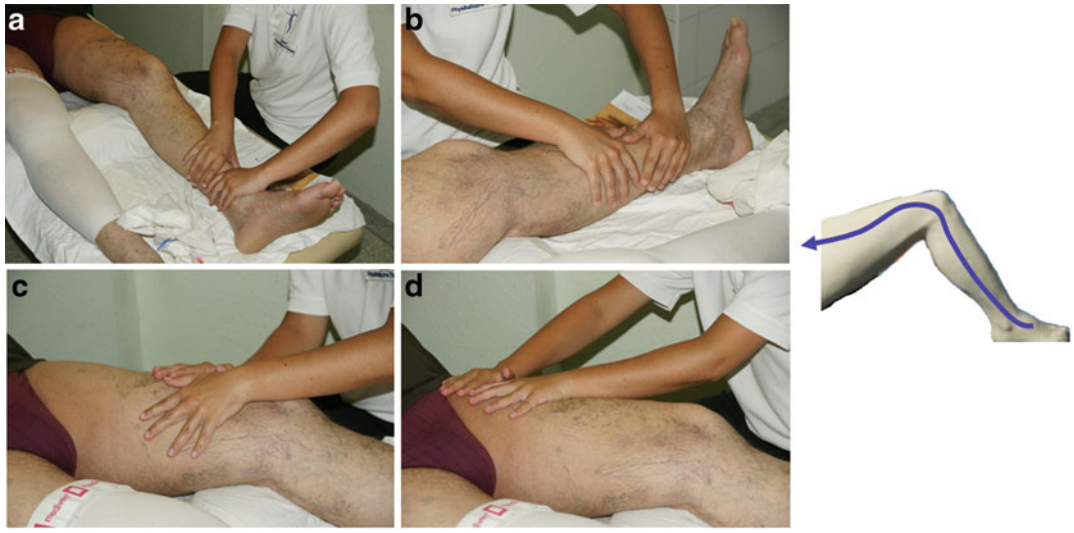

Fig. 16 Manual lymph drainage (a→d) of the lower extremity

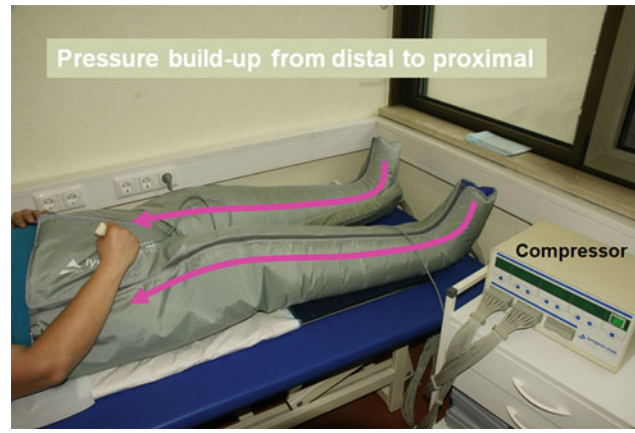

Fig. 17 Lymph drainage using positive pressure device

sealed by iris diaphragm (Fig. 18). The preselected negative pressure (−20 mbar) and atmospheric pressure repeatedly change in the chamber in defined time intervals. Compared to manual lymphatic drainage and positive pressure treatment, a further improvement of the lymphatic drainage could be demonstrated by follow-up of the size reduction of postoperative inguinal lymphoceles (Zellner 2015).

Compression Bandages

In manifest lymphedema, lymphatic drainage is supplemented by compression bandages and in the case of leg edema by compression stockings. By reducing the formation of lymphatic ultrafiltrates, edema formation is prevented or reduced. Simultaneous improvement of the vasomotor property of the lymph vessels stimulates the lymphatic drainage (Herpetz 2010).

Home Exercises for Lymphatic Drainage

During rehabilitation, the patient should be taught exercises for the decongesting movement therapy, which are consistently continued at home. In doing so, on the one hand, muscle-compressing has an effect on lymph vessels and veins, especially the deep lymph system, and on the other hand, by excitation of the lymphatic vasomotor

Fig. 18 Lymph drainage using intermittent negative pressure device

system, the lymphatic drainage is exploited by utilizing the gravitational force when the legs are raised. The sessions begin with the supraclavicular lymph nodes, with simultaneous slow, deep breathing, to evacuate the thoracic duct. The lymphatic drainage from the lumbar and iliac lymphatics, as well as the cisterna chyli, is promoted by deep breathing against the hands, which are pressed broadly against the abdomen. This is followed by activation of the muscle groups in the legs. The simultaneous complementary techniques of respiratory therapy also promote lymphatic drainage from the lower extremities by recurrent intrathoracic pressure changes.

Lymphoceles After Pelvic Lymphadenectomy

While undergoing pelvic lymphadenectomy, it is not possible to ligate all lymph vessels which can lead to accumulation of lymphatic fluid in the retroperitoneum with a surrounding pseudo capsule (lymphoceles). This occurs due to low coagulability of lymph fluid and absence of spontaneous closure. The incidence of lymphoceles after pelvic lymphadenectomy is reported in the literature with a wide range between one and 58% (Weinberger et al. 2014).

Symptomatic lymphocele is recorded in 5–18%. They can manifest as pelvic pain, leg edema, gastrointestinal obstruction, obstructive uropathy, and deep venous thrombosis. They can be complicated through infections to septic progression and the formation of lymphatic fistulae (Tinelli et al. 2013).

An important goal of rehabilitation is to prevent the development or progression of an existing lymphocele and to promote its reduction, eventually preventing invasive interventions (drainage, sclerotherapy, or laparoscopic intervention) by means of intensive lymphatic drainage therapy. Accordingly by manual and instrumental lymph drainage, the volume of inguinal lymphoceles can be reduced by 32% and by even 40% with accompanying IVT, and thus invasive intervention can be avoided in many cases (Zellner 2015).

The absolute indications for intervention include compression of the inguinal venous system with detection of venous drainage disturbance and/or deep venous thrombosis in venous Doppler as well as infected lymphoceles.

Complications of Urethral Anastomosis

The scarring of the (neo)vesicourethral anastomosis leads to weakening of the urine stream, dysuria, and occasionally increased residual urinary volume with an incidence up to 30% after prostatectomy or cystectomy. If an anastomotic stricture is diagnosed during the repeated screening using uroflowmetry and measuring sonographic

residual urinary volume, an attempt can be made to eliminate the infravesical obstruction by a single gentle catheter dilatation under local anesthesia. Because of a frequently accompanying recurrence following this kind of tissue trauma, the majority of surgeons already recommend a primary transurethral anastomotic slit in the original hospital.

Psychological Rehabilitation

After the diagnosis of a tumor disease, in addition to the primary traumatization by the diagnosis "cancer," there is a long-lasting fear of recurrences or metastases. But also, the disturbance following a changed body figure (stoma!) and the impairment of body functions (e.g., bladder dysfunction, erectile potency) are particularly stressful factors. The medical and psychological care must therefore be guided by the following frequently mentioned factors:

- Fear of pain, helplessness, and disability
- Fear of not being able to support the family
- Fear of serious disturbances in partnership and friendships
- Inferiority and embarrassment
- Increasing nervousness, tension, and sleep disorders
- Loss of sense and target perspectives

In this context, a substantial relief and help in the processing of the illness can be offered to the patient with detailed expert and competent interviews, as well as group discussions with persons with the same interests under expert guidance (doctor, psychooncologist). Relaxation techniques (e.g., autogenous training, Feldenkrais method) supplemented by modern device relaxation methods based on biofeedback principle (e.g., by derivation and immediate feedback of vegetative parameters, e.g., skin conduction value, forehead EMG, skin temperature during the apparatus-guided therapy units) provide essential assistance in the management of disease.

Informing the patient about disease-specific self-help groups and psychosocial counseling centers of oncological societies gives the patient more sense of security when discharged from rehabilitation center especially if new or urgent questions arise, especially in everyday problems (Zellner et al. 2008).

Social Counseling and Professional Rehabilitation

As a rule, a number of sociomedical problems arise with a tumor disease. Therefore, frequent consultations may be needed:

- Information on the possibilities of getting help from social service
- Practical assistance in dealing with authorities (severely handicapped, recognition of additional disabilities)
- Advice about severely handicapped persons (protection of rights, tax advantages)
- Questions on social insurances (health insurance, pension allowances, employment services)
- Care and household issues (housing allowance, social assistance)
- Problems at the workplace

A physician should undergo a careful assessment of the nature of work at the workplace. Restrictions, disabilities, and preventive measures must be communicated according to the specific circumstances. This includes all questions about professional adaptation, further training and possible retraining. The cooperation between the clinical social service during rehabilitation and the working physician should be established as early as possible (Zellner et al. 2008).

Social Medical Assessment

Physical disabilities that result from tumor disease and all therapeutic measures are of a great meaning to cancer patient. Especially in the case of

ongoing treatment measures, patients are unable to work for a long time.

It should be emphasized that the diagnosis of a cancer alone is not equivalent to complete relief from duty. Also, the prognostic facts of a tumor disease that are precisely collected medically are not important for the duration of a performance limitation and the success prospects of rehabilitation measures. The sociomedical assessment must be based on the "actual state" and not on the prognosis criteria.

In addition to the tumor disease or possible therapy success, some particular secondary diseases or comorbidities are decisive for the limitation of the performance. For sociomedical assessment, not individual limitations, but the overall performance must be determined.

For the self-esteem of the affected, their philosophy of life, and promotion of social contacts, occupational practice is of great importance.

Since time-limited pension is often not welcomed by employers and results in a termination of the employment relationship, these aspects are of central importance in an assessment.

When assessing performance, quantitative and qualitative performance as well as possible forms of work organization must be considered.

Quantitative performance (full time/part time/inable to work) must be assessed by the medical expert as a function of physical and psychological performance. With respect to the work organization, tumor patients are generally not restricted in their ability to work in a single night shift. At least the number of consecutive night shifts should be as minimal as possible in order to prevent the negative influences of chronodisruption, e.g., on immune system and repair procedures of the genome.

Piecework is only possible in teams with a representative regulation, by means of which patient is given the option to exceptionally go to toilets, e.g., in the presence of urge syndrome or for hygiene purpose and catheterization.

Limitations regarding the qualitative performance are expected in patients after radical surgical therapy of urothelial carcinoma, e.g., from the possible incontinence, from restrictions on the physical resilience as a function of the urinary diversion, as well as from restrictions on renal function and possibly postoperative lymphedema.

In the case of urinary diversions, care must be taken that the stress in the workplace does not lead to damage, e.g., stomaprolapse, parastomal hernia, or descent with consecutive emptying problems (e.g., residual urine due to urethral kinking) by increased intra-abdominal pressure during lifting and carrying loads. Thus, after the establishment of an ileal conduit, only slight activities are allowed (lifting and carrying weights of up to 10 kg). After neobladder or pouching, weights of less than 15 kg are possible.

In the case of "continent urinary diversions," a weight-dependent urinary incontinence must be considered during the assessment. Because all patients with urinary diversion are limited in carrying and lifting weights – as shown before – in this term activities that require continuous standing should be considered. In addition, full access to sanitary facilities must be ensured.

In case of ureteral urinary obstruction after cystectomy or loss of kidney after nephro(ureter)ectomy with consecutive reduction of nephron mass, activities with risk of falling, infection, and exposure to potentially nephrotoxic substances should be avoided in order to prevent further deterioration of renal function due to traumatic, infection-related, or toxic damage.

Ability to work in case of lymphedema after lymphadenectomy is stage dependent. In stage I lymphedema, the performance is rarely affected. Activities in a continuous standing posture should be avoided, as well as risk of contamination (to avoid possibly complicating superinfections in the sense of erysipelas) or work in high temperatures.

In stage II, light to medium activities are possible; hot workplaces as well as activities with smudge exposure should be avoided.

In the case of resistant lymphoedema in stage III, performance is severely restricted due to markedly increased risk of infection in case of minor injuries and possible pain.

The limitations of disease, including work restrictions, lead to development of worries

about occupational competency and financial security.

For this reason, not only the assessment and the elucidation of illness-related restrictions are important, but also competent information about possibilities for compensation of illness and disability regulated by social law (e.g., restructuring of the workplace, career change) should be part of qualified medical rehabilitation (Zellner et al. 2008).

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Follow-Up of Bladder Cancer

30

Helena Bock and Stephan Madersbacher

Contents

Abstract

The follow-up scheme of bladder cancer represents a balance between invasiveness, costs, and the risk of delaying a high-grade non-muscle-invasive/muscle-invasive tumor in the case of non-muscle-invasive bladder cancer (NMIBC) and of early detection of local and/or distant recurrence in muscle-invasive disease (MIBC). All recommendations are largely based on retrospective data analysis; prospective studies to determine, e.g., the frequency of control cystoscopies and imaging are lacking. The follow-up scheme of NMIBC is driven by the risk group and of MIBC regarding the risk for local or distant metastases and of a recurrence in the upper urinary tract. More than 50% of all recurrences being detected are symptomatic; therefore a lifelong follow-up in asymptomatic patients is a matter of debate. Following radical cystectomy, follow-up should also include functional and metabolic aspects. The recommendations presented herein are primarily based on the recent guidelines of European Association of Urology *(EAU)*. The guidelines compliance in daily practice regarding follow-up of bladder cancer remains low.

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Non-muscle-Invasive Bladder Cancer

The high recurrence rate, the intense follow-up, and the potential need for, e.g., intravesical instillation therapy or radical cystectomy/trimodal therapy in the case of progression/muscle-invasive disease make bladder cancer one of the most expensive tumor entities. Therefore, the issue of follow-up is also a socioeconomical one.

The follow-up scheme of non-muscle-invasive bladder cancer (NMIBC) is based on cystoscopy and – depending on the risk group – on urine cytology and upper urinary tract imaging. Despite intensive research within the past two decades, no technique (including molecular urine marker) can currently supplement cystoscopy and urine cytology.

The main goal of the follow-up of NMIBC is to detect a progression to muscle-invasive disease or recurrent high-grade NMIBC as early as possible because a delay in diagnosis is associated with a worse oncological outcome. For low-risk recurrences, however, a successful therapy and even cure is not necessarily linked to early identification (Borhan et al. 2003; Fujii et al. 2003; Gofrit et al. 2006; Holmäng et al. 2001; Soloway et al. 2003). Hence, the optimal follow-up scheme is largely dependent on whether the initial diagnosis was a low-risk or an intermediate-/high-risk tumor.

All NMIBC have to undergo a control cystoscopy 3 months after the initial diagnosis. The findings of this cystoscopy are important predictors for the risk of future progression and recurrence (Gofrit et al. 2006; Holmäng et al. 2002; Palou et al. 2009; Power and Izawa 2016; Solsona et al. 2000).

Low-Risk NMIBC

The first control cystoscopy should be performed 3 months after the initial resection, thereafter another one 12 months after diagnosis. For the next 5 years, yearly cystoscopies should be obtained. Because of the low risk of recurrence 5 years after diagnosis, follow-up visits and control cystoscopies are no longer indicated. No upper urinary tract imaging is recommended for low-risk NMIBC (Mariappan et al. 2005).

High-Risk NMIBC

For the first 2 years, all patients should undergo a cystoscopy and urine cytology at 3-month intervals, thereafter at 6-month intervals for further 3 years. After 5 years, cystoscopy and urine cytology should be obtained annually. Because at 10 years after initial diagnosis recurrence is not uncommon, lifelong control visits are indicated beyond this time point. Upper urinary tract imaging should be considered at 1–2-year intervals preferentially by contrast CT scans including urography.

Muscle-Invasive Bladder Cancer

The optimal follow-up scheme for MIBC needs to incorporate the following aspects: overall risk of disease recurrence, timing of the recurrence, risk for local and/or distant metastases, risk for an upper urinary tract and/or urethral recurrence, and functional and metabolic consequences of the type of urinary diversion chosen.

Local Recurrence

A local recurrence after radical cystectomy comprises a soft tissue recurrence in the resection area or a lymph node recurrence in the area of the previous lymphadenectomy. The risk of a local recurrence following radical cystectomy is in the range of 5–15% and usually occurs within the first 2 years after surgery, in most cases within the first 6–18 months.

Risk factors for the development of a local recurrence are advanced local tumor stage at cystectomy, positive surgical margin, and positive pelvic lymph nodes. The prognosis of patients with a local recurrence is dismal (Mathers et al. 2008). Despite chemotherapy, radiotherapy, and surgical interventions, the median survival in these patients ranges between 4 and 8 months (Gofrit et al. 2006).

Urethral recurrence: the incidence of urethral recurrences in men is in the range of 1.5–6% and in women in 0.9%–4.0% following orthotopic bladder substitution and 6.4–11.1% following heterotopic bladder substitution. Urethral recurrences occur usually within the first 3 years after radical cystectomy. Prophylactic urethrectomy is no longer recommended in most patients. Independent predictors for urethral recurrence are cystectomy for NMIBC, prostate involvement, and a history for recurrent NMIBC. In women, the main risk factor is bladder neck disease (Gofrit et al. 2006).

There is little agreement on the follow-up, with some recommending routine surveillance with urethral wash and urine cytology, while others doubt on this approach. Urethral washes and urine cytology do not appear to affect survival. In men, however, there is a significant survival advantage if the urethra is detected asymptomatically versus symptomatically. Therefore, routine urethral follow-up seems to be justified in men with a high risk of urethral recurrence (e.g. in those with carcinoma in situ (Cis) in the blasser and particularly in the prostatic urethra).

Upper urinary tract urethral carcinomas (UTUC): UTUC occur in 1.8–6.0% of cases and represent the most common site for late recurrences (Gofrit et al. 2006). Median overall survival of affected patients is 10–55 months, and 60–67% of patients die of metastatic disease. A recent meta-analysis noted that 38% of UTUC recurrences were detected by routine follow-up, whereas in the remaining 62% because of symptoms (hematuria, pain). Multifocality increased the risk of UTUC threefold, while positive surgical ureteral or urethral margins increased the risk sevenfold. Radical nephroureterectomy can prolong survival (Sanderson et al. 2007).

Distant Recurrences

Up to 50% of patients develop distant metastases after radical cystectomy, in pT3/pT4 tumors this percentage lies between 32 and 62%, and in those with positive lymph nodes, the risk further increases to 52–70%. Almost 90% of all distant metastases (extra pelvic lymph nodes, liver, bone, and lung) occur within the first 3 years after radical cystectomy. Despite regular follow-up more than 50% of distant recurrences are detected because of symptoms; hence the rationale for a close follow-up in asymptomatic patients remains controversial (Cagiannos et al. 2009; Mathers et al. 2008; Vrooman et al. 2010). Some studies have demonstrated no impact on survival despite routine monitoring; others have shown that early detection improves survival (e.g., lung metastases) (Giannarini et al. 2010; Volkmer et al. 2009).

Although general recommendations are not based on a high level of evidence, a closer follow-up could be considered in patients with locally advanced disease or positive lymph nodes. The suggested follow-up includes imaging of the chest, the upper urinary tract, the abdomen, and the pelvis at 3–6-month intervals, thereafter as clinically indicated. In the case of bladder preservation, cystoscopy and urine cytology with selected bladder mapping should be performed at 3–6-month intervals for 2 years, thereafter as clinically indicated.

Urethral wash cytology is recommended in patients with Cis within the bladder and – particularly – within the prostatic urethra.

Follow-Up of Functional Outcomes and Complications

Apart from oncological surveillance, patients who received a urinary diversion deserve also a functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first 5 years after surgery; this rate further increases over time (Soukup et al. 2012). The functional complications are diverse and include vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infection, urolithiasis, stenosis of ureteral-intestinal anastomosis, stoma complications in patients with ileal conduits, and neobladder continence and emptying problems (Soukup et al. 2012). In women, two-thirds need to catheterize their orthotopic bladder substitutes, while almost 45% do not void their bladder substitutes spontaneously at

all. More recently, also a 21% increased risk of fractures was described as compared to no cystectomy, due to chronic metabolic acidosis and subsequent long-term bone loss (Gupta et al. 2014).

Therefore, liver- and renal function tests and serum electrolytes should be quantified at 3–6 month intervals for 2 years and thereafter as clinically indicated. If a continent urinary reservoir was created, the patient should be monitored for Vitamin B12 deficiency annually.

Follow-Up After Chemotherapy: Cardiovascular Aspects

Platinum-based chemotherapy (cisplatin, carboplatin) represents the first-line chemotherapy for transitional cell cancer in both the neoadjuvant and adjuvant setting. These substances harbor cardiovascular toxicity including acute coronary syndrome, angina pectoris, myocardial infarction, arterial thromboembolic events, cerebrovascular events, and pulmonary emboli.

In retrospective studies the risk for thromboembolic event in bladder cancer patients receiving cisplatin/carboplatin was in the range of 13–20%. The long-term risk is largely unknown (Gupta et al. 2016).

Bladder cancer is a tumor of the elderly, and many patients with advanced/metastatic bladder cancer have cardiovascular comorbidities and risk factors. There is a need to identify risk factors for developing cardiovascular events and to develop strategies to reduce risk of cardiovascular events during/after chemotherapy. In any case, the follow-up of these patients should also comprise cardiovascular and thromboembolic complications.

Adherence to Follow-Up Guidelines

There are considerable concerns that practice patterns in patients with bladder cancer deviate substantially from guideline recommendations. Chamie et al. analyzed this issue based on a SEER database for patients with high-grade NMIBC. Of the 4545 patients, only one received all the recommended measures (routine cystoscopy, cytology, upper urinary tract imaging). Approximately 42% of physicians have not performed at least one cystoscopy, one cytology, and one instillation of immunotherapy for a single patient nested to their practice (Chamie et al. 2011). Ehdaie et al. investigated the same issue in 3757 patients following radical cystectomy – again – based on the SEER database. Adherence to all recommended investigations was only 17% for the first and the second year. Among patients surviving 2 years, only 9% had a complete surveillance over this time period (Ehdaie et al. 2014). Both studies demonstrate that practice patterns deviate considerably from the respective guideline recommendations. Guideline adherence seems to be correlated to surgical volume. These data suggest an important opportunity for quality improvement in bladder cancer care by a higher penetration of follow-up guidelines in daily practice.

Conclusions

In a recent review, Power and Izawa reviewed the guidelines on non-muscle-invasive bladder cancer, including recommendations of EAU, CUA, AUA, NCCN, and NICE (Power and Izawa 2016). The authors concluded that these guidelines provide considerable consensus regarding disease management. Regarding follow-up the authors state that – despite the fact that there is no high-level evidence to support definitive recommendations on specific follow-up schedules – all guidelines recommend comparable schedules including cystoscopy/cytology and upper urinary tract imaging in high-grade NMIBC every 1-2 years (Figs. 1 and 2). Guidelines compliance in daily practise remains low; strategies are required to further enhance their acceptance/implemantation.

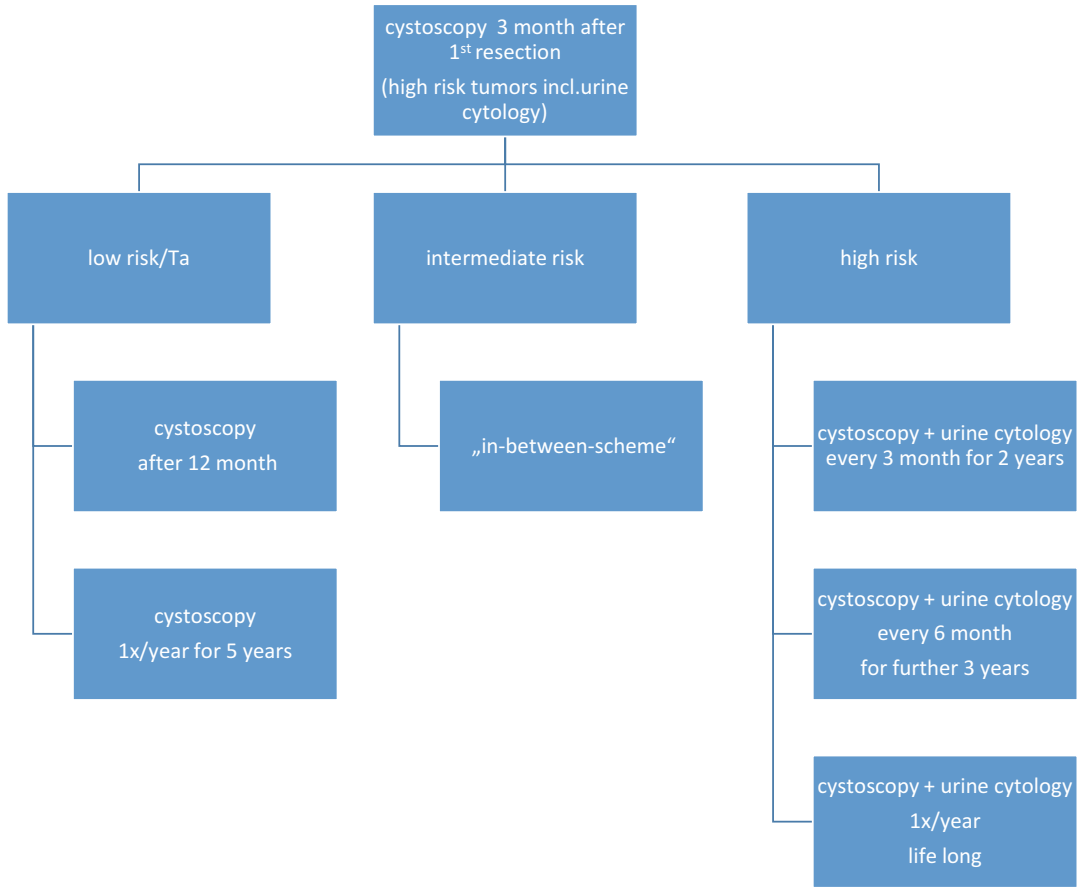

Fig. 1 Follow-up scheme of non-muscle-invasive bladder cancer

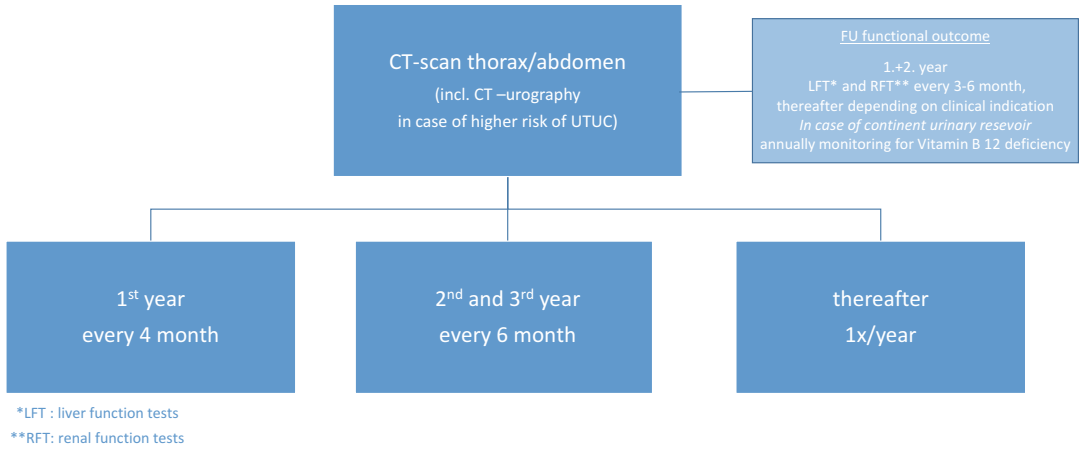

Fig. 2 Follow-up scheme of muscle-invasive bladder cancer

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Part IV

Renal Cancer

Epidemiology of Renal Cell Carcinoma and Its Predisposing Risk Factors

31

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Contents

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Abstract

A more complete picture of the epidemiology and risk factors for developing renal cell carcinoma (RCC) is rapidly emerging at the confluence of the seemingly disparate fields of toxicology, epidemiology, pathology, pharmacology, information technology, genomic medicine, and clinical oncology. The Cancer Genome Atlas (TCGA) of the National Cancer Institute and the National Human Genome Research Institute of the United States was launched in 2005. The primary goal for constructing the Cancer Genome Atlas was to provide researchers with comprehensive catalogs of the key genomic changes that occur in many major types and subtypes of cancer in order to accelerate advances in developing more effective ways to diagnose, treat, and prevent cancer. The collection of samples is complete for the three most common forms of RCC: clear cell, papillary, and chromophobe. Extensive amounts of data are now publicly available via the Data Portal for the Genomic Data Commons (GDC). In addition, in 2011, the International Agency for Research on Cancer (IARC), a division of the World Health Organization (WHO) of the United Nations, published an updated monograph in an extended series on human

carcinogens and preventable exposures associated with human cancers. Subsequently, the IARC also published an update of the classification of renal tumors in 2016 based, in large part, on an extensive review of the literature that was conducted by the International Society of Urological Pathology (ISUP). Furthermore, multiple, large-scale epidemiologic studies and meta-analyses have helped to clarify the magnitude of the impact of certain predisposing risk factors for developing RCC including poorly understood and poorly appreciated differences in racial predisposition for the common histologic subtypes. The goal of this chapter is to present an update of these wide-ranging findings in a way that is well documented and easily understood.

Introduction

Cancers of the kidney are generally referred to as renal cell carcinomas (RCCs); however, this term is not specific as it encompasses a number of histologic subtypes. Historically, kidney cancers were referred to as "hypernephromas," a term that can be traced back to the German pathologist, Paul Grawitz, who first proposed a theory in 1883 that these tumors originate in the adrenal gland and not the kidney (Delahunt *knowledge hub*). Though this theory was eventually proven to be incorrect, it illustrates the historical perspective of defining pathology exclusively on the basis of a specified tissue of origin. This can be particularly valuable when tumors arise in contiguous anatomic structures such as the adrenal gland, the kidney, and the renal pelvis. However, it is important to bear in mind that tumors of the kidney are not always malignant and that malignant tumors may be derived from different histologic structures within the kidney such as the cortex, the medulla, or the collecting ducts. Mixed histologic subtypes may also occur. Of note, cancers of the renal pelvis are typically of urothelial origin making them similar to bladder cancer but unrelated to RCC. Since kidneys are paired organs, tumors may arise in one or the other or in both, either simultaneously or sequentially. Furthermore, some patients have a genetic predisposition to developing RCC though most do not. If no germline mutations can be found, as is usually the case, the tumor is classified as "sporadic." Even when specific risk factors and molecular pathways have been identified for carcinogenesis in sporadic RCC, it is not clear why these cancers develop in some patients, but not in others who have similar risk profiles. Sporadic tumor types that are commonly seen in adults are rarely seen in children and vice versa. In addition, the proportional distribution of histologic subtypes among African-American adults is distinct from that of Caucasians to a degree that is clinically meaningful (Olshan et al. 2013). These are just some of the challenges investigators must face when they attempt to organize this vast array of information into protocols and guidelines that are useful and user-friendly for everyone involved in the care of patients with RCC. Data published in recent years have helped to more clearly define the lifestyles, medical conditions, and environmental exposures that increase the risk of developing sporadic forms of RCC.

The fourth edition of the World Health Organization (WHO) classification of urogenital tumors, the "WHO blue book," was published in 2016 (Moch et al. 2016). New findings with respect to the molecular and cellular interactions that define malignant behavior were reviewed and incorporated with an appreciation for the presence of a spectrum of genetically heterogeneous clones within the primary tumor as well as metastatic sites. Though standards for quantifying changes in mutational status over time were not specifically addressed, behavior codes were added with the goal of systematically conveying the malignant potential of each entity. As summarized in Table 1, this system identifies 16 types of renal cell tumors in adults. Two of these entities are benign as reflected in the behavior code of "/0" (papillary adenoma and oncocytoma). Two others were assigned a behavior code of "/1" indicating that they have low malignant potential (multilocular cystic renal neoplasm of low malignant potential and clear cell papillary RCC). The remaining 12 tumor types received a malignant designation

Table 1 The 2016 World Health Organization classification of tumors of the kidney

Renal cell tumors	**Codes**
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1*
Papillary renal cell carcinoma	8260/3
Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma	8311/3
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3*
MiT family translocation renal cell carcinomas	8311/3*
Succinate dehydrogenase-deficient renal cell carcinoma	8311/3
Mucinous tubular and spindle cell carcinoma	8480/3*
Tubulocystic renal cell carcinoma	8316/3*
Acquired cystic disease-associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8260/0
Metanephric tumors	–
Metanephric adenoma	8325/0
Metanephric adenofibroma	9013/0
Metanephric stromal tumor	8935/1
Nephroblastic and cystic tumors occurring mainly in children	–
Nephrogenic rests	–
Nephroblastoma	8960/3
Cystic partially differentiated nephroblastoma	8959/1
Pediatric cystic nephroma	8959/0
Mesenchymal tumors	–
Mesenchymal tumors occurring mainly in children	–
Clear cell sarcoma	8964/3
Rhabdoid tumor	8963/3
Congenital mesoblastic nephroma	8960/1
Ossifying renal tumor of infancy	8967/0
Mesenchymal tumors occurring mainly in adults	–
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Synovial sarcoma	9040/3
Ewing sarcoma	9364/3
Angiomyolipoma	8860/0
Epithelioid angiomyolipoma	8860/1*
Leiomyoma	8890/0
Hemangioma	9120/0
Lymphangioma	9170/0
Hemangioblastoma	9161/1
Juxtaglomerular cell tumor	8361/0
Renomedullary interstitial cell tumor	8966/0
Schwannoma	9560/0
Solidarity fibrous tumor	8815/1
Mixed epithelial and stromal tumor family	–
Cystic nephroma	8959/0
Mixed epithelial and stromal tumor	8959/0
Neuroendocrine tumors	–
Well-differentiated neuroendocrine tumor	8240/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Pheochromocytoma	8700/0
Miscellaneous tumors	–
Renal hematologic neoplasms	–
Germ cell tumors	–
Metastatic tumors	–

(*continued*)

Table 1 (continued)

* New morphology codes that were approved by the Committee for the International Classification of Diseases for Oncology (ICD-O) of the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO)

with a behavior code of "/3." Four of these malignant tumors were reported as new entities including renal medullary carcinoma, MiT family translocation RCCs, mucinous tubular and spindle cell carcinoma, and tubulocystic RCC.

The updated WHO classification system also lists other neoplasms of the kidney as shown in Table 1 under the following categories: metanephric tumors (3 types), nephroblastic and cystic tumors occurring mainly in children (4 types), mesenchymal tumors occurring mainly in children (4 types), mesenchymal tumors occurring mainly in adults (16 types), mixed epithelioid and stromal tumor family (2 types), neuroendocrine tumors (4 types), miscellaneous tumors (2 types), and metastatic tumors. The remainder of this chapter will be dedicated to a review of the 12 types of tumors in the renal cell tumors category that exhibit malignant behavior in adults with an emphasis on the three most common histologic subtypes: clear cell, papillary, and chromophobe.

Incidence and Mortality

It is estimated that there will be 63,990 new cases of kidney and renal pelvis cancer in the United States in 2017 as well as 14,400 deaths (Siegel et al. 2017). The incidence of RCC has rapidly increased for more than 20 years as computerized tomography and other imaging modalities have become widely accessible (National Cancer Institute 2014). Internationally, cancer incidence and mortality estimates were reported in 2012 for 25 cancers in the 40 countries of the four United Nations-defined areas of Europe and for the European Union (EU-27) (Ferlay et al. 2013). A total of 115,200 new cases of cancer of the kidney, renal pelvis, and ureter were reported in these countries. Of note, these three cancers are considered to be a single cancer site in tumor registries. The kidney was the seventh most common cancer site with respect to the number of new cases and eighth in terms of age-standardized rates per 100,000 in the population. A total of 49,000 deaths were reported with an age-standardized rate of 4.7 per 100,000 for mortality. International trends generally show an increase in incidence for RCC though trends for decreases in mortality appear to vary geographically (Znaor et al. 2015).

Age and Gender

Sporadic RCC is typically seen in older patients with a median age at the time of diagnosis of 64. RCC is uncommon under the age of 40 and is rarely seen in children. In the United States, the incidence of kidney and renal pelvis cancer was 1.9 times higher for men relative to women from 2009 to 2013 with a mortality rate that was 2.3 times higher for men in this time frame (Siegel et al. 2017). The underlying reasons for these gender-associated differences are not clear.

Race and Ethnicity

Age-adjusted rates per 100,000 population for the incidence of kidney and renal pelvis cancer in the United States were highest for American Indian/Alaska Natives followed by non-Hispanic blacks, non-Hispanic whites, Hispanics, and Asian/Pacific Islanders in 2009 to 2013. Likewise, the rates of death in 2010 to 2014 varied widely being highest in American Indian/Alaska Natives and lowest among Asian/Pacific Islanders. Geographic variations are prominent in this data set which may reflect differences in the prevalence of risk factors for sporadic RCC such as obesity, smoking, and hypertension (White et al. 2014).

While genomic and transcriptomic data on differences in clinical outcome by race are extremely limited, potential differences in somatic mutation rates and RNA expression were examined in a recent study of clear cell RCC (ccRCC) (Krishnan et al. 2016). The discovery cohort consisted of 419 ccRCC tumor data sets for whites and 19 for blacks from The Cancer Genome Atlas-Kidney Renal Clear Cell Carcinoma (TCGA-KIRC) database repository versus 125 whites and 10 blacks in the external validation cohort from a publicly available single nucleotide polymorphism (SNP) data set in the Gene Expression Omnibus database repository of the National Center for Biotechnology Information (accession code: GSE25540). These investigators found that African-American patients have less frequent inactivation of the von Hippel-Lindau (VHL) gene along with decreased upregulation of hypoxia-inducible factor (HIF)-associated gene signatures than white patients. Additional studies were carried out that focused on inter-tumor heterogeneity with respect to the ccA and ccB molecular subtypes of ccRCC that have recently been described (Serie et al. 2017). Significant enrichment of the ccB molecular subtype was detected in tumors from African-Americans relative to whites. Taken as a whole, one may infer that these genomic differences could lead to higher rates of drug resistance to vascular endothelial growth factor (VEGF)-targeted therapy in blacks, the most widely used form of targeted target for RCC. Though this explanation is biologically plausible, the degree to which it actually contributes to the persistence of racial disparities in overall survival (OS) in the targeted therapy era has yet to be determined.

There is evidence that the relative distribution of histologic subtypes of RCC varies by race

(Olshan et al. 2013). Data from the US Surveillance, Epidemiology and End Results (SEER) Program (18 sites) were used to track changes in the incidence of RCC between 2001 and 2009 for the most common histologic subtypes with an analytic focus on racial differences. The final cohort included a total of 52,924 patients with clear cell, papillary, and chromophobe RCC. Unfortunately, this SEER database does not capture subtype-specific classifications such as papillary type 1 and papillary type 2. Furthermore, a substantial number of tumors in this database were characterized as NOS (not otherwise specified) with respect to subtype, though there were no significant differences in this regard with respect to race (37% for whites and 41% for blacks). Overall, 48% of the tumors were clear cell, 37% were NOS, 10% were papillary, and 5% were chromophobe. After excluding RCC NOS cases from the primary analysis, 77% of the tumors were clear cell, 16% were papillary, and 7% were chromophobe. The proportion of patients with ccRCC was significantly higher for whites when compared to blacks (50% vs. 31%, respectively). Conversely, blacks were much more likely to have papillary RCC than whites (23% vs. 9%). Moreover, racial differences in the proportionate incidence of RCC subtypes appear to be increasing with time.

Disparities in Clinical Outcome

The associations of demographic and clinical characteristics with patient survival have been studied from the perspective of potential racial disparities (Chow et al. 2013). This study included 4359 black patients and 34,991 white patients in the SEER database (12 registries) spanning the years of 1992 to 2007 which largely encompasses the era when surgery and cytokine therapy were the standard forms of treatment along with the emerging era of targeted therapy that began in December of 2005. These authors concluded that patients with RCC who are white consistently have a survival advantage over those who are black, regardless of age, gender, tumor stage or size, histological subtype, or surgical treatment. The relative OS rate at 5 years was 72.6% with a 95% confidence interval (CI) of 72.0%–73.2% for whites versus 68.0% for blacks (95% CI 66.2%–69.8%). Survival was higher for women than men, and younger patients tended to live longer than older patients. These data confirm that whites were more likely to have ccRCC than blacks, whereas the papillary and chromophobe subtypes were relatively more common in blacks. OS at 5 years for patients who did no undergo nephrectomy (10.5% of whites and 14.5% of blacks) was equally poor when compared to patients who had the primary tumor removed. Comorbid conditions such as hypertension were more common in blacks than in whites and may contribute to the observed discrepancies in OS by race.

Lifestyle Factors

Cigarette Smoking

Cigarette smoking is a well-established risk factor for developing RCC that is completely avoidable. The impact of tobacco exposure on the incidence and mortality of bladder cancer and RCC was recently updated in a systematic review of original articles in the English literature that had been published as of August of 2013 and listed in PubMed (Cumberbatch et al. 2016). The possible correlation between smoking cessation and a decrease in the risk of death was also explored. Of the 2683 articles that were identified, 107 met inclusion criteria of which 24 specifically investigated RCC. These articles were either case-control, cohort, or nested case-control studies with incidence or disease-specific mortality reported as the outcome in terms of odds ratio (OR), hazard ratio (HR), or relative risk (RR) estimates with 95% CIs. A meta-analysis of risks was performed that revealed a pooled RR for RCC incidence of 1.31 (95% CI 1.22–1.40) for all smokers, 1.36 (95% CI 1.19–1.56) for current smokers, and 1.16 (95% CI 1.08–1.25) for former smokers. The corresponding risk of disease-specific mortality was 1.23 (95% CI 1.08–1.40), 1.37 (95% CI

1.19–1.59), and 1.02 (95% CI 0.90–1.15). The observation that incidence and risk of death were highest among current smokers and lowest among former smokers was the basis for the conclusion that smoking cessation confers benefit.

Alcoholic and Nonalcoholic Beverage Consumption

The National Institute on Alcohol Abuse and Alcoholism has established that a standard alcoholic drink in the United States contains 14.0 grams (0.6 ounces) of pure alcohol (https://pubs.niaaa.nih.gov/publications/Practitioner/pocketguide/pocket_guide2.htm accessed 04/07/2017). This is the amount of alcohol that is typically found in 12 ounces of beer, 8 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces (a "shot") of 80 proof of liquor. In the Dietary Guidelines for Americans 2015–2020, the federal government defined moderate alcohol intake as one drink a day for women and up to two drinks a day for men (https://health.gov/dietaryguidelines/2015/accessed 04/07/2017). For women, heavy alcohol consumption was defined as having more than 3 drinks on any day or more than 7 drinks a week versus more than 4 drinks on any day or more than 14 drinks per week for men. Extensive epidemiological research has led to strong consensus that an association exists between drinking alcohol and the risk of developing certain types of cancer including cancers of the head and neck, esophagus, liver, breast, colon, and rectum. The data have been inconsistent for other forms of cancer. However, a dose-response association has been reported for RCC indicating that alcohol may actually decrease the risk of developing RCC (Bellocco et al. 2012).

Dose-response meta-analysis was performed for 15 case-control studies that were published in the English literature between 1980 and March of 2010 reporting categorical risk estimates for a series of exposure levels to alcohol. Surprisingly, an inverse association was observed between alcohol consumption and RCC for the overall alcohol intake group (OR 0.67, 95% CI 0.62–0.73) as well as subgroups that were stratified by gender, study design, geographical region, specific beverages, and alcohol assessment. A dose-response meta-analysis showed that an increase in alcohol consumption of 12 g of ethanol per day was associated with a 5% statistically significant decreased risk of RCC. These findings were confirmed in an independent meta-analysis of 20 observational studies published through November of 2010 (4 cohort, 1 pooled, and 15 case-control), the dose-risk relation was assessed in terms of RR and 95% CI. The estimated RRs were 0.85 (95% CI 0.80–0.92) for any alcohol drinking, 0.90 (95% CI 0.83–0.97) for light drinking of 0.01–12.49 g/day, 0.79 (95% CI 0.71–0.88) for moderate drinking of 12.5–49.9 g/day, and 0.89 (95% CI 0.58–1.39) for heavy drinking of $\geq$50 g/day (Bellocco et al. 2012).

The potential impact of total fluid consumption on the risk of RCC has been examined in a Canadian study to explore the hypothesis of a possible diluting effect on carcinogens (Hu et al. 2009). Questionnaires were completed by 1138 newly diagnosed, histologically confirmed RCC cases and 5039 population controls between the years of 1994 and 1997 in 8 Canadian provinces. Higher total fluid intake was associated with an increased risk of RCC with an OR for the highest versus the lowest quartile of 1.49 (95% CI 1.20–1.85). Similarly, the total intake of juices and coffee was related to the risk of RCC with ORs for the highest versus the lowest quartile of 1.53 (95% CI 1.18–1.99) and 1.33 (95% CI 1.07–1.66), respectively. These positive associations were stronger in men, but not in women. Higher coffee intake was more strongly associated with RCC in normal weight subjects. As confirmed in subsequent studies, total intake of alcohol was inversely associated with the risk of RCC. Intake of tap water (not in coffee or tea), bottled water, tea, soft drinks, and milk was not related to RCC.

Physical Activity

The association between physical activity and RCC risk was examined in a systematic review and meta-analysis of 19 studies based on a total of 2,327,322 subjects and 10,756 cases in which

high versus low levels of physical activity were compared (Behrens and Leitzmann 2013). An inverse association was observed with a summary RR from random-effects meta-analysis of 0.88 (95% CI 0.79–0.97). When risk estimates were restricted to high-quality studies, the inverse association between physical activity and risk of RCC was strengthened (RR 0.78; 95% CI 0.66–0.92). These investigators did not detect an effect modification by adiposity, hypertension, type 2 diabetes, smoking, gender, or geographic region.

Sedentary behavior has also been assessed as a risk factor for RCC in older adults (George et al. 2011). In this study, sedentary behavior was defined as a cluster of activities adopted in a sitting or lying posture where little energy is being expended. This prospective investigation of prolonged sitting time and risk of RCC was conducted among 300,000 older adults. After controlling for known risk factors for RCC, the investigators did not find evidence of an association between RCC risk in the elderly and time spent sitting while watching television or videos per day.

Clinical Conditions

Excess Body Weight and Obesity

Obesity is a well-established predisposing factor for carcinogenesis. Body mass index (BMI) is a parameter that has been used to uniformly define overweight (BMI 25.0–29.9) and three classes of obesity: class 1 (BMI 30.0–34.9), class 2 (BMI 35.0–39.9), and class 3 (BMI $\geq$40.0). BMI is defined as the weight in kilograms divided by the square of the height in meters. The International Agency for Research on Cancer (IARC) recently convened a working group to reassess the preventive effects of weight control on cancer risk (Lauby-Secretan et al. 2016). More than 1000 epidemiological studies were reviewed. These investigators concluded that the RR of developing RCC was 1.8 (95% CI 1.7–1.9) for the highest BMI category versus the normal BMI. They also determined that the strength of the evidence was sufficient to draw this conclusion (vs. strength of evidence that is either limited or inadequate).

The fact that obesity increases the risk of RCC makes the results of studies on the impact of obesity on clinical outcome in patients who undergo nephrectomy counterintuitive. A meta-analysis of the English literature through September of 2011 was conducted of studies that had an endpoint of OS (10 studies; 6518 patients), cancer-specific survival (CSS; 15 studies; 12,175 patients), or recurrence-free survival (RFS; 8 studies; 7165 patients). A multivariate analysis showed higher OS (HR 0.45, 95% CI 0.29–0.68) and CSS (HR 0.47, 95% CI 0.29–0.77)) in obese patients than in normal weight patients. The investigators concluded that preoperative BMI is an independent prognostic indicator for survival among patients with RCC (Choi et al. 2013).

Hypertension

The relative contribution of BMI and hypertension to the risk of developing RCC was explored in a study of 759 Swedish men with RCC along with 136 men with cancers of the renal pelvis (Chow et al. 2000). These men were diagnosed between 1971 and 1992 and followed until death or the end of 1995. Estimates of RR were adjusted for age, smoking status, BMI, and diastolic blood pressure. A dose-dependent association was observed for BMI as well as hypertension. The risk of RCC increased by 30% to 60% for the middle group and nearly doubled for the upper group when patients were divided into three groups (lower 3/8ths vs. middle 3/8ths vs. upper 2/8ths) with respect to BMI (p value for the trend, $<$0.001). Similarly, there was a direct association between higher blood pressure and higher risk of RCC (p value for the trend, $<$0.001 for the diastolic pressure, and 0.007 for the systolic pressure). The authors concluded that higher BMI and elevated blood pressure independently increase the long-term risk of RCC in men, whereas a reduction in blood pressure lowers the risk.

The relationship between hypertension, antihypertensive treatments, and the risk of RCC was examined in a meta-analysis of 18 studies published from 1966 to 2006 (Corrao et al. 2007). The authors fit random effect models to

the original data to obtain pooled estimates for the effects of interest. These investigators reported a significant increase in the risk of RCC in patients with hypertension (pooled OR 1.62, 95% CI 1.24–2.12). In addition, increased risk was detected in patients who used diuretic antihypertensives (1.43, 95% CI 1.12–1.83) as well as those who used non-diuretic antihypertensives (1.51, 95% CI 1.21–1.87). However, the effect of diuretics was only significant in women (1.92, 95% CI 1.59–2.33), but not in men (1.18, 95% CI 0.93–1.49). When known risk factors for RCC were taken into account, the effect of non-diuretic antihypertensives on the pooled estimate of risk was no longer significant (1.17, 95% CI 0.94–1.46). The authors concluded that these data are not sufficient to provide a definitive answer regarding hypertension, antihypertensive treatments, and the risk of developing RCC.

Diabetes Mellitus

The role of diabetes mellitus as a predisposing factor for developing RCC has not clearly been established. The incidence of RCC in patients with diabetes was explored in a meta-analysis of 7 case-control studies and 17 cohort studies (Bao et al. 2013). While an increase in the incidence of RCC was observed for patients with diabetes (RR 1.40, 95% CI 1.16–1.69), there was no increase in mortality (RR 1.12, 95% CI 0.99–1.20). The increased risk of RCC was independent of alcohol consumption, BMI/obesity, and smoking. The authors concluded that diabetes mellitus may increase the risk of RCC for both women and men.

Chronic Kidney Disease and End-Stage Renal Disease

Patients with end-stage renal disease (ESRD) have a higher risk of developing RCC (Yanik et al. 2016). Recently a cohort of 202,195 kidney transplant candidates and recipients was identified by linking the Scientific Registry of Transplant Recipients to cancer registries in the United States. The incidence of cancer was assessed based on intervals of kidney function (time with a transplant) versus the incidence during intervals of nonfunction (waitlist or time after transplant failure), adjusting for demographic factors. Interestingly, the investigators found that the incidence of specific forms of cancer changed in an alternating fashion with each successive interval. Higher rates of non-Hodgkin's lymphoma, melanoma, and cancers of the lung, pancreas, and non-epithelial skin were noted during intervals of function versus higher rates for RCC and thyroid cancers during intervals of nonfunction.

The predisposition of patients with chronic kidney disease (CKD) to developing RCC is less well established. The association between level of kidney function and subsequent cancer risk was assessed in a retrospective cohort study of 1,190,538 adults who were $\geq$40 years of age, who were also receiving care within a health-care delivery system and who had their kidney function assessed between 2000 and 2008 with no prior history of cancer (Lowrance et al. 2014). During the period of follow-up, 76,809 cancers were identified in 72,875 subjects. Though no significant associations were observed between the estimated glomerular filtration rate (eGFR in terms of milliliters per minute per 1.73 m^2) and the incidence of prostate, breast, lung, colorectal, or any cancer overall, reduced eGFR was associated with an independently higher risk of RCC and urothelial cancer (eGFR $<$30). After adjustment of the HR for age, sex, race, socioeconomic status, comorbidities, proteinuria, hematuria, BMI, smoking status, imaging use, health-care use, and specific prescription medications, the rate of any incident RCC increased by 39% for eGFR 45–59 and more than twofold for eGFR $<$30 when eGFR 60–89 was used as the reference range. The increased rate was greater for ccRCC than non-clear cell though the sample size was small.

Polycystic Kidney Disease

A recent population-based cohort study was conducted in Taiwan that employed a propensity score-matched analysis to assess the risk of

developing cancer in patients with polycystic kidney disease who did not have CKD or ESRD (Yu et al. 2016). In this study, 4346 patients who met the criteria for polycystic kidney disease were compared to 4346 controls who did not have kidney disease. The specific risks (adjusted subhazard ratios) were significantly higher in the polycystic kidney disease cohort than in the non-polycystic kidney disease cohort for liver cancer (1.49, 95% CI 1.04–2.13; $p = 0.030$), colon cancer (1.63, 95% CI 1.15–2.30; $p = 0.006$), and kidney cancer (2.45, 95% CI 1.29–4.65; $p = 0.006$). Additional data are sparse on this subject.

Sickle Cell Disease

Renal medullary carcinoma (RMC) is a rare and aggressive variant of collecting duct RCC that occurs in patients with sickle cell trait and sickle cell disease. A specific genetic defect that interferes with normal chromatin remodeling may the cause of this disease (Calderaro et al. 2016).

Autoimmune Diseases

The Swedish National Database was used to assess the subsequent risk of urologic malignancies (prostate, kidney, and bladder) in individuals who had previously been diagnosed with any of 33 autoimmune diseases from 1964 through 2008 (Liu et al. 2013). Individuals who were identified in this manner were matched to cases of cancer that were recorded in the national Swedish Cancer Registry during the same time frame among individuals who were hospitalized for autoimmune disease. Subsequent risk was estimated on the basis of the standardized incidence ratio (SIR) which was calculated as the ratio of observed to expected cases along with an estimated HR for OS. These investigators found that the SIR for urologic malignancies was increased for 26 autoimmune diseases along with an increased HR for CSS after 4 autoimmune diseases. The highest SIRs for RCC were 2.85 (95% CI 1.22–5.64) after polyarteritis nodosa and 2.68 (95% CI 1.33–4.80) after polymyositis/dermatomyositis. Of note, chronic severe inflammation is not only a predisposing factor for developing RCC but a poor prognostic factor for patients with advanced disease (Harris et al. 2017).

Immunosuppression with Organ Transplantation

Chronic immunosuppression after organ transplantation is a well-established risk factor for developing certain forms of cancer (Hall et al. 2013). The Transplant Cancer Match Study links the US transplantation registry with 14 state/regional cancer registries. In this study, 8520 incident cancers were identified among 164,156 transplant recipients with comparisons of the incidence of cancer after transplantation in two different periods of time: 2000 to 2008 and 1987 to 1999. The 5-year cumulative incidence was estimated for six preventable or screen-detectable cancers after stratification by organ, sex, and age at transplantation. The 5-year cumulative incidence was also calculated for the same cancers in the general population at representative ages using data from the Surveillance, Epidemiology, and End Results (SEER) database as a reference point. Of note, a small but statistically significant increase in the absolute risk of cancer was observed for transplant recipients during the period from 2000 to 2008 relative to the those who received transplants in 1987 to 1999 (5-year cumulative incidence: 4.4% vs. 4.2%; $p = 0.006$). This difference was attributed to a decrease in the risk of competing events (5-year cumulative incidence of death, graft failure, or re-transplantation: 26.6% vs. 31.9%; $p < 0.001$). The kidney was the most commonly transplanted organ in both eras (range, 61.1%–63.2%). Kidney recipients, especially those aged >35 years, had a greater 5-year cumulative incidence of kidney cancer than observed in the US general population at any age.

Urinary Tract Infections

The potential role of urinary tract infections (UTIs) as a predisposing factor for RCC was

explored in a population-based, case-control study of 372 cases of RCC in Iowa (233 males, 139 females) that were identified through the Iowa Cancer Registry (Parker et al. 2004). Controls were randomly selected from the general population based on state driver's license records and listings provided by the US Health Care Financing Administration for the 1986–1989 time frame and frequency matched to the study cohort with respect to age and sex. Analysis based on a self-reported history of a physician-diagnosed kidney or bladder infection yielded an OR for risk of RCC of 1.9 (95% CI 1.5–2.5) for patients with a history of a UTI versus those reporting no such history. The risk of RCC was modified by gender and smoking status with the strongest risk being for males (OR 2.7, 95% CI 1.9–3.8) and current smokers (OR 4.3, 95% CI 2.7–6.7).

Chronic Hepatitis C Infection

Chronic infection with hepatitis C virus (HCV) predisposes patients to CKD (Gordan et al. 2010). Administrative data from a large, integrated, and ethnically diverse health-care system were used to identify a cohort of 67,063 HCV-tested patients between 1997 and 2006 who were followed for the development of RCC until April 2008. RCC was diagnosed in 0.6% (17 of 3057) of HCV-positive patients versus 0.3% (177 of 64,006) of HCV-negative patients. The mean age at RCC diagnosis was significantly younger in HCV-positive individuals (54 vs. 63; $P < 0.001$). The univariate HR for RCC among HCV patients was 2.20 (95% CI 1.32–3.67). Age, African-American race, male gender, and CKD were risk factors that were included in a multivariate model that yielded an overall HR for RCC among HCV patients of 1.77 (95% CI 1.05–2.98). The investigators concluded that chronic HCV infection increases the risk of developing RCC.

Kidney Stones

Patients who have a history of kidney stones appear to have an increased risk of developing cancers of the kidney, renal pelvis, and ureter (Cheungpasitporn et al. 2015). The risk for RCC was evaluated in a meta-analysis of seven studies (six case-control studies and one retrospective cohort study) that comprised a total of 62,925 patients with a history of nephrolithiasis. The pooled risk ratio for RCC was 1.76 (95% CI 1.24–2.49). Similarly, these investigators assessed the risk of developing a urothelial carcinoma of the upper tract in a meta-analysis of five studies (four case-control studies and one retrospective cohort study) that included a total of 62,377 patients with a history of kidney stones. The pooled risk ratio for upper tract carcinoma was 2.14 (95% CI 1.35–3.40) for patients with kidney stones. Self-reporting was the primary limitation of these studies.

Gallstones

Significant increases in the risk of cancers of the small bowel, prostate, and kidney have been reported in a network of case-control studies conducted in Italy and Switzerland from 1982 to 2009 for patients with a history of cholelithiasis (Tavani et al. 2012). ORs were calculated for a variety of cancers including cancers of the oropharynx (1997), esophagus (917), stomach (999), small intestine (23), colon and rectum (3726), liver (684), pancreas (688), larynx (1240), breast (6447), endometrium (1458), ovary (2002), prostate (1582), kidney (1125), and bladder (741) with 21,284 controls. No significant association was observed for the other cancers with the exceptions of small bowel and prostate.

Reproductive and Hormonal Factors

Increased Number of Pregnancies

In a meta-analysis of six prospective and eight case-control studies that reported RR estimates and 95% confidence intervals, a sample of 5389 cases and 651,072 non-cases was identified (Guan et al. 2013). In a dose-response analysis, the summary RR per one live birth was 1.08 (95% CI

1.05–1.10). This study provides evidence that ever parity and higher parity number are significantly associated with increased risk of kidney cancer.

Hysterectomy Status

Though women are less lightly to develop RCC than men, women who undergo a hysterectomy have an increased risk of developing RCC when compared to women who do not. A meta-analysis of seven cohort and six case-control studies published between 1950 and 2012 was conducted using random-effects models to estimate summary relative risks (SRRs) for developing RCC based on hysterectomy status, age at hysterectomy (<45 vs. ≥ 45), and time since hysterectomy (<10 years vs. ≥ 10 years) (Karami et al. 2014). The SRR for hysterectomy and kidney cancer for all published studies was 1.29 (95% CI 1.16–1.43). A significant summary effect was observed irrespective of age at hysterectomy, time since the procedure and model adjustment for BMI, smoking status, and hypertension. The investigators highlight the clinical relevance of their data in that roughly 45% of women are estimated to undergo this procedure by the age of 70 in the United States.

Medications and Medical Therapies

Analgesics

The possible association of analgesics with increases in the incidence of RCC has been studied in a meta-analysis of 12 case-control studies (7075 cases/579,285 controls) and 8 cohort studies (1165 cases among 579,285 subjects) that were reported in English (Choueiri et al. 2014). A total of 8240 incident cases of RCC from 6 countries met the inclusion criteria of the meta-analysis. The analgesics were grouped into three categories: acetaminophen (14 studies), aspirin (13 studies), and other nonsteroidal anti-inflammatory drugs (NSAIDs; 5 studies). The pooled RR for RCC was 1.28 (95% CI 1.15–1.44) for acetaminophen and 1.25 (95% CI 1.06–1.46) for nonaspirin NSAIDs. No overall increase in risk was observed for aspirin use (pooled RR 1.10; 95% CI 0.95–1.28), though the pooled RR for five non-US studies was 1.17 (95% CI 1.04–1.33). The increased risk of RCC was stronger when the intake of acetaminophen was higher with a pooled RR of 1.68, (95% CI 1.22–2.30). This was also true for high levels of ingestion of nonaspirin NSAIDs (pooled RR 1.56, 95% CI 1.11–2.19). A biologic mechanism for these findings has yet to be defined.

Exposure to Chemotherapy as a Child

In a study of 39 genetically confirmed translocation RCCs, six (15%) arose in patients who had received cytotoxic chemotherapy (Argani et al. 2006). These six patients were diagnosed with RCC between the ages of 6 and 22. At the molecular level, three tumors contained the *ASPL-TFE3* fusion, two contained *Alpha-TFEB*, and one contained *PRCCTFE3*. The intervals between chemotherapy and the diagnosis of RCC ranged from 4 to 13 years. The authors concluded that exposure to cytotoxic chemotherapy as a child may predispose to the development of translocation RCCs.

Occupational and Environmental Exposures

Trichloroethylene

RCC is not generally considered to be a cancer that is associated with occupational exposures. However, the task of linking toxicology with epidemiology is not simple in that dose and duration of exposure to toxic agents are variables that frequently are difficult to quantify. Recently, the IARC listed the solvent trichloroethylene (TCE) as an occupational risk for developing kidney cancer (Cogliano et al. 2011; Guha et al. 2012). High levels of exposure to TCE occur in certain occupations that require degreasing as well as dry cleaning. The IARC defines the term carcinogen as any substance or mixture or form of radiation

that is directly involved in causing cancer. Carcinogens may cause cancer by damaging the genome or by disrupting cellular metabolic processes. The IARC groups carcinogens into specific categories comprising groups 1, 2A, 2B, 3, and 4. To be classified as group 1, the carcinogen must cause cancer in humans with an exposure circumstance that predisposes to carcinogenesis in humans. There is also a requirement that the level of evidence for carcinogenicity in humans be "sufficient," although in exceptional circumstances, this designation can be made when there is "sufficient evidence" of carcinogenicity in experimental animals and "strong evidence" that a relevant mechanism of carcinogenicity exists in exposed humans. Occupational exposure to TCE has been associated with an increased risk of RCC for subjects who had an active GSTT1 enzyme (OR 1.88, 95% CI 1.06–3.33), but no increased risk for those who did not have GSTT1 activity (OR 0.93, 0.35–2.44) (Moore et al. 2010). As such, genetic susceptibility to kidney carcinogenesis may be the result of gene variants in reductive metabolism with respect to the capacity for glutathione conjugation.

The risk of ccRCC appears to increase after years of unusually high-dose occupational exposure to TCE leading to chronic damage to the proximal tubules of the kidney and bio-activation of pathways that disrupt the function of the *vHL* gene. As such, the rationale for designating TCE as a specific carcinogen for clear cell RCC is based on a combination of findings from experimental, mechanistic, and epidemiologic studies. However, there appears to be a practical threshold below which a significant carcinogenic effect is unlikely (Scott and Jinot 2011). Of note, the use of TCE has declined significantly since the 1970s due to environmental concerns.

Metals, Coal, and Petroleum Products

Though specific details regarding exposure levels are frequently missing from studies of cancer risks associated with occupational exposures, there is evidence that the risk of developing sporadic RCC may increase with exposure to cadmium, asbestos, and TCE. One large Canadian study used questionnaires to obtain data on patients with newly diagnosed, histologically confirmed cases of RCC between 1994 and 1997 (Hu et al. 2002). The study cohort of 1279 cases consisted of 691 males and 588 females. The control cohort of 5370 patients without RCC was obtained from 8 Canadian provinces. Variables included socioeconomic status, smoking habits, alcohol use, diet, residential and occupational histories, and years of exposure to any of 17 chemicals. The ORs that were calculated revealed an increased risk of RCC for male patients who had experienced occupational exposures to benzene (OR 1.8, 95% CI 1.2–2.6); benzidine (OR 2.1, 95% CI 1.3–3.6); coal tar, soot, pitch, creosote, or asphalt (OR 1.4, 95% CI 1.1–1.8); herbicides (OR 1.6, 95% CI 1.3–2.0); mineral, cutting, or lubricating oil (OR 1.3, 95% CI 1.1–1.7); mustard gas (OR 4.6, 95% CI 1.7–12.5); pesticides (OR 1.8, 95% CI 1.4–2.3); and vinyl chloride (OR 2.0, 95% CI 1.2–3.3). The risk was also elevated with cadmium salts (OR 1.7, 95% CI 1.0–3.2) and isopropyl oil (OR 1.6, 95% CI 1.0–2.6). A positive correlation with duration of exposure was also observed with benzene, benzidine, cadmium, herbicides, and vinyl chloride. Very few females were exposed to the specific chemicals that were the subject of this study. A related study of 64 patients with RCC revealed a marked increase in the incidence of RCC for cadmium workers who also smoked relative to patients with colon cancer and noncancer controls (Kolonel 1976).

Radiation

The Life Span Study of 86,611 victims of radiation exposure from atomic bomb blasts with follow-up from 1950 to 2003 has reported an increase in the risk of cancer mortality for many forms of cancer including cancers of the stomach, lung, liver, colon, breast, gallbladder, esophagus, bladder, and ovary. However, no increased risks were detected for cancers of the rectum, pancreas, uterus, prostate, or kidney parenchyma (Ozasa et al. 2012).

Men have an increased risk for developing RCC as a second malignancy after treatment with radiotherapy alone for testicular cancer with curative intent (Travis et al. 2005). Inclusion criteria were met by 40,576 men in a large international study from the United States, Ontario, Denmark, Sweden, Norway, and Finland (all forms of therapy). For men who survived at least 10 years after radiotherapy alone, the RR for kidney cancer was 2.8 (95% CI 2.1–3.8). The RR for other second malignancies was also found to be significantly increased including the risk for cancers of the stomach, colon, rectum, pancreas, lung, pleura, prostate, bladder, connective tissue, and thyroid as well as malignant melanoma.

Similarly, women treated with radiotherapy alone with curative intent for cervical cancer have a lifelong increased risk of second malignancies (Chaturvedi et al. 2007). These investigators explored the risk of second cancers among very long-term survivors by using data from 104,760 1-year survivors of cervical cancer reported to 13 population-based cancer registries in Denmark, Finland, Norway, Sweden, and the United States. The standardized incidence ratio (SIR) for RCC as a second malignancy was 1.34 (1.15 to 1.55) for women who had received any radiotherapy versus 1.26 (0.97 to 1.63) for those who received none. Unfortunately treatment information was not available for nearly 25,000 patients on this study.

Family History: Relatives with Kidney Cancer and Other Forms of Cancer

Family members who have a first-degree relative (parent or sibling) with kidney cancer are prone to developing sporadic RCC at a rate that is 2.2-fold higher (95% CI 1.6–2.9) than others (Clague et al. 2009). This study employed three analytic strategies to investigate the association between a family history of kidney cancer and risk of RCC including a case-control analysis, a family-based population analysis, and a meta-analysis. Other researchers utilized the Swedish Family-Cancer Database of 12.2 million individuals to retrieve cancer data on 8513 patients with RCC from the Swedish Cancer Registry for the years 1961–2008 (Liu et al. 2011). The SIR for RCC for the offspring of a parent with kidney cancer was 1.75 (95% CI 1.49–2.04) versus 2.61 (95% CI 2.00–3.34) for the brother or sister of a sibling with kidney cancer. The risk of RCC was also higher for the offspring of a parent with lung or prostate cancer. In addition, an increased risk of RCC was observed for the siblings of patients with bladder cancer, thyroid cancer, melanoma, or non-Hodgkin's lymphoma.

Hereditary Disorders with Renal Tumors

Von Hippel-Lindau Syndrome

Hereditary forms of RCC are rare (Bausch et al. 2013; Haas and Nathanson 2014). The VHL syndrome is the most common hereditary form of kidney cancer. Carcinogenesis in this setting is driven by germline mutations in the *VHL* tumor suppressor gene that was first identified in 1993 (Latif et al. 1993). The primary neoplasm associated with this disorder is ccRCC which also represents the leading cause of death. The disease occurs as a consequence of mutations in the *VHL* gene on chromosome 3p25.3. Clinical manifestations of the disease may vary in a manner that reflects the specific mutation(s) present within the *VHL* gene. There are five classical phenotypes that have been designated 1, 1B, 2A, 2B, and 2C. Most patients will develop hemangioblastomas (benign vascular tumors) in the retina, brain, and spinal cord. A variety of tumors may arise in other organs such as pheochromocytomas, benign tumors of the endolymphatic sac of the inner ear, neuroendocrine tumors of the pancreas, as well as cystadenomas of the epididymis and broad ligament. Cysts may occur in the pancreas and the kidney where renal cysts have the potential for malignant transformation. Of note, somatic mutations that inactivate the *VHL* gene can be detected in at least 50% of patients with sporadic RCC. The HIF-VEGF pathway that leads to *VHL*-mediated carcinogenesis has been extensively characterized

(TCGA Research Network 2013). A summary of the principal genetic alterations for hereditary forms of RCC are listed in Table 2.

Hereditary Papillary Renal Cancer

Hereditary papillary renal cancer (HPRC) is an autosomal dominant disease that is associated with an inherited form of RCC as a consequence of a germline mutation in the *MET* gene. These patients develop multiple, bilateral, type 1 pRCCs without known clinical manifestations outside of the kidney. Both sporadic and germline mutations in the *MET* gene are associated with alterations that cluster in the tyrosine kinase catalytic domain of the gene product (TCGA Research Network 2016).

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant syndrome that is caused by mutations in the gene encoding fumarate hydratase, a respiratory enzyme that has an important role in the Krebs cycle and the electron transport chain. The characteristic clinical features of HLRCC are multiple cutaneous and uterine leiomyomas as well as leiomyosarcomas and an aggressive form of papillary RCC type 2 or collecting duct RCC. Sporadic papillary RCC type 2 is associated with a variety of genetic alterations in addition to mutations of the *FH* gene (TCGA Research Network 2016). The prognosis for HLRCC-associated RCC is poor (Moch et al. 2016).

Birt-Hogg-Dubé Syndrome

Patients with Birt-Hogg-Dubé disease (BHD) suffer from an autosomal dominant syndrome that is characterized by dysplastic hair follicles (fibrofolliculomas), lung cysts with spontaneous pneumothorax, and RCC. The gene for BHD maps to 17p11.2, a locus where point mutations and large genomic rearrangements have been described in the folliculin gene *FLCN* (Schmidt et al. 2001; Davis et al. 2014). The function of the folliculin protein is unclear with no homology to other proteins. The histologic subtypes of renal tumors vary widely in this disorder and include ccRCC, papillary, chromophobe, oncocytomas, and hybrid oncocytomas which feature both chromophobe and oncocytic histology. The presence of fibrofolliculomas in an adult and the detection of a genetic mutation that disrupts the signature folliculin gene are the two major diagnostic criteria for this disorder (Haas and Nathanson 2014).

Table 2 Renal neoplasms associated with hereditary syndromes

Syndrome	Gene	Locus	Renal neoplasm								
			CC	PAP1	PAP2	UPAP	CHR	ONC	HYB	AML	EAML
VHL	*VHL*	3p25	x								
HPRC	*MET*	7q31		x							
HLRCC	*FH*	1q25–32			x						
BHD	*FLCN*	17p11.2	x			x	x	x	x		
PGL1	*SDHD*	11q23	x								
PGL3	*SDHC*	1q21	x			x					
PGL4	*SDHB*	1p35-p36	x				x	x			
TSC	*TSC1*	9q34						x		x	x
TSC	*TSC2*	16p13.3						x		x	x

Abbreviations: *AML* angiomyolipoma, *BHD* Birt-Hogg-Dubé, *CC* clear cell, *CHR* chromophobe, *EAML* epithelioid angiomyolipoma, *FH* fumarate hydratase, *FLCN* folliculin, *HLRCC* hereditary leiomyomatosis and renal cell cancer, *HPRC* hereditary papillary renal cancer, *HYB* hybrid oncocytoma, *ONC* oncocytoma, *PAP1* papillary type 1, *PAP2* papillary type2, *PGL* paraganglioma (types 1–4), *SDH* succinate dehydrogenase (B–D), *TSC* tuberous sclerosis complex (types 1–2), *UPAP* unclassified papillary, *VHL* von Hippel-Lindau

Paraganglioma Syndromes

Four autosomal dominant hereditary paraganglioma syndromes (PGL1–4) have been described that are clinically associated with paragangliomas of the head and neck and a tendency to develop various forms of RCC in three of the four syndromes (Bausch et al. 2013; Haas and Nathanson 2014). Paragangliomas are neuroendocrine neoplasms that may be benign or malignant. Each PGL syndrome is associated with a susceptibility gene that encodes for a specific subunit of succinate dehydrogenase (*SDHB*, *SDHC*, *SDHD*, and *SDHAF2*), a respiratory enzyme that plays a critical role in linking the Krebs cycle with the electron transport chain. Little is known about succinate dehydrogenase-associated RCCs, though they have been classified as clear cell, papillary, or chromophobe. Oncocytomas have also been observed. In general, succinate dehydrogenase-deficient RCC has good prognosis, though the prognosis is less favorable when sarcomatoid differentiation and necrosis are present (Moch et al. 2016).

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder that is attributed to the inactivation of the *TSC1* gene (chromosome 9q34) that encodes hamartin or to the disruption of the *TSC2* gene (chromosome 16p13.3) that encodes tuberin. These patients develop hamartomas throughout their bodies including the brain, kidney, skin, and lung resulting in severe neurologic disorders, including epilepsy, mental retardation, and autism as well as facial angiofibromas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis. Oncocytomas, malignant epithelioid angiomyolipomas, and the more common types of renal cancer have been reported. Heterodimers of hamartin and tuberin inhibit downstream pathways of mammalian target of rapamycin (mTOR) leading to the upregulation of the HIF pathway. Rapamycin analogs that inhibit mTOR pathways have demonstrated sufficient clinical efficacy to warrant approval from the US Food and Drug Administration (FDA) for the treatment of angiomyolipomas and subependymal astrocytomas based on a double-blinded placebo-controlled trial showing a response rate of 42% (95% CI 31–55%) (Bissler et al. 2013).

Other Rare Disorders

Recent summaries of hereditary disorders review other rare syndromes in more detail (Bausch et al. 2013; Haas and Nathanson 2014). These include familial ccRCC, a condition that has been associated with somatic mutations in *BAP1* (BRCA-associated protein (1) and other neoplasms including mesothelioma and melanomas of the uvea and the skin. Balanced translocations of chromosome 3 are also associated with renal carcinogenesis since multiple susceptibility genes for ccRCC are located on chromosome 3p such as *VHL*, *PBRM1*, *BAP1*, and *SETD2*. In addition, ccRCC has been reported in the setting of mutations of the *PTEN* gene which has been linked to tumors of the thyroid, breast, and endometrium that may be benign or malignant.

The Cancer Genome Atlas

Clear Cell RCC

Acquired genetic predisposition to renal carcinogenesis may occur through somatic mutation. Investigators with the Cancer Genome Atlas (TCGA) Research Network have used a variety of platforms to conduct extensive genomic surveys on a collection of tumors from patients with sporadic clear cell, papillary, and chromophobe RCC. Nineteen significantly mutated genes were identified in a study of 417 samples that were obtained from primary clear cell tumors at the time of nephrectomy (TCGA Research Network 2013). As anticipated, a significant number of alterations in genes that regulate cellular oxygen sensing were identified such as the *VHL* gene. In addition, mutations were observed recurrently in the phosphatidylinositol-4, 5-bisphosphate

3-kinase/protein-kinase 8 (PI3K/AKT) signaling pathway. Furthermore, a metabolic shift was detected in aggressive tumors with down-regulation of genes that control the tricarboxylic acid cycle (TCA) in conjunction with decreased AMPK and PTEN protein levels while genes that control the pentose phosphate pathway and the glutamine transporter genes were upregulated in conjunction with increased levels of the acetyl-CoA carboxylase protein and altered promoter methylation of miR-21 and GRB10. Mutations in genes involved with the SWI/SNF chromatin remodeling complex (PBRM1, ARID1A, SMARCA4) were also noted. Moreover, certain types of mutations were identified that could have prominent effects on other pathways such as widespread DNA hypomethylation as a result of mutations of the H3K36 methyltransferase SETD2. In the future, these types of genomic analyses will be extended to metastatic sites.

Papillary RCC

The genetic basis for sporadic papillary RCC has been explored in a study of 161 primary tumors that were clinically subclassified as type 1 (75 cases), type 2 (60 cases), or uncharacterized (26 cases) papillary RCC and subjected to analysis by whole-exome sequencing, copy-number analysis, messenger RNA and microRNA sequencing, DNA-methylation analysis, and proteomic analysis (TCGA Research Network 2016). These investigators concluded that specific genetic alterations distinguish type 1 from type 2 papillary RCC and that type 2 can be further classified into three molecular subgroups that correlate with differences in patient survival. While alterations in the *MET* pathway were detected in type 1 tumors, type 2 tumors were characterized by *CDKN2A* silencing, *SETD2* mutations, *TFE3* fusions, and increased expression of the NRF2-antioxidant response element (ARE) pathway. Poor survival was noted for a subgroup of type 2 in which a CpG island methylator phenotype (CIMP) was detected as well as a mutation of the *FH* gene that encodes fumarate hydratase.

Chromophobe RCC

TCGA investigators have also surveyed somatic genomic alterations in sporadic chromophobe RCC (Davis et al. 2014). Multidimensional and comprehensive characterization of a collection of 66 chromophobe tumors was carried out including mitochondrial DNA and whole-genome sequencing. These analyses confirmed that the site of origin for chromophobe RCC is the distal nephron versus a more proximal origin for other forms of RCC. Genomic rearrangements showed recurrent structural breakpoints within the telomerase reverse transcriptase (TERT) promoter region, which correlates with highly elevated TERT expression and kataegis (localized hypermutation). The investigators concluded that mitochondrial function is an important component of the disease biology.

Less Common Renal Neoplasms

Oncocytoma

Oncocytomas are considered to be a heterogeneous group of benign renal neoplasms that are entirely composed of large, well-differentiated neoplastic cells (oncocytes) with abundant mitochondria. Oncocytomas are similar to chromophobe carcinomas in that the cells of origin are the intercalated cells of the collecting ducts. Typically sporadic oncocytomas are single and unilateral; however, oncocytomas may be multiple and bilateral when they are associated with hereditary syndromes such as Birt-Hogg-Dubé, tuberous sclerosis complex (TSC), or hereditary paraganglioma (Bausch et al. 2013). Clinically benign oncocytomas must be distinguished from malignant chromophobe RCCs. A gene expression profiling study of nine cases of chromophobe RCC and nine cases of benign oncocytoma detected 11 candidate genes showing consistent differential expression (Rohan et al. 2006). These investigators reported that only 5 of the 11 genes were needed to effectively separate these two tumor groups (AP1M2, MAL2, PROM2, PRSS8, and FLJ20171). At present, "malignant" oncocytomas are generally considered to be cases of

chromophobe RCC that were not correctly characterized. Of note, when multiple tumors are present, one may not assume that each tumor is an oncocytoma simply because this diagnosis has been established for one of the tumors. Benign oncocytomas may coexist with other renal neoplasms that are actually malignant. Hybrid oncocytomas have also been described with features of both chromophobe RCC and oncocytoma (Waldert et al. 2010). The clinical outcome for these entities is generally favorable.

Collecting Duct RCC

Collecting duct carcinoma (also known as Bellini duct carcinoma) is a rare form of kidney cancer that is more likely to occur in younger patients of African descent and follow a clinical course that is rapidly fatal. The disease tends to be locally advanced or metastatic at the time of diagnosis. Collecting duct carcinomas have also been characterized by comprehensive genomic profiling (Pal et al. 2016). The 17 patients in this study (14 primary and 3 metastatic sites) underwent genomic profiling during the course of clinical care with targeted interrogation of genes known to be implicated in other cancers. Thirty-six genetic alterations were detected with an average of 2.1 per case. The most common alterations were in NF2 (5/17, 29%), SETD2 (4/17, 24%), SMARCB1 (3/17, 18%), and CDKN2A (2/17, 12%). Two of nine patients who were assessed for alterations in the *FH* gene had homozygous loss. The investigators commented that mutations outside of those that were targeted for interrogation cannot be excluded.

Renal Medullary Carcinoma

Renal medullary carcinoma (RMC) is an aggressive variant of collecting duct RCC that is typically seen in young adult males who have sickle cell trait or sickle cell disease. As such, most patients are of African descent. As with collecting duct RCC, this renal neoplasm tends to be metastatic at the time of diagnosis and is typically resistant to chemotherapy and radiation. A study of five frozen samples from patients with RMC was conducted with analysis by gene expression profiling and array comparative genomic hybridization in conjunction with RNA and whole-exome sequencing (Calderaro et al. 2016). One patient had sickle cell trait and the remaining four had sickle cell disease. The investigators detected the inactivation of the tumor suppressor gene SMARCB1, a component of the chromatin remodeling complex, in all tumors. Moreover, each of the four patients with sickle cell disease had a balanced interchromosomal translocation in the chromosome 22q11 region that disrupted the SMARCB1 sequence in the setting of a hemizygous SMARCB1 deletion. Since no other recurrent genetic alterations were observed and the overall genome was stable, the oncogenic potency of SMARCB1 inactivation was underscored. These investigators also confirmed that RMCs share some SMARCB1-deficiency signatures with rhabdoid neoplasms of the kidney.

Translocation Carcinomas

Mutations in the microphthalmia-associated transcription factor (MiT) family of transcription factors are associated with renal carcinogenesis involving mutations of the TFE3 and TFEB genes (Moch et al. 2016). Translocation carcinomas are more common in children and young adults including Xp11.2 translocation RCC (Ellis et al. 2014).

Sarcomatoid Tumors

Sarcomatoid RCC is not considered to be a specific subtype but rather a morphologic feature described as high-grade malignant spindle cells that are associated with aggressive clinical behavior irrespective of the RCC subtype of origin. The presence of sarcomatoid features is considered to be clinically meaningful even when it is only detected in a small fraction of the cells within a tumor. The convention established at the 2012 Consensus Conference of the International

Society of Urologic Pathology (ISUP) is that no minimum proportion of tumor is required to report this morphologic feature. In the event, the underlying subtype of RCC cannot be determined; the tumor is referred to as grade 4 unclassified carcinoma with a sarcomatoid component (Moch et al. 2016).

Clinical Outcomes

Observations regarding clinical outcome from the 2016 update of renal tumor classification by the IARC for a variety of rare tumors may be summarized as follows (Moch et al. 2016):

- Most carcinoids of the kidney have poor prognosis.
- Though tubulocystic RCC has been assigned a malignant behavior code, the summary of data from the WHO 2016 update indicates that only 4 of 70 patients have been reported to have metastasis to the bone, liver, and lymph nodes.
- Acquired cystic disease-associated RCC usually does not exhibit aggressive behavior.
- Clear cell papillary RCC is considered to be a malignant tumor that behaves in an indolent manner.
- There are presently no predictive molecular biomarkers that are suitable for routine use.

Rare Mechanisms of Renal Carcinogenesis: ALK Rearrangements

The anaplastic lymphoma kinase gene (ALK) at 2p23 may undergo chromosomal rearrangements that lead to fusion with various partner genes leading to aberrant production of oncogenic protein products in a number of tumor types. Crizotinib is an ALK protein inhibitor that has clinical efficacy in patients with ALK-rearranged non-small cell lung cancer. However, a fluorescence in situ hybridization (FISH) study of 534 consecutive adult patients listed in the Mayo Clinic Nephrectomy Registry only detected ALK rearrangements in two cases (0.4%) (Sukov et al. 2012). Both cases proved to be fatal.

Summary

1. The kidney, renal pelvis, and ureter are reported as a single cancer site in tumor registries and many epidemiologic studies even though they do not share a common histology.
2. Though clear cell is the most common histologic subtype overall, the proportion of patients with papillary and other non-clear cell forms of RCC is significantly higher among patients of African descent. This may be a contributing factor to disparities in clinical outcome.
3. The incidence of RCC has been rising in the United States with a divergence of trends with respect to histologic subtypes between Caucasians and African-Americans.
4. RCC is uncommon in patients under 40 years of age. Risk factors include smoking, obesity, hypertension, low levels of physical activity, diabetes mellitus, CKD, ESRD, polycystic kidney disease, sickle cell disease, autoimmune diseases, immunosuppression after organ transplantation, urinary tract infections, chronic hepatitis C infection, kidney stones, gallstones, increased number of pregnancies, history of hysterectomy, high analgesic intake, exposure to chemotherapy as a child, occupational exposures such as trichloroethylene, cadmium, coal products, petroleum products, X-radiation, gamma radiation, and RCC in a first-degree relative and rare hereditary disorders.
5. Alcohol consumption is associated with lower rates of RCC but higher rates of other malignancies.
6. While the current understanding of renal carcinogenesis is incomplete, disruption of tumor suppression appears to be a broad theme throughout.

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Symptoms of Kidney Cancer and Appropriate Diagnostic Tools

32

Milan Hora

Contents

Abstract

Currently, more than 50 (60)% of renal cell carcinomas (RCCs) are detected incidentally on abdominal ultrasound (US) or computed tomography (CT)/ magnetic resonance imaging (MRI). These tumours are usually smaller and of lower stage. Many patients with renal masses (RMs) remain asymptomatic until the late stages of the disease. RCC can become very large without any symptoms, due to the retroperitoneal position of the kidney. It has been reported that the prevalence of the classic triad of flank pain, gross haematuria, and a palpable abdominal mass in some parts of the world is lower than previously observed (now 6–10%) and correlates with advanced disease and subtypes associated with poor prognosis. Paraneoplastic syndromes are found in approximately 20-30% of patients with symptomatic RCCs (anaemia, hypercalcemia, production of adrenocorticotrophic hormone, polycytemia, hepatic dysfunction, amyloidosis, fever and weight loss). A few

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patients present with symptoms caused by metastatic RCC (mRCC), such as bone pain, pathological fractures, deterioration of performance status (PS) including fatigue, anorexia, weight loss, pulmonary symptoms (persistent cough), neurological symptoms (result from intracranial and spinal column metastases). Despite the advances in diagnosis, especially improved imaging techniques, about 20–30% of all patients are diagnosed with metastatic disease (symptomatic or asymptomatic metastases). Diagnostic tools as a history, physical examination and laboratory have limited information, mostly in advanced RCC only. Crucial role plays imaging: US is crucial mainly for primary diagnosis, but not sufficient for staging and planning of surgery. Contrast-enhanced multiphase abdominal CT (and/or MRI) are the most appropriate imaging modalities for renal tumour diagnosis/characterisation and staging. CT features cannot reliably distinguish even oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms. Chest CT is recommended for staging assessment of the lungs and mediastinum and it is more accurate than chest X-ray. MRI: In most clinical aspects, MRI is very similar to CT. Main advantages of MRI are no risk of allergy to iodine contrast fluid and no exposure to radiation (important mainly in pregnancy). MRI may provide additional information to CT on venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT and probably in cystic lesions, but this topic is under investigation. PET CT (MRI): For routine investigation, PET CT is not currently recommended. Interventional imaging techniques (digital subtraction angiography of the renal artery and inferior cavography) were replaced with non-invasive methods (CT, MRI). Angiography is indicated only in therapeutic procedures e.g. embolization of angiomyolipoma and solving of complication following kidney resection (bleeding, arteriovenous fistula). Bone scintigraphy. A bone scan is not routinely recommended, in only special cases, e.g. pathological fractures etc. It can be replaced with FDG PET CT. Chest X-ray. A routine chest X-ray should be done as a minimum in staging and in follow-up. As mentioned above, chest CT is more accurate. Biopsy of primary kidney tumour is indicated in following indications: Small renal masses – before active surveillance (if potential clinical benefit), before ablative treatments and in metastatic RCC to select the most suitable form of medical and surgical treatment strategy. Performing of biopsy is following: Percutaneous, under ultrasound or CT guidance, under local anaesthesia, with core needle about 18G core and with coaxial technique (allowing multiple biopsies – at least two, to avoid tumour seeding).

Keywords
Renal cell carcinoma · Symptoms · Ultrasound · CT · Biopsy

Symptomatology

Currently, more than 50 (60)% of renal cell carcinomas (RCCs) are detected incidentally when abdominal ultrasound (US) or computed tomography (CT)/magnetic resonance imaging (MRI) is carried out for other medical reasons. These tumors are usually smaller and of lower stage (Ljungberg et al. 2015; Petejova and Martinek 2016). This has led to an increase in the incidence of small renal masses (RMs), defined as contrast-enhancing masses with a greatest dimension of 4 cm or less on abdominal imaging (Ljungberg et al. 2015). Many patients with RMs remain asymptomatic until the late stages of the disease. RCC can become very large without any symptoms, due to the retroperitoneal position of the kidney. It has been reported that the prevalence of the **classic triad** of flank pain, gross hematuria, and a palpable abdominal mass in some parts of the world is lower than previously observed (now 6–10%) and correlates with advanced disease and subtypes associated with poor prognosis (Ljungberg et al. 2015). **Paraneoplastic syndromes (Paraneoplastic manifestations: Hypercalcemia** is caused by release of parathyroid hormone-related peptide (PTHrP), interleukins IL-6 and IL-1, and tumor necrosis factor α (TNFα) from cancer tissue. The mechanism by which PTHrP causes hypercalcemia involves many of the normal hormonal pathways of calcium

homeostasis. PTHrP binds to the PTH receptor in both bone and renal tissue. This binding leads to increased bone resorption and decreased renal clearance of calcium as well as increased phosphorus excretion. Nonmetastatic nephrogenic **hepatic dysfunction syndrome (Stauffer's syndrome)** is a unique and rare paraneoplastic manifestation of renal cell carcinoma that usually manifests as anicteric cholestasis. This syndrome, originally described in 1961 by M. H. Stauffer, is characterized by elevated alkaline phosphatase, erythrocyte sedimentation rate, α-2-globulin, and γ-glutamyltransferase, thrombocytosis, prolongation of prothrombin time, hepatosplenomegaly, and the absence of hepatic metastasis and jaundice due to the possible role of IL-6 overexpression by the primary tumor. **Polycythemia (or erythrocytosis)** is caused by ectopic production of erythropoietin by RCC cells. Nonspecific symptoms such as **fever, weight loss, and fatigue** (common to many malignancies) are thought to be mediated by cytokines especially TNFα and IL-6). Many other endocrine abnormalities are associated with RCC, such as elevated human chorionic gonadotropin and adrenocorticotropic hormone, manifesting themselves as clinical syndromes such as Cushing's syndrome and hyper-/hypoglycemia. Other conditions associated with RCC include amyloidosis due to pathological production and deposition of AA (amyloid A) protein with typical clinical presentation related to the specific organ systems affected including the cardiovascular, renal, and gastrointestinal systems. A number of other syndromes such as light chain nephropathy, vasculitis, coagulopathies, neuromyopathies, and Wells syndrome (eosinophilic cellulitis) have been also described in patients with RCC but a less commonly (Petejova and Martinek 2016).) are found in approximately 20–30% of patients with symptomatic RCCs (anemia, hypercalcemia, production of adrenocorticotrophic hormone, polycythemia, hepatic dysfunction, amyloidosis, fever, and weight loss). A few patients present with **symptoms caused by metastatic RCC (mRCC)**, such as bone pain, pathological fractures, and deterioration of performance status (PS) including fatigue, anorexia, weight loss, pulmonary symptoms (persistent cough), and neurological symptoms (result from intracranial and spinal column metastases) (Ljungberg et al. 2015; Petejova and Martinek 2016). Despite the advances in diagnosis, especially improved imaging techniques, about 20–30% of all patients are diagnosed with metastatic disease (symptomatic or asymptomatic metastases) (Petejova and Martinek 2016) (Fig. 1).

Diagnostic Tools

History

History is focused on familiar incidence of RCC and symptoms.

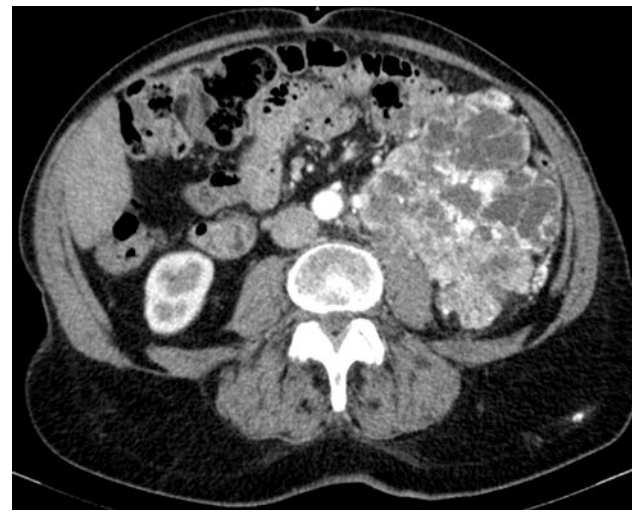

Fig. 1 Postcontrast CT, arterial phase, in a 73-year-old woman. Partially necrotic tumor of the lower pole of the left kidney growing to the psoas muscle and mesocolon, metastases to the lungs, and histology clear RCC high grade. The woman suffered from paraneoplastic syndromes (anemia, weight loss)

Physical Examination

Clinical examination may reveal an abdominal mass in the loin/subcostal abdominal area but only in advanced cases. Sign of metastases in mRCC, e.g., lymphadenopathy (e.g., enlarged nodes in the supraclavicular fossa) and varicocele (tumor extended into the left renal vein), and sign of inferior vena cava (IVC) obstruction (bilateral leg edema and collateral venous circulation) can be seen.

Laboratory

Commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium, coagulation study, and urinalysis. No special laboratory markers are used in common clinical practice. The value of hemoglobin, LHD, and serum corrected calcium is an integral part of risk stratification for strategy of treatment of mRCC. Two main systems are used: the Memorial Sloan-Kettering Cancer Centre (MSKCC) and/or the Metastatic Renal Cancer Database Consortium (IMDC) risk models (Ljungberg et al. 2015).

Imaging

Ultrasound

Ultrasound is crucial mainly for primary diagnosis, but not sufficient for staging and planning of surgery. Doppler US is not a standard part of investigation with exception of special indications, e.g., control of blood supply following nephron-sparing surgery with suspicious vascular complications.

CEUS (contrast-enhanced ultrasound) is indicated only in specific cases (e.g., end-stage kidney disease, ESKD, when contrast fluid – iodine or gadolinium – cannot be applied). Its main limitations are the experience required, a special software, and being observer dependent (Sanz et al. 2016) (Fig. 2).

CT

Contrast-enhanced multiphase abdominal CT and MRI are the most appropriate imaging modalities for renal tumor diagnosis/characterization and staging (Ljungberg et al. 2015). It is a basis of diagnosis of renal tumors. It allows accurate diagnosis of RCC and provides information on primary tumor extension, tumor postcontrast enhancement (it should be in CT > 15 HU), venous involvement, enlargement of locoregional lymph nodes, function and morphology of the

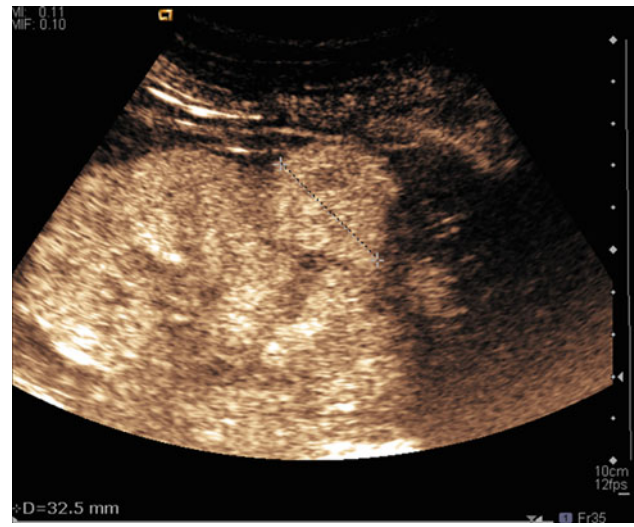

Fig. 2 CEUS (contrast-enhanced ultrasound) of the tumor of the kidney convexity (in man with end-stage kidney disease)

contralateral kidney, and condition of the adrenal glands and other solid organs. CT (and MRI as well) cannot reliably distinguish different histological types of renal tumor with exception typical angiomyolipoma. CT features cannot reliably distinguish even oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms (Ljungberg et al. 2015). **Biphasic CT angiography** (both arteries and vein are depicted, the best even their topographic anatomy) is useful in selected cases for detailed information on renal vascular supply (Ferda et al. 2007), e.g., for planning of surgery. **Chest CT** is recommended for staging assessment of the lungs and mediastinum and it is more accurate than chest X-ray. Chest CT should be part of primo diagnosis of renal tumor and should be implemented in follow-up instead of chest X-ray. **Brain CT** is indicated in only suspicious brain or skull metastasis, e.g., neurological symptoms (Figs. 3, 4, 5, 6, and 7).

MRI

In most clinical aspects, MRI is very similar to CT. Main advantages of MRI are no risk of allergy

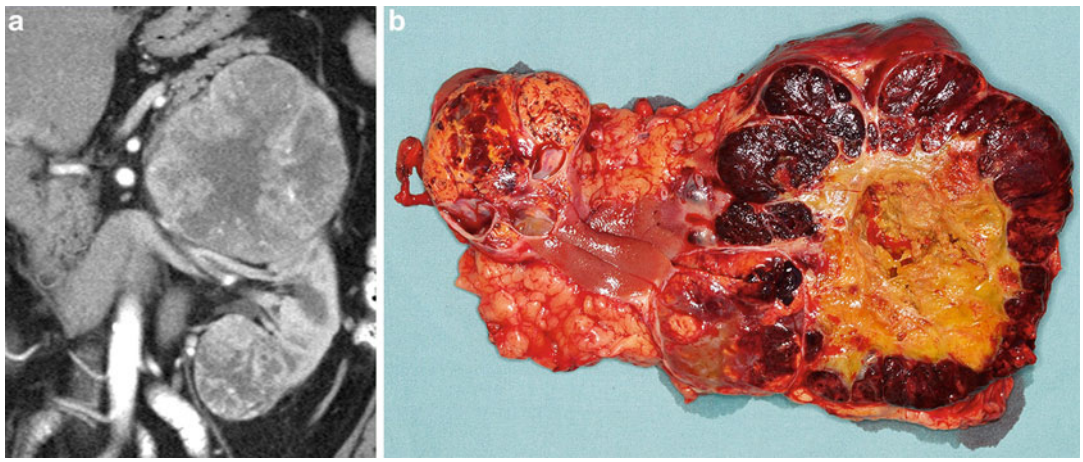

Fig. 3 (**a**) Contrast-enhanced CT of the left kidney, coronary view: duplex tumor (bigger one on the upper pole, smaller on the lower pole) (**b**) Specimen at operation

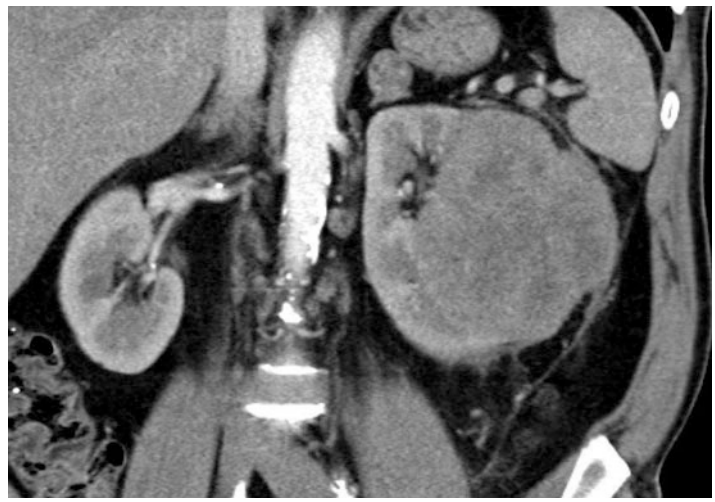

Fig. 4 Postcontrast CT, coronary view. Tumor of the left kidney and the left adrenal gland as well

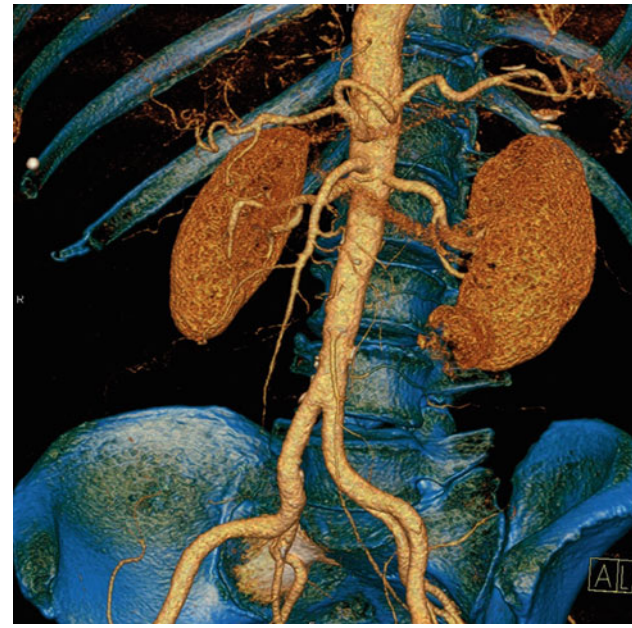

Fig. 5 CT biphasic angiography and tumor of the lower pole of the left kidney located medially

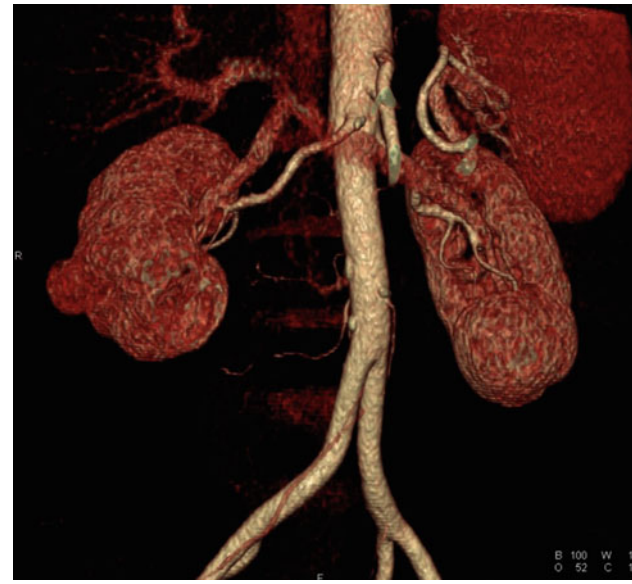

Fig. 6 CT biphasic angiography and tumor of the convexity of the right kidney

to iodine contrast fluid and no exposure to radiation (important mainly in pregnancy). MRI may provide additional information to CT on venous involvement if the extent of an inferior vena cava (IVC) tumor thrombus is poorly defined on CT and probably in cystic lesions, but this topic is under investigation. Main disadvantages are as follows: MRI is contraindicated in foreign metallic bodies and cardiac pacemakers. MRI is not appropriate for chest imaging (combined in one session with abdominal imaging) due to a lengthy of a procedure. The new generation of 3T MRI has improved spatial and time resolutions, which are favorable in imaging of the renal vasculature and part of investigation. Therefore, 3T

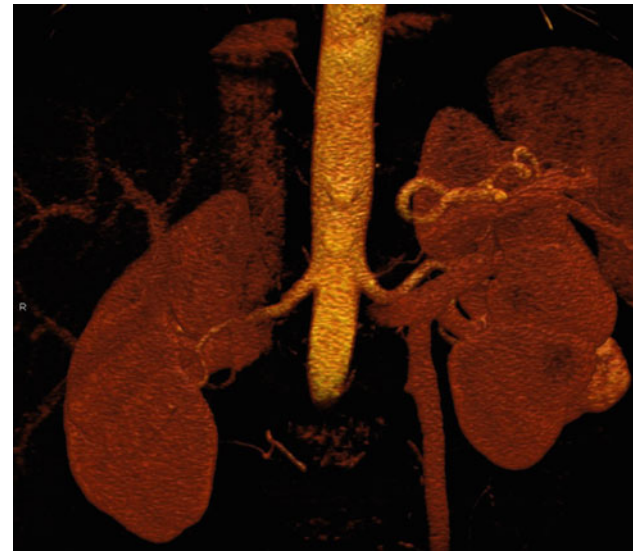

Fig. 7 CT biphasic angiography and tumor of the convexity of the lower pole of the left kidney, noticeable left ovarian vein

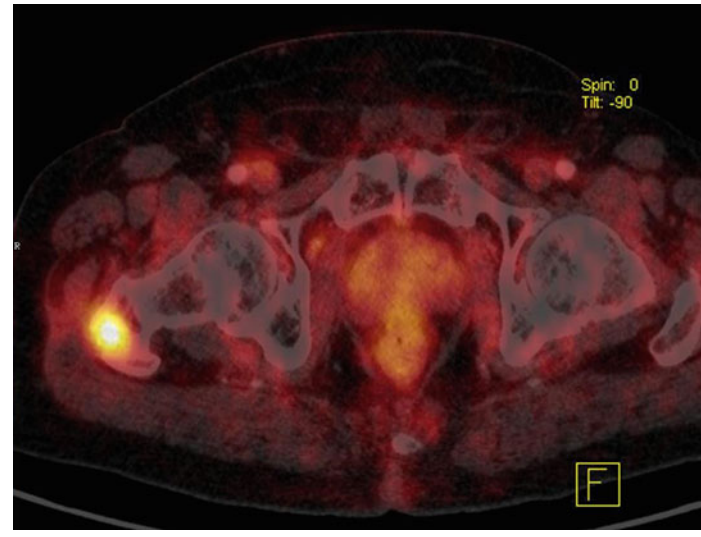

Fig. 8 FDG PET-CT of metastasis of RCC to the right femur (greater trochanter of the thigh bone)

MRI biphasic angiography can be part of investigation, but small aberrant vessels are more frequently missed than with CTA, and the 3D reconstruction is highly depending on the skills of the radiologist (Hora et al. 2013).

PET-CT (MRI)

Positron emission tomography-computerized tomography (PET-CT) with ^{18}F-fluorodeoxyglucose (FDG) currently has lower sensitivity compared to enhanced CT for diagnosis of primary renal masses but better sensitivity for diagnosis of metastases. Predicting and monitoring response to targeted therapy could direct the clinician toward drug selection or modification during therapy. The possibility of treating patients with advanced renal cell carcinoma with 124I-girentuximab attached to 177Lu, a strong beta-emitter, is investigated (Gofrit and Orevi 2016). For routine investigation, PET-CT is not currently recommended (Ljungberg et al. 2015) (Figs. 8 and 9).

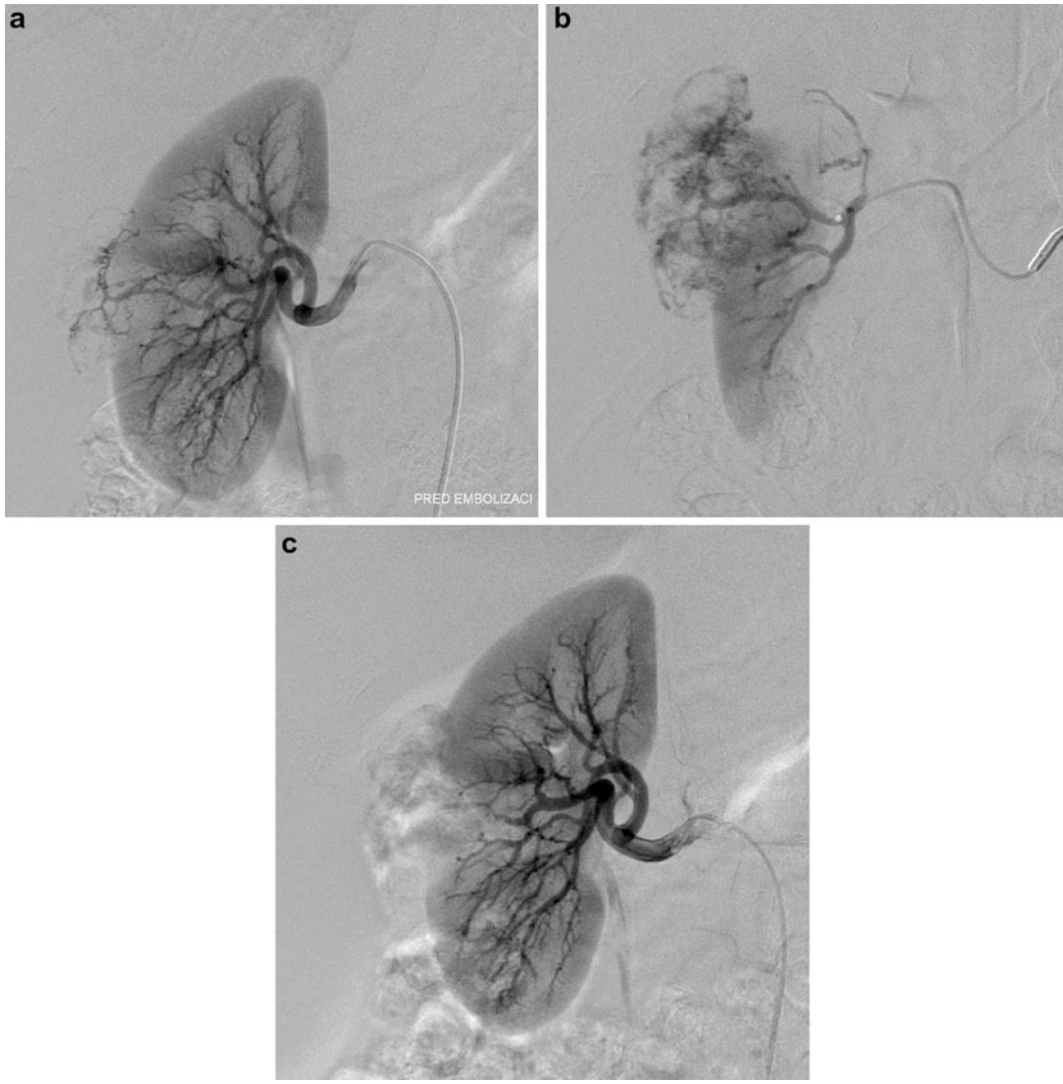

Fig. 9 (**a**, **b**) Arteriography of the right kidney with angiomyolipoma of convexity of the kidney. (**c**) After embolization

Interventional imaging techniques (digital subtraction angiography of the renal artery and inferior cavography) were replaced with noninvasive methods (CT, MRI) (Ljungberg et al. 2015). Angiography is indicated only in therapeutic procedures, e.g., embolization of angiomyolipoma and solving of complication following kidney resection (bleeding, arteriovenous fistula).

Bone scintigraphy. A bone scan is not routinely recommended, in only special cases, e.g., pathological fractures, etc. It can be replaced with FDG PET-CT.

Chest X-ray. A routine chest X-ray should be done as a minimum in staging and in follow-up. As mentioned above, chest CT is more accurate (Ljungberg et al. 2015).

Biopsy of Primary Kidney Tumor

Biopsy is discussed in a special chapter of this textbook. Indications are the following: small renal masses – before active surveillance (if potential clinical benefit), before ablative

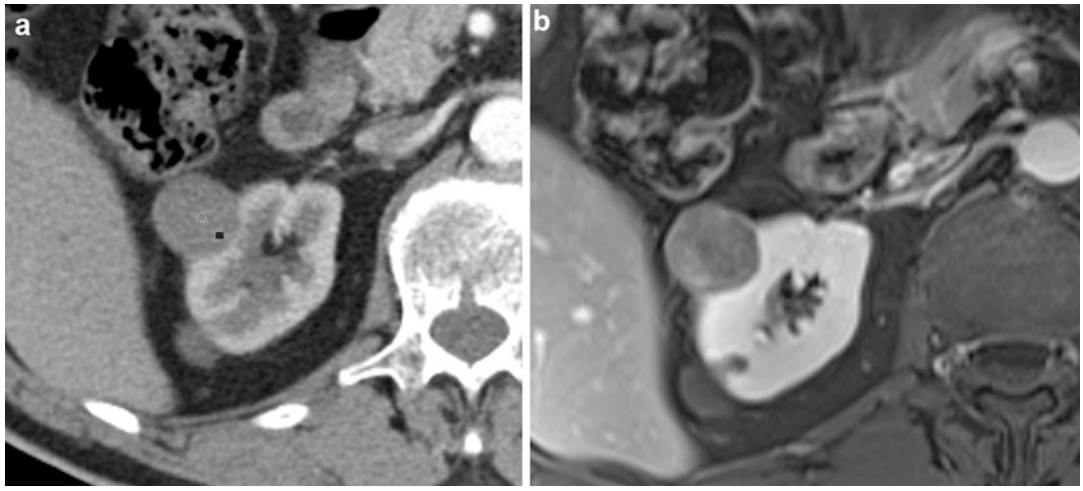

Fig. 10 (**a**) Postcontrast CT, tumor of the right kidney, postcontrast density 39 HU only. Histology of resected tumor was papillary RCC type 1 pT1a G1 pR0 (**b**) MRI of the same tumor

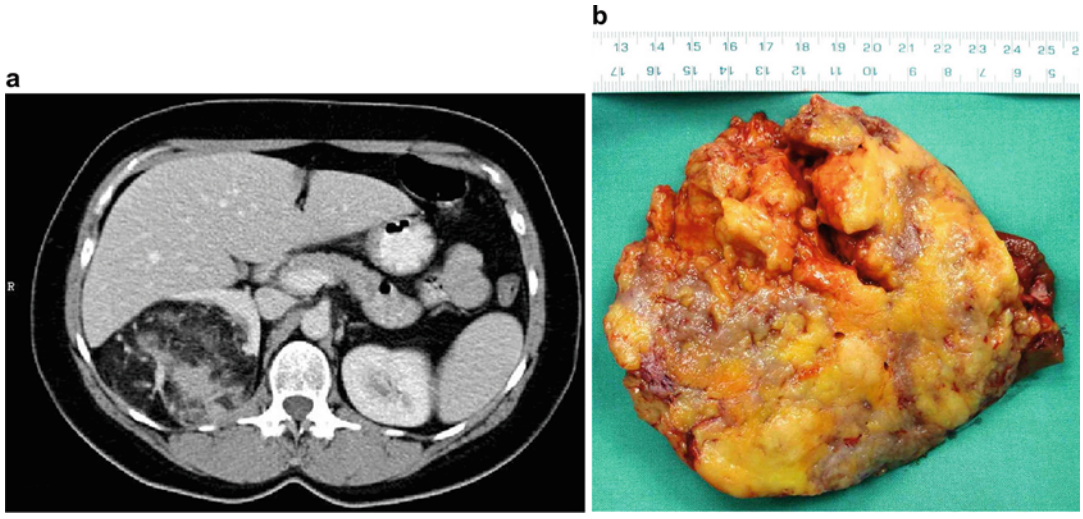

Fig. 11 (**a**) CT of huge angiomyolipoma of the upper pole of the right kidney (**b**) Specimen at operation (open resection)

treatments, and in metastatic RCC to select the most suitable form of medical and surgical treatment strategy (Kutikov et al. 2016). Performing of biopsy is the following: percutaneous, under ultrasound or CT guidance, under local anesthesia, with core needle about 18G core, and with coaxial technique (allowing multiple biopsies – at least two – to avoid tumor seeding) (Marconi et al. 2016).

TNM Classification and Staging of Renal Cell Carcinoma (RCC)

TNM classification of RCC according to the American Join Committee on Cancer (AJCC) 2010	
Primary tumor (T)	
Tx	Primary tumor cannot be assessed

(*continued*)

TNM classification of RCC according to the American Join Committee on Cancer (AJCC) 2010		
Primary tumor (T)		
T0		No evidence of primary tumor
T1		Tumor ≤ 7 cm in greatest dimension and limited to the kidney
	T1a	Tumor ≤ 4 cm
	T1b	Tumor > 4 cm but ≤ 7 cm
T2		Tumor >7 cm in greatest dimension and limited to the kidney
	T2a	Tumor >7 cm but ≤ 10 cm
	T2b	Tumor >10 cm
T3		Tumor extends into major veins or perinephric tissues but not beyond Gerota's fascia
	T3a	Tumor extends into the renal vein or directly invades perinephric tissues, but not beyond Gerota's fascia
	T3b	Tumor grossly extends into the vena cava below the diaphragm
	T3c	Tumor grossly extends into the vena cava above the diaphragm or invades wall of the vena cava
T4		Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in the regional lymph node

Note: There is no longer any distinction between N1 metastasis in a single regional lymph node and N2 metastases in more than one regional lymph node. Instead, N1 comprises metastasis in regional lymph node(s) (Ljungberg et al. 2015).

Distant metastasis (M)			
M0		No distant metastasis	
M1		Distant metastasis	
Staging			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1-2	N1	M0
	T3-4	Any N	M0
Stage IV	Any T	Any N	M1

In the fourth version of TNM supplement (2012), different staging is proposed for stages III and IV. In stage III remains category T3N0M0 only, categories T4NXM0 and TXN1M0 were shifted from stage III to stage IV (Wittekind et al. 2012).

Specific Characteristics of Different Histological Types

Papillary RCC Type 1

Regular pRCC1 has some typical gross morphological characteristics. On ultrasound, it imitates pathologically changed cysts with hyperdense contents. On CT and MRI, it is rounded and homogenous, with minimal postcontrast

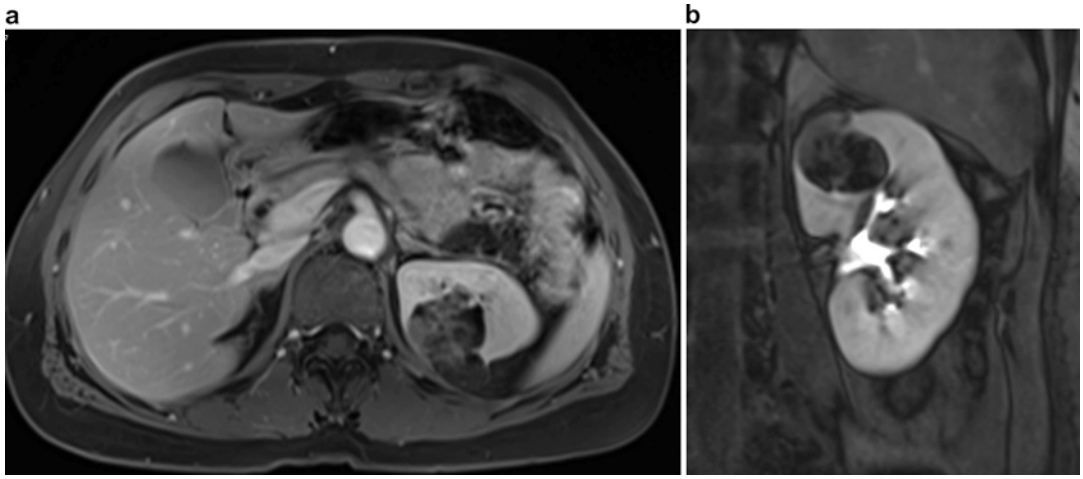

Fig. 12 (**a**) MRI angiomyolipoma of the upper part of the left kidney (**b**) The same case, MRI, coronary view

Table 1 Renal cystic lesions – Bosniak classification (Ljungberg et al. 2015; Warren and McFarlane 2005)

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft tissue elements. This category also includes totally intrarenal, non-enhancing, high-attenuation renal lesions > 3 cm. Generally well marginated	Follow-up. Some are malignant
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement	Surgery or active surveillance. Over 50% are malignant[a]
IV	Clearly malignant containing enhancing soft tissue components	Surgery. Most are malignant

[a]The percentage of malignant tumor in categories IIF–III can be changed due to formal shift of former "malignant" entity multilocular cystic RCC to "benign" entity multilocular cystic renal neoplasm of low malignant potential – MCRNLMP (WHO renal tumor classification 2016) (Moch et al. 2016) (Fig. 13).

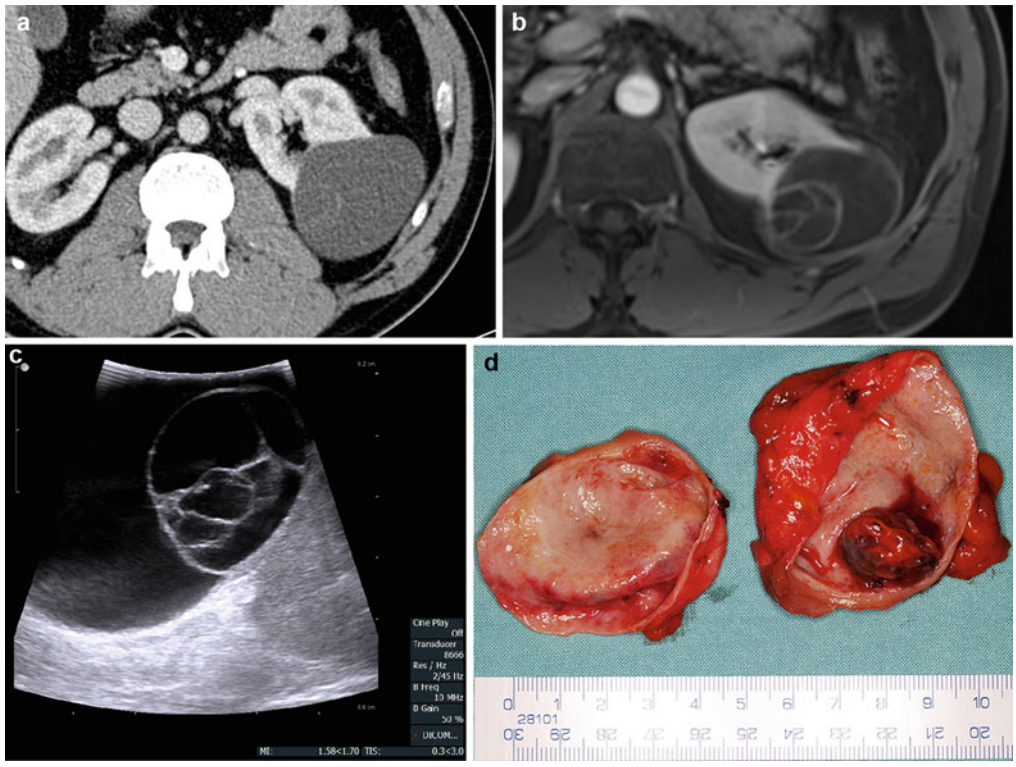

Fig. 13 Man 43-year-old with cystic renal lesion of the middle part of the left kidney Bosniak types IIF–III (**a**) CT (**b**) 3T MRI – T1. In comparison with CT, septa are very well visible (**c**) Peroperative ultrasound (high-frequency sound) – excellently visible septa in tumor (**d**) Specimen at operation following laparoscopic resection. Histology was multilocular cystic renal neoplasm of low malignant potential – MCRNLMP (Moch et al. 2016)

enhancement. In bigger tumors, there is a hypodense central area with a narrow, irregular, contrast-enhancing margin. The characteristic spherical appearance of pRCC1 on CT/MRI is similar to Bosniak IIF or III cysts. Tumors dissected in situ are ochre, soft, and protruding from the pseudocapsule like a "minced meat sausage." It is fragile and therefore it can rupture easily (Prochazkova et al. 2017) (Fig. 10).

Angiomyolipoma

Ultrasound, CT, and MRI often lead to diagnosis due to the presence of adipose tissue. Biopsy is rarely useful. Preoperatively, it may be difficult to differentiate between smooth muscle cell tumors and epithelial tumors including epithelioid AML. Due to benign course of AML, active surveillance based on imaging only is recommended for most of AMLs (Ljungberg et al. 2015) (Figs. 11 and 12; Table 1).

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33 Prognostic and Predictive Markers, and Stratifications Tables, for the Detection and Treatment of Renal Cell Carcinoma

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Abstract

Despite knowledge of disease stage, grade, and histological subtype (HS), patient outcome in RCC remains elusive. Therefore, a vast number of predictive and prognostic models as well as biological markers have been proposed. Many show promise in stratifying the survival curves or discriminating between stage distributions, while others achieved independent predictor status in specific end points of interest.

There is an increased interest in composite biomarker, such as the BioScore (Parker et al., Cancer 115(10):2092–2103, 2009), which has increased accuracy compared to other models. The search continues for an ideal model that is relevant, simple to use and understand, and that will be able to distinguish between different patient diseases and characteristics. The future in prognostic factors and predictive models lies in finding biomarkers that will assist in choosing select target therapies, immunotherapies, and chemotherapies. To improve patient prognosis, treatment sequences, with targeted agents and novel drugs, need to be individualized by using the patient's genomic classifications.

Presently, Immune oncology agents (IO), notably immune checkpoint inhibitors targeting PD-1, are the most promising in treatment of RCC. It is postulated that a preestablished immune response can optimize immune checkpoint inhibition therapy. Therefore, even though past studies found few desired results, vaccinations may hold the key to future therapeutic success (Curtis et al., Curr Oncol Rep 18 (9):57, 2016; Hammers H, Curr Opin Urol 26 (6):543–547, 2016).

This chapter will focus on prognostic models specifically for metastatic RCC and models for all types of RCC. Second, this chapter will focus on molecular biomarkers, including tissue-based biomarkers, blood-based biomarkers, and immune system biomarkers.

Introduction

The natural history of renal cell carcinoma (RCC) is unpredictable. Up to 7% of patients with indolent tumors (≤4 cm) present with metastatic disease and are at an elevated risk of disease-specific mortality. On the other hand, up to 40% post-nephrectomy patients with lymph node metastases survive 5 years after surgery(Sun et al. 2011). Prognostic markers measure clinical or biological characteristics that can predict patient outcome regardless of disease treatment. Predictive markers measure clinical or biological characteristics that are used to optimize treatment selection (Maroto and Rini 2014; Li et al. 2015). There are two types of predictive markers, static and dynamic. Static markers are used to determine the likelihood of responding to a certain treatment, whereas dynamic markers predict tumor response to ongoing treatment (Li et al. 2015). Prognostics are important for risk stratification, counseling, and targeted therapy selection. Studies have shown that watchful waiting is beneficial in select patients with low-risk prognostic profiles, rather than subjecting them the ill effects of therapy (Li et al. 2015). Prognostics in RCC look at four different groups: patient performance status, tumor burden, pro-inflammatory markers, and treatment-related factors (Li et al. 2015).

Several prognostic factors and predictive markers have been proposed to distinguish between poor and favorable risk patients as well as predict RCC natural history. This chapter will address the history of prognostics, existing prognostic factors, factors predicting response to targeted therapy, and established prognostic models.

Prognostics in Renal Cell Carcinoma

Prediction of Overall Survival and/or Progression-Free Survival in Metastatic Renal Cell Carcinoma

Multivariable modeling in the prediction of cancer-specific mortality was pioneered by Elson et al. in 1988 (Elson et al. 1988) (Table 1). Their model relied on American patients and included ECOG-PS, time from initial diagnosis, number of metastatic sites, prior cytotoxic chemotherapy, and weight loss. In 1999, Motzer et al. (Motzer et al. 1999) examined the Memorial Sloan-Kettering Cancer Center (MSKCC) patient database and suggested five predictors of metastatic RCC (mRCC) mortality: Karnofsky performance status [KPS], lactate dehydrogenase [LDH], hemoglobin, corrected calcium, and nephrectomy status. They stratified patients in three risk groups: favorable (zero risk factors), intermediate (one to two risk factors), and poor (three or more risk factors). The median overall survival (OS) was found to be 30, 14, and 5 months for the favorable-, intermediate-, and poor-risk groups, respectively (Li et al. 2015). In 2002, nephrectomy status was replaced with time from diagnosis to start of interferon (Motzer et al. 2002). The 2002 Motzer model was externally validated in 2013 with an accuracy of 66% (Heng et al. 2013). The Motzer score was further updated in 2004, reducing its number of predictor variables from five to three: KPS, hemoglobin, and corrected calcium (Motzer et al. 2004). In 2005, Mekhail et al. (2005) suggested updating the 2002 Motzer score by adding previous exposure to radiotherapy as well as the presence of metastatic sites. Finally, in 2007, Escudier et al. (2007) suggested replacing KPS with the number of metastatic sites. Unfortunately, other than the 2002 Motzer, no other models were formally subjected to internal or external validation, and therefore, their accuracy, performance, and effect on clinical decision remain unknown (Sun et al. 2011).

In 2005, Negrier et al. (2005) introduced a different prognostic model based on European patients. This model identified four variables that were associated with disease progression despite immunotherapy: time from RCC diagnosis to metastases, number of metastatic sites, presence of hepatic metastases, and neutrophil count. It was externally validated by Heng et al. (2013) in 2013 with an accuracy of 64%.

In 2009, Heng et al. (2009) pioneered the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model for patients with mRCC who were treated with targeted therapies. This model included neutrophil and platelet counts to the following four Motzer criteria: hemoglobin, corrected calcium, KPS, and time from diagnosis to treatment. The IMDC was internally validated with an accuracy of 73% and was externally validated in 2013 with an accuracy of 66% (Heng et al. 2013). It has been suggested that the IMDC can be used to select patients for first- and second-line therapy as well as cytoreductive surgery (Li et al. 2015). For example, Heng et al. 2014 (2014) showed that patients who have survived 1 year and have $\leq$3 IMDC prognostic factors were more likely to benefit from cytoreductive nephrectomy. Studies have shown that specific location of metastatic sites predisposed to worse prognosis. For example, Mckay et al. (2014) found that patients treated with targeted therapy had a worse survival with bone and lung metastases. Additionally, Trihn et al. (2013) found that every additional positive node increased cancer-specific mortality in patients undergoing cytoreductive nephrectomy. Therefore, inclusion of disease location to nomograms was suggested by several authors. Of note, in 2008, Motzer et al. (2008) devised a pre-sunitinib treatment nomogram for mRCC, taking into account metastatic sites.

Last but not least, in 2011, Karakiewicz et al. (2011) proposed a model that included KPS, time from primary diagnosis to treatment, baseline albumin, and baseline alkaline phosphatase. This model showed 75% accuracy in prediction of

Table 1 Prediction of overall survival and/or progression-free survival in mRCC

Model	Target population	Predictors
Elson et al. (1988)	mRCC	ECOG-Ps Time from initial diagnosis Number of metastatic sites Prior cytotoxic chemotherapy Weight loss
Motzer et al. (1999)	mRCC treated with NT	Lactate dehydrogenase >ULN Hemoglobin >ULN KPS Corrected serum calcium >ULN Absence of NT
Motzer et al. (2002)	mRCC treated with NT/IFN	KPS Lactate dehydrogenase <UL Hemoglobin >ULN Corrected serum calcium >ULN Time from diagnosis to IFN
Motzer et al. (2004)	mRCC treated with NT/IFN	KPS Hemoglobin >ULN Corrected serum calcium >ULN
Négrier et al. (2005)	mRCC treated with cytokine	Presence of biologic signs of inflammation Short time interval from renal tumor to mRCC Elevated neutrophil count Liver metastases Bone metastases Performance status Number of metastatic sites Alkaline phosphatase Hemoglobin
Leibovich et al. (2005)	Metastatic ccRCC treated with NT	Age Gender Symptoms at NT Time from NT to mRCC Location/surgical treatment of metastases Presence/level of tumor thrombus Histologic subtype TNM (2002) Tumor size Perinephritic fat invasion Lymph node invasion Nuclear grade Tumor necrosis Sarcomatoid differentiation
Mekhail et al. (2005)	mRCC	Multifocality Time from diagnosis to study entry Lactate dehydrogenase >ULN Corrected serum calcium >ULN Previous radiotherapy Presence of hepatic/pulmonary/retroperitoneal/ lymph node metastases
Escudier et al. (2007)	mRCC patients who failed IO	Alkaline phosphatase >ULN Corrected serum calcium >ULN Lactate dehydrogenase >ULN Number of metastatic sites Time from diagnosis to metastatic diagnosis

(*continued*)

Table 1 (continued)

Model	Target population	Predictors
Motzer et al. (2008)	mRCC patients treated with sunitinib	Corrected serum calcium Number of metastatic sites Hemoglobin >ULN Prior NT Lung metastases Liver metastases ECOG-Ps Thrombocytosis Time from diagnosis to treatment Alkaline phosphatase Lactate dehydrogenase
Heng et al. (2009) IMDC	mRCC patients treated with VEGF agents	KPS Time from diagnosis to treatment Hemoglobin >ULN Corrected serum calcium >ULN Neutrophil >ULN Platelet >ULN
Karakiewicz et al. (2011)	mRCC patients treated with bevacizumab plus IFN or IFN alone	KPS Time from primary diagnosis to treatment Baseline albumin Baseline alkaline phosphatase

mRCC metastatic renal cell carcinoma, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *NT* nephrectomy, *ULN* upper limit normal, *KPS* Karnofsky performance status, *IFN* interferon, *IL-2* interleukin-2, *VEGF* vascular endothelial growth factor

mortality after therapy with bevacizumab with or without IFN, compared to the 52% accuracy for the 2002 Motzer model (Motzer et al. 2002) tested within the same cohort. This model awaits external validation.

Prediction of Overall Survival and/or Progression-Free Survival in all Types of Renal Cell Carcinoma

The previously discussed models, Motzer et al., Mikhail et al., Negrier et al., and IMDC, apply exclusively to patients with metastatic RCC (mRCC). Many other models have been developed for patients with all types of RCC. In 2001, Zisman et al. pioneered an integrated staging system (UISS) for survival prediction in patients with all stages of RCC (Zisman et al. 2001) (Table 2). This model includes TNM stage, Fuhrman grade, and ECOG-PS. It has been widely tested and validated with an accuracy ranging from 84% to 86% (Sun et al. 2011). In 2007, Karakiewicz et al. (2007a) devised a nomogram targeting patients with all types of RCC. This model included pT stage, pN stage, M stage, tumor size, Fuhrman grade, and symptom classification. This model has the highest predictive accuracy, of 88–91%, and has been externally validated by multiple groups.

In 2009, Karakiewicz et al. (2009) developed and externally validated a conditional nomogram for predicting RCC-specific mortality, using TNM stage, Fuhrman grade, tumor size, and symptom classification for predictor variables. This model has a high accuracy of 91% indicating survival probability 1, 2, 5, and 10 years after nephrectomy in patients with RCC (Karakiewicz et al. 2009). Conditional survival (CS) provides dynamic data on a patient's probability of surviving x years, given that he/she has already survived y years after the diagnosis (Harshman et al. 2012). In other words, CS provides data on prognosis of long-term cancer survivors, specifically poor-risk patients, compared to newly diagnosed patients (Li et al. 2015). For example, Harshman et al. (2012) found a 24% increase in the 2-year CS in mRCC patients from the International mRCC Database Consortium treated with VEGF-targeted

Table 2 Prediction of overall survival and/or progression-free survival in all types of RCC

Model	Target population	Predictors
Zisman et al. (2001) UISS	RCC of all stages	AJCC Fuhrman grade ECOG-Ps
Frank et al. (2002)	Localized ccRCC	TNM (1997) Tumor size Nuclear grade Tumor necrosis
Kim et al. (2005)	Metastatic ccRCC	T stage ECOG-Ps CAIX Vimentin p53 PTEN
Karakiewicz et al. (2007a)	Papillary, chromophobe, ccRCC	pT stage pN stage M stage Tumor size Fuhrman grade Symptom classification
Karakiewicz et al. (2009) Conditional survival	RCC of all stages	pT stage pN stage M stage Tumor size Fuhrman grade Symptom classification
Parker et al. (2009) BioScore	ccRCC	B7-H1 Survivin Ki-67
Kutikov et al. (2010) Competing risk	Localized papillary, chromophobe, ccRCC	Race Sex Tumor size Age Death due to • Non-cancer • Kidney cancer • Other cancers

RCC renal cell carcinoma, *AJCC* American Joint Committee on Cancer, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *CAIX* carbonic anhydrase IX, *PHEN* phosphatase and tensin homolog

therapy for 18 months. It is noteworthy that the 2-year CS of the poor-risk patients in this study increased from 11% to 73% (Harshman et al. 2012). They further demonstrated that CS can enhance prognostic nomograms (Harshman et al. 2012).

Considering many RCC patients are elderly with multiple comorbidities, survival benefits after RCC treatment are unknown. In 2010, Kutikov et al. (2010) proposed a competing-risk nomogram predicting mortality due to RCC-specific, non-cancer, and other cancers, in patients with surgically treated RCC. This nomogram was externally validated by Lughezzani et al. (2010) in 2010, with a reasonable accuracy of 73%, 70%, and 71% for non-cancer, RCC-specific, and other cancer mortalities, respectively.

Multiple models have been proposed for cancer-specific mortality, estimation of recurrence-free survival, and metastatic progression in patients before and after nephrectomy. Furthermore, multivariable models with better prognostics have been described, such as the

UISS (Zisman et al. 2001), the BioScore (Parker et al. 2009), and the SSIGN score (tumor stage, size, grade, necrosis) (Frank et al. 2002). Despite their adequate prognostic ability, none of these models are 100% accurate, and none are designed to account for the effect of targeted therapies. In consequence, the search for more accurate markers continues.

Molecular Biomarkers

Over the past two decades, studies have focused on molecular events that can unveil the biologic heterogeneity underlying the varied clinical behavior of RCC, in the hope that the identification of accurate markers would individualize prognostication and risk-stratified clinical decision-making as well as predict the responses to the existing systemic therapies (Sun et al. 2011). Molecular biomarkers are associated with clinical and/or pathologic characteristics of RCC and have an effect on progression-free survival, OS, cancer-specific mortality, and prognosis. Furthermore, studies have shown that the integrity of biomarkers alone may be more accurate than any nomograms. For example, Schmitz-Dräger et al. (2015) showed that multiple markers have the potential in screening and surveillance of bladder cancer in the future. Kattan et al. (2003) developed and internally validated a biomarker-based nomogram for prostate cancer. This model was externally validated by Shariat et al. (2008) who showed that the addition of biomarkers increased the nomogram predictive accuracy by 8%. Similarly, biomarker panels have increased the accuracy of prognostic and predictive models in RCC. For example, the BioScore, developed by Parker et al. (2009) in 2009, which included tumor expression level of B7-H1, survivin, and Ki-67, enhanced clear cell RCC (ccRCC) outcome prediction of multiple models. Additionally, a biomarker panel proposed by Su Kim et al. (2013) in 2013 including nicotinamide N-methyltransferase, L-plastin, and non-metastatic cells 1 protein showed promising results for early detection o2f malignant kidney tumors. Despite the promising results of molecular biomarkers, none have entered into clinical practice, and they further require validation in ideally prospective studies.

The following paragraphs outline the existing biomarkers that have demonstrated a potential for improving the predictive and/or prognostic ability of clinical and pathologic variables.

Renal Cell Carcinoma Biomarkers

Tissue-Based Biomarkers

The tissue-based biomarkers include the Von Hippel-Lindau (VHL) gene, hypoxia-inducible factor (HIF-α), vascular endothelial growth factor (VEGF), and carbonic anhydrase IX (CAIX). Furthermore, recent data have been published on Polybromo 1 (PBRM1), BRCA1-associated protein 1 (BAP1), and SET domain-containing protein 2 (SETD2). The biologic pathways and markers in RCC are illustrated in Fig. 1. Even though multiple treatment options in RCC target these biomarkers, their predictive and prognostic values have yet to be externally and internally validated. For example, all tyrosine kinase inhibitors, such as bevacizumab, target VEGF, while others, like cabozantinib, target a wider range of receptors including AXL and c-met proto-oncogene.

The Von Hippel-Lindau (*VHL*) *gene* is a tumor suppressor gene on chromosome 3p, originally identified in deficient protein isoforms pVHL19 and pVHL30. This gene is inactivated in almost all patients with VHL familial tumor syndrome and is approximately 70% of sporadic clear cell RCC. Patients with VHL syndrome are predisposed to multiple bilateral clear cell RCC lesions, as well as retinal angiomas, pheochromocytomas, central nervous system hemangioblastomas, and pancreatic tumors (Sun et al. 2011). The VHL gene is responsible for the regulation of the cell cycle arrest via p53, deposition of extracellular matrix, and degradation of hypoxia-inducible factor (HIF) 1-α. Yao et al. (2002) found that mutation or hyper-methylation of VHL predicts longer progression-free survival and lower mortality for stage I–III clear cell RCC. On the other hand, Schraml et al. (2002) found no difference in survival rates of patients with VHL

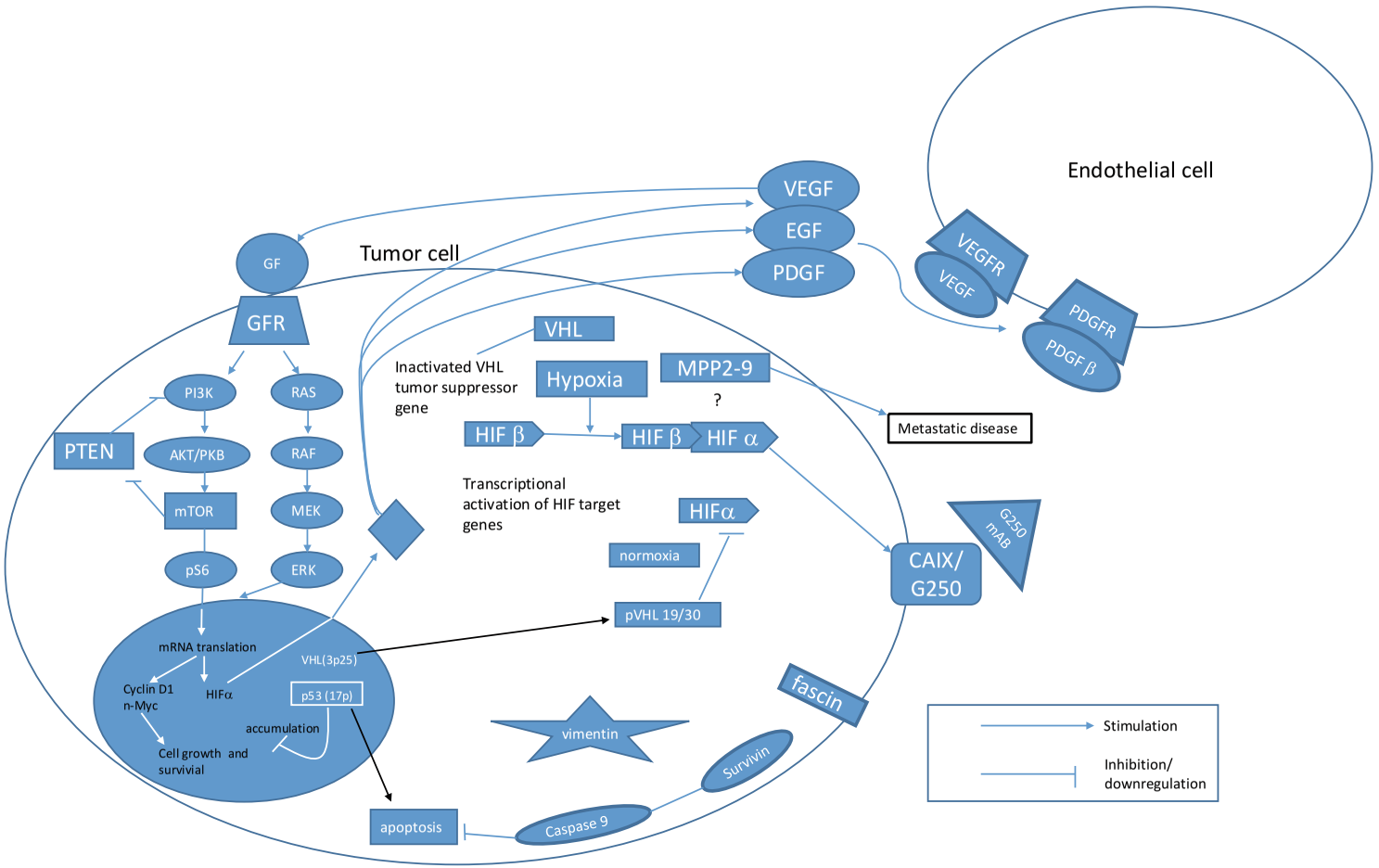

Fig. 1 Biological Pathways and markers in RCC. *AKT/PKB* akt/protein kinase B (gene), *CAIX* carbonic anhydrase IX, *EGF* endothelial growth factor, *ERK* extracellular signal-regulated kinase, *GF* growth factor, *GFR* growth factor receptor, *HIF* hypoxia-induced factor, *MEK* methyl ethyl ketone, *MMP* matrix metalloproteinase, *mTOR* mammalian target of rapamycin, *PDGF* platelet-derived growth factor, *PDGFR* platelet-derived growth factor receptor, *PTEN* phosphatase and tensin homolog, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *VHL* Von Hippel-Lindau

mutation compared to those without. It is postulated that "loss-of-function" VHL mutations, rather than VHL mutations on regulation of angiogenesis and proliferation of RCC, directly influence the progression of RCC (Sun et al. 2011).

As was previously mentioned, VHL is responsiplble for *hypoxia-inducible factor* (HIF-α) degradation. Therefore, in addition to hypoxic cell conditions, HIF-α accumulation will result from alterations in the VHL proteins. HIF-α is a key player of tumor pathogenesis, activating about 30 genes responsible for tumor growth and angiogenesis, specifically upregulation of tumor VEGF. HIF-α expression is significantly increased in ccRCC compared with papillary or chromophobe RCC variants. Studies have not found survival differences between patients with high and low HIF-α expression in either clear cell or papillary RCC variants, while others found a worse survival with elevated HIF 1-α tumor tissue levels (Sun et al. 2011).

The vascular endothelial growth factor (VEGF) is a dimeric glycoprotein that affects angiogenesis in both normal and pathologic conditions, facilitating tumor growth and metastases. VEGF expression is upregulated in ccRCC due to the dysregulation of HIF-α as well as hypoxia secondary to inadequate blood supply in larger tumors. Increased VEGF concentration and production occur in RCC patients with VHL gene alterations and advanced tumor grade (Sun et al. 2011; Maroto and Rini 2014). In addition to tumor grade and size in ccRCC, VEGF expression correlates with Fuhrman grade, tumor necrosis, tumor stage, and microvessel invasion. Studies have shown that increased VEGF decreases RCC progression-free and OS rates. Despite its promising characteristics, the added value of VEGF awaits confirmation and external validation (Sun et al. 2011; Maroto and Rini 2014).

C-met is a proto-oncogene as well as a receptor tyrosine kinase. It is responsible for angiogenesis, tissue repair, cell growth, and differentiation. Multiple cancers, including all types of RCC, have been associated with mutations of c-met pathways. For example, VHL mutation in ccRCC has been associated with c-met upregulation. Furthermore, C-met expression has been especially elevated in papillary and sarcomatoid differentiation tumors. Gibney et al. (2013) found that increased c-met expression decreased cancer-specific mortality. Further studies are needed to understand the true value of c-met in RCC pathogenesis (Ngo et al. 2014).

Carbonic anhydrase IX (CAIX) is a transmembrane protein associated with neoplastic growth, aggressive tumor phenotype, and poor prognosis. CAIX is regulated by HIF-α and is thought to be involved in the regulation of tumor microenvironments, notably alterations in intracellular and extracellular pH levels in response to tumoral hypoxia. CAIX is expressed in >80% of RCC samples and 90% of ccRCC specimens and, therefore, can be used to establish RCC diagnosis. High CAIX expression has been associated with better prognosis and survival in localized RCC and mRCC and has been inversely related to metastatic spread. On the other hand, low CAIX expression was not associated with RCC mortality. Due to its high prevalence and tumor specificity in RCC, CAIX is an excellent target for imaging and therapy using monoclonal antibodies, such as 124 I girentuximab used for PET scans (Ngo et al. 2014). Despite the promising retrospective results, CAIX expressions were not found to be predictive nor prognostic in mRCC patients treated with sorafenib in the TARGET trial (Choueiri et al. 2013). CAIX may be more useful in characterization of small renal masses (Sun et al. 2011; Ngo et al. 2014).

With increasing technology, three genes have been found to be mutated in more than 10% of sporadic clear cell RCC: *PBRM1*, BAP1, and SETD2. We can assume that these genes play a central role in RCC, since similar to the VHL, these three genes are two-hit tumor suppressor genes and are located short arm of chromosome 3p (Brugarolas 2013). Studies have found that PBRM1 and SETD2 mutations occur simultaneously, while mutations in PBRM1 and BAP1 occur separately and are associated with different RCC pathological features and outcomes (Zhang et al. 2016). Furthermore, BAP1 and SEDT2 mutations were associated with poor-risk groups with decreased OS, decreased PFS, and worse response to everolimus compared to PBRM1

mutation. Similar results were found using data from the Cancer Genome Atlas (The Cancer Genome Atlas (TCGA) Data portal 2016). Further studies are needed (Maroto and Rini 2014; Li et al. 2015).

Mechanistic Target of Rapamycin

The mechanistic (formerly mammalian) target of rapamycin (mTOR) pathway is an important component of cellular response to environmental stressors, regulating cell growth, protein degradation, and angiogenesis. The pathway's upstream molecules include phosphatase and tensin homolog [PTEN], and its downstream molecules include phosphorylated S6 ribosomal protein. The National Comprehensive Cancer Network and European Association of Urology guidelines (Molina and Motzer 2011; Ljungberg et al. 2010) recognize its importance in RCC pathogenesis and therefore recommend the use of temsirolimus, an mTOR inhibitor, as first-line treatment for poor-risk patients. Furthermore, Haddad et al. (2015) found that altered mTOR pathway regulators increased prognostic model accuracy estimates as well as improve the ability to predict recurrence in post-nephrectomy ccRCC patients. However, despite promising results, the prognostic and predictive role of mTOR as a biomarker is sparse and inconclusive (Sun et al. 2011; Li et al. 2015).

The ribosomal protein S6 (pS6) is a downstream mTOR target and has been associated with the activation of the mTOR pathway. It has an S6 kinase activity that alters mRNA translation due to the phosphorylated pS6 effect. PS6 is overexpressed in clear cell mRCC and may be a predictor of survival in both localized mRCC (Sun et al. 2011).

Protein kinase B (pAkt) phosphorylates substrates in the cytoplasm and the nucleus, regulating both growth and survival mechanisms. Elevated pAkt is associated with higher grade, higher metastatic progression, and worse RCC-specific survival. Conversely, elevated pAkt expression was found to have a favorable prognosis in localized RCC. Pantuck et al. (2007) hypothesized that localization of pAkt may be important for determining tumor behavior and resulting prognostic value. They found higher nuclear pAkt in localized RCC tissue compared to mRCC tissue (Sun et al. 2011).

Phosphatase and tensin homolog (PTEN) is a tumor suppressor protein, upstream to mTOR, encoded by the tumor suppressor gene PTEN. PTEN inhibits pAkt phosphorylation through PI3K. PTEN mutation is rare and is associated with adverse prognosis in RCC. High PTEN expression improves survival and is found in tumors with lower T stage and non-clear cell histological subtype (HS) (Sun et al. 2011).

Additional Biomarkers

Additional biomarkers include survivin, p53, matrix metalloproteinases, insulin-like growth factor II mRNA-binding protein 3, ki-67, caveolin-1, tumor necrosis, c-reactive protein, vimentin, fascin, and cytokine and angiogenic factors (CAF).

Survivin is part of the inhibitor of apoptosis gene family and plays a role in the intrinsic and extrinsic caspase pathways (Li et al. 2015). It controls mitotic progression and induces change in gene expressions associated with tumor cell invasiveness. Survivin mRNA is usually expressed during embryonic and fetal development, becoming undetectable in most differentiated normal adult tissues. In human cancers, including all variants of RCC, survivin is overexpressed. Since deregulation of apoptosis is a hallmark in human carcinogenesis, it is not surprising that high survivin expression is associated with poor differentiation, aggressiveness, and decreased survival in ccRCC (Sun et al. 2011).

The p53 protein is a DNA-binding molecule that plays an important role in regulation of transcription and cell growth. When DNA damage occurs, p53 stops the cell cycle by inducting apoptosis. P53 overexpression was found in all types of RCC, specifically in papillary (70%). Even though p53 was found to be an independent predictor of metastasis-free survival in patients with localized clear cell RCC, its prognostic role in RCC remains controversial (Sun et al. 2011).

The matrix metalloproteinase (MMP) is a family of enzymes composed of extracellular matrix

remodeling proteases. Their activity has been implicated in normal processes as well as pathologic processes including tumor growth, progression, metastasis, and angiogenesis dysregulation. These proteinases are overexpressed in all types of RCC, especially in non-clear cell RCC tumors, and are associated with aggressive behavior, tumor grade, and survival. MMPs are important therapeutic and diagnostic targets for the treatment and detection of human cancers. For example, MMP inhibitors such as batimastat (synthetic) and bryostatins (natural) may help in the treatment and prevention of MMP-overexpressing cancers (Sun et al. 2011).

Insulin-like growth factor II mRNA-binding protein 3 (IMP3) is an oncofetal RNA-binding protein. It regulates transcription of insulin-like growth factor II mRNA. In early stages of embryogenesis, IMP3 is expressed in multiple developing tissues such as epithelium, muscle, and placenta. Conversely, it is expressed at low or undetectable levels in adult tissues. IMP3 is associated with cell proliferation and invasion in various cancers, including RCC. IMP3 is associated with higher RCC stage, grade, sarcomatoid differentiation, regional lymph node involvement, distant metastases, and cancer-specific mortality. Jiang et al. (2008) showed that the addition of IMP3 expression to tumor stage improves prediction of metastatic progression. Hoffman et al. (2008) externally validated the prognostic value of IMP3 in ccRCC. They found a 42% increase in cancer-related mortality in patients with localized disease and increased IMP3 expression. Furthermore, an increased expression of IMP3 increased the risk of progression to metastatic disease by 4.7-fold. Assessing IMP3 expression may be useful for identifying at-risk patients who might benefit from aggressive adjunctive therapy after primary tumor resection as well as provide useful targets to improve clear cell RCC therapy. However, further studies are warranted (Sun et al. 2011).

Ki-67 is a cell proliferation marker associated with an aggressive ccRCC phenotype, higher recurrence rates, and worse OS. In cancer-specific mortality analyses, the combination of Ki-67 and CAIX increases the prognostic ability of nuclear grade. Its importance as a predictor of prognosis has not yet been established (Sun et al. 2011).

Caveolin-1 is a structural component of plasma membrane microdomains, caveolae, that are involved in the intracellular signaling pathways regulating cell adhesion, growth, and survival. Caveolin-1 is expressed in 86% of ccRCC and <5% of chromophobe or papillary RCC. Increased caveolin-1 expression has been associated with a poor clinical outcome in several malignancies (Sun et al. 2011).

Tumor necrosis is one of the components of the scoring algorithm of Leibovich et al. (2005). There are controversial results regarding its importance in RCC prognostics. Multiple studies showed no added value of tumor necrosis when standard clinical and/or pathologic tumor characteristics were considered. Conversely, Lam et al. (2005) showed that tumor necrosis improved prediction of survival in patients with localized RCC.

C-reactive protein is a marker for inflammation, found to be a strong predictor of metastasis and overall mortality after nephrectomy for localized RCC. It increased the predictive accuracy of several established clinical and pathologic predictors by up to 10%. Karakiewicz et al. (2007b) showed that CRP was an independent predictor of RCC-specific mortality. Furthermore, they found that CRP increased predictive accuracy of the UISS model. Michigan et al. (2011) found that increased CRP was associated with increased mortality in patients undergoing nephrectomy. Another marker of inflammation, *erythrocyte sedimentation rate* (ESR), has also been associated with increased overall mortality. These markers are highly promising because they are inexpensive and widely available (Sun et al. 2011; Ngo et al. 2014).

Vimentin is a cytoplasmic intermediate filament that is not usually expressed in epithelial cells. Its overexpression was found in up to 51% in ccRCC and up to 61% in papillary RCC and predicted poor prognosis, independent of T stage and grade (Sun et al. 2011).

Fascin is a globular actin cross-linking protein involved in cell adhesion and motility. Its overexpression correlated with sarcomatoid

transformation; high tumor stage, grade, and size; as well as metastatic progression (Sun et al. 2011).

Blood-Based Biomarkers

Blood-based biomarkers include lactate dehydrogenase (LDH), thrombocytosis, neutrophils, VEGF, serum amyloid A (SAA), CAIX, neutrophil gelatinase-associated lipcalin (NGAL), insulin-like growth factor I (ILGF-I), circulating tumor cells (CTCs), circulating endothelial cells (CECs), circulating progenitor cells (CEPs), and cytokine and angiogenic factors (CAF). Additionally, new blood-based biomarkers, circulating cell-free DNA (cfDNA) and microRNAs (miRNAs), will be discussed in this section.

LDH

LDH is an intracellular enzyme that plays an important role in glycolysis and gluconeogenesis. LDH levels rise with cellular stress due to hypoxia or injury. LDH is an important prognostic and predictive biomarker, that has been associated with poor OS, increased response to treatment, and has been included in multiple prognostic models, such as the model proposed by Motzer et al. in 1999 (Motzer et al. 1999; Zhang et al. 2016).

Thrombocytosis

In patients with mRCC treated with VEGF-targeted agents, thrombocytosis achieved independent predictor status for OS. On the other hand, it did not add value to a model proposed by Karakiewicz et al. (2007c) that comprised TNM stage, age, tumor size, Fuhrman grade, histologic subtype, and preoperative hemoglobin.

Neutrophils

Serum and intratumoral neutrophils have shown to have a shorter recurrence-free survival and poor OS and be an independent predictor status for mortality. Serum neutrophils were found to be among the most informative predictors in the IMDC model. Furthermore, serum neutrophils increased the predictive accuracy of the Leibovich et al.'s (2005) scoring algorithm by 6%. Templeton et al. (2016) found that an elevated neutrophil and lymphocyte ratio (NLR), a marker of subclinical inflammation, was an independent factor for worse outcome in mRCC patients treated with targeted therapy. Despite these promising results, further studies and external validation are necessary (Sun et al. 2011; Li et al. 2015).

VEGF and CAIX

Important tissue-based markers, VEGF and CAIX, have also been identified as valuable blood-based biomarkers. Serum *VEGF* levels correlate with tissue VEGF expression as well as vascular invasion, survival, and tumor stage, grade, and size. In patients treated with sunitinib, serum VEGF predicted treatment response as well as disease progression. In other studies, serum VEGF failed to achieve independent predictor status (Sun et al. 2011).

Multiple VEGF ligands, such as VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E, have been identified. These ligands play an important role in angiogenesis and tumor growth. Multiple studies found VEGF-A to be a good prognostic biomarker, but not a good predictive biomarker. Furthermore, there has been growing interest in VEGF-C and VEGF-D as potential biomarkers, due to their potential role in resisting VEGF-A blockade. Low VEGF-C and VEGFR-3 have been liked to longer PFS and better response to treatment (Zhang et al. 2016).

High serum *CAIX* levels correlated with ccRCC, disease recurrence, mortality, as well as tumor size and stage. Conversely, others found that CAIX levels were inversely correlated with metastatic disease and predicted better survival. Further studies are warranted because CAIX's role as a diagnostic biomarker is unclear (Sun et al. 2011).

SAA

SAA is a high-density lipoprotein that plays an important role in modulation of inflammation as well as in the metabolism and transport of cholesterol. SAA may be a useful biomarker in various tumors, including RCC. Ramankulov et al. (2008) found higher SAA concentrations in metastatic patients. They showed that SAA levels were an

independent predictor of all-cause survival. Unfortunately, it is difficult to use SAA as potential biomarker because in addition to neoplasia, SAA levels may increase up to 1000-fold in response to trauma, inflammation, and liver affliction (Sun et al. 2011).

NGAL

NGAL is a protein that has a protective effect against acute ischemic injury and is upregulated in distressed cells. It is high in several human cancers and has shown to decrease progression-free survival in RCC patients treated with sunitinib. A high correlation with NGAL and MMP-9 was found. As was previously mentioned, MMP-9 is a protein involved in extracellular matrix remodeling and has been associated with aggressive tumor behavior, survival, and grade (Sun et al. 2011)

IGF-1

IGF-1 has many varied roles and is associated with multiple health- and exercise-related outcomes. Other than cancer cells, elevated IGF-1 concentrations are beneficial in most tissues including the muscle and tendon as well as body composition and cognitive function. In 2004, (2004) found that increased serum IGF-1 levels were associated with all-cause survival. Further studies are needed to understand the prognostic role of the IGF axis in RCC.

CAF

There has been an interest in CAF due to the theory that tumor angiogenesis can be affected by the balance of pro- and antiangiogenic factors. Zurita et al. (2012) found that patients with a 6-marker CAF pro-antigen signature, including osteopontin, VEGF, CAIX, collagen IV, VEGFR-2, and TRAIL, had an increased progression-free survival when treated with sorafenib. Similarly, Tran et al. (2012) found that patients with lower levels of IL-6 and hepatocyte growth factor and higher levels of E-selectin had an increased progression-free survival in pazopanib-treated patients. The importance of CAF in tumor pathogenesis is still in its infancy and warrants further studies (Maroto and Rini 2014).

CTC, CEC, and CEP

Increased *CTC* levels have been associated with lymph nodes and metastatic disease at diagnosis as well as decrease OS. Unfortunately, due to the lack of cytokeratin, an epithelial cell marker, in RCC cells, it is difficult to evaluate CTC levels (Wang et al. 2012).

CEC and CEP are increased with vascular injury, repair, and neovascularization. Elevated levels have been associated with tumor vascularization and growth. Elevated CECs and CEPs have been found in rapidly progressing and metastatic RCC as well as in RCC patients with VHL disease. Furthermore, elevated CEC levels have been associated with favorable treatment response. Despite promising results, further studies are warranted to establish the role of CTCs, CECs, and CEPs in RCC as prognostic and predictive markers (Maroto and Rini 2014; Zhang et al. 2016).

Circulating cfDNA

cfDNA levels increase with apoptosis- and tumor-associated necrosis. cfDNA has been shown to be increased in patients with malignancies compared to their healthy counterparts. However, this increase is not specific to RCC and, therefore, is not applicable in clinical practice. Furthermore, increased cfDNA has been associated with advanced RCC and disease recurrence. Studies found that a drop in cfDNA was associated with favorable response to treatment. It is hoped that cfDNA will be used in treatment surveillance, allowing for early detection of disease recurrence; however further studies are warranted before clinical use (Zhang et al. 2016).

miRNA

miRNAs are RNA molecules that are responsible in regulating DNA gene expression. They are believed to regulate multiple tumor suppressors and oncogenes that are responsible for tumorigenesis and metastasis as well as RCC pathway regulation, such as the HIF-VHL hypoxia pathway. Furthermore, it is believed that miRNAs play a role in immune dysregulation by regulating anti-apoptosis pathways through MCL-1 and T-cell proliferation through JAK3. Increased miRNA levels, such as miRNA-378 and miRNA-210,

have been associated with RCC occurrence and were decreased after CN. Additionally, it was found that patients with a panel of eight oncogene miRNAs and ten tumor suppressor miRNAs had decreased OS and CSS. Further studies are warranted to establish the role of miRNAs as prognostic and predictive markers (Ngo et al. 2014; Zhang et al. 2016).

Immune System Markers

The immune system's role in cancer is complex. It can suppress tumors as well as promote their growth. Immunologic markers include tumor-inflating lymphocytes, natural killer cells, regulatory T cells, and B7-H1.

Due to RCC less durable response to chemotherapies and targeted therapies, there has been a growing interest in immune oncology (IO). IO with INF-α and IL-2 cytokines was the standard of care, with a 5-year survival of 10% (Curtis et al. 2016). Unfortunately, both cytokines had major side effects. INF-α caused liver toxicity after long-term treatment, while IL-2 treatment was restricted to mRCC patients in specialized centers due to its severe acute toxicity (Hammers 2016). Due to these complications, the search continued for more effective immunotherapies. Today, there is a growing interest in IL-6 cytokines as well as immune checkpoint inhibitors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death receptor 1 (PD-1), and programmed death receptor ligand 1 (PD-L-1) inhibitors, which will be discussed in this section.

IL-6

IL-6 is a pro-inflammatory cytokine that plays a key role in systemic inflammation. It regulates genes that control cell proliferation, angiogenesis, and apoptosis suppression. High IL-6 was found to be the most promising negative prognostic marker as well as favorable predictive marker, increasing OS and PFS in patients treated with VEGF inhibitors. These findings need to be validated before clinical use (Zhang et al. 2016; Funakoshi et al. 2014).

Tumor-Infiltrating Lymphocytes (TILs)

TILs are the host immune reactions against cancers. Increased TILs were found in RCC and were positively correlated with increased tumor stage and grade (Sun et al. 2011).

Natural Killer Cells (NK Cells)

An increased number of NK cells were found in RCC. NK cells attack tumor cells that have reduced major histocompatibility complex (MHC) class I expression, which was observed 38% of ccRCC. A reduced MHC-1 expression was associated with a worse prognosis. Furthermore, in patients treated with interleukin-2, low intratumoral NK cells ($CD57^{+}$) were associated with worse survival (Sun et al. 2011).

Regulatory T Cells (Treg)

Treg maintains the activation of other T cells. It has an important role in immune surveillance against cancer by hampering antitumor immunity and suppressing proliferation of autologous T cells in vitro. Levels >10% of Tregs in intratumoral areas of RCC are associated with increased tumor stage and size as well as coagulative tumor necrosis and cancer-specific mortality (Sun et al. 2011).

B7-H1

B7-H1 is a part of B7 family of T-cell costimulatory molecule. This cell-surface glycoprotein inhibits tumor-specific T-cell-mediated immunity by inducing T-cell apoptosis, impairing cytokine production, and diminishing cytotoxicity of activated T cells. In RCC, high B7-H1 expression is associated with metastatic progression and higher mortality, especially in combination with survivin expression (4).

CTLA-4, PD-1, and PD-L

CTLA-4 is found on the surface of cytotoxic T cells. It is believed to limit inflammation by blocking tumor-infiltrating lymphocytes (TILs) and T-cell activation by inhibiting the binding of tumor cell B71 on CD28. Studies have shown that the presence of CTLA-4 increased the risk of developing RCC and having a high grade of RCC. Anti-CTLA medication, such as ipilimumab, is of interest in RCC treatment; however, further studies are warranted (Curtis et al. 2016).

PD-1 is a cell-surface receptor expressed on lymphocytes. It is part of the immunoglobulin family, binding to ligands, *PD-L1 and PD-L2*, that are expressed on most cells, including tumor cells. They are thought to promote apoptosis by inhibiting cytotoxic T-cell activity (Curtis et al. 2016). Furthermore, it is believed that tumor cells may express PD-L1/B7-H1 to limit tissue destruction secondary to the activated immune system (Sun et al. 2011; Ngo et al. 2014). Multiple studies have focused on PD-1 inhibitors, notably nivolumab, and have shown promising results. Of note, in 2015, the US Food and Drug Association approved nivolumab as a second-line treatment for RCC, based on the CHEKCMATE 025 trial (Motzer et al. 2015) data that showed OS benefit, in addition to excellent tolerability and improved health-related quality of life with nivolumab treatment. It is noteworthy that ongoing trials are showing promising results with combination of targeted therapies, such as anti-VEGFs, with nivolumab (Health UNIo 2016).

Use of Biomarkers in the Prognostic Models

Inclusion of biomarkers in existing prognostic models has significantly increased their accuracy. For example, Su Kim et al. (2013) proposed a prognostic model for prediction of survival in RCC using p53, CAIX, gelsolin, vimentin, and metastatic status as predictors. This model's predictive accuracy was 79%. Another model including CAIX, PTEN, vimentin, and p53 had predictive accuracy of 64%, which was subsequently increased by 4% with the addition of ECOG-PS and tumor stage. Furthermore, Kim et al. (2005) found that the predictive accuracy relying on clinical and molecular markers was higher than that of the UISS system alone, 68 vs 62%, respectively.

Conclusion

Despite knowledge of disease stage, grade, and HS, patient outcome in RCC remains elusive. Therefore, a vast number of predictive and prognostic models as well as biological markers have been proposed. Many show promise in stratifying the survival curves or discriminating between stage distributions, while others achieved independent predictor status in specific end points of interest.

There is an increased interest in composite biomarker, such as the BioScore (Parker et al. 2009), which has increased accuracy compared to other models. The search continues for an ideal model that is relevant and simple to use and understand and that will be able to distinguish between different patient diseases and characteristics. Further studies are warranted to validate the biomarkers that have been found as well as find new biomarkers that can predict treatment response and disease outcomes. The future in prognostic factors and predictive models lies in finding biomarkers that will assist in choosing select target therapies, immunotherapies, and chemotherapies (Sun et al. 2011; Li et al. 2015). To improve patient prognosis, treatment sequences, with targeted agents and novel drugs, need to be individualized by using the patient's genomic classifications (Calvo et al. 2016).

Presently, IO agents, notably immune checkpoint inhibitors targeting PD-1, are the most promising in treatment of RCC. It is postulated that a preestablished immune response can optimize immune checkpoint inhibition therapy. Therefore, even though past studies found few desired results, vaccinations may hold the key to future therapeutic success (Curtis et al. 2016; Hammers 2016).

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Molecular Heterogeneity of Renal Cell Carcinoma

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Abstract

Renal cell carcinoma (RCC) is characterized by extensive inter- as well as intratumoral heterogeneity (ITH). The range of ITH in clear cell RCC, the most common histological subtype, extends from histopathological features over functional and mutational ITH to topological ITH. Functional and genomic ITH are major determinants of disease progression and therapy resistance since they promote clonal evolution and the ability to overcome selection barriers. This notion applies also to systemic therapeutic interventions, which inevitably result in changes of the molecular architecture of a tumor. This chapter will review the different forms of ITH in RCC

including open questions and emerging concepts. The translational relevance of ITH within the conceptual framework of mutation and selection will be discussed.

Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer, and over 300,000 new patients are diagnosed worldwide each year resulting in nearly 100,000 deaths annually (Shaw 2016). The most common histological subtypes of RCC are clear cell renal cell carcinoma (ccRCC, ~75%), followed by papillary RCC (~15%) and chromophobe RCC (~5%) (Frew and Moch 2015). A common denominator of RCC is a strong metabolic component, which has led to RCC being referred to as "metabolic disease" (Linehan et al. 2010). Recent analyses powered by next-generation sequencing (NGS) underscore that RCC is not only characterized by intertumoral but also extensive intratumoral heterogeneity (ITH) (Gerlinger et al. 2015). Since the majority of these studies have been performed in ccRCC, this subtype will also be the focus of this chapter that will highlight the various levels of ITH in RCC.

RCC is, similar to CML, one of the success stories of early genetic investigation. The fact that RCCs harbor recurrent cytogenetic alterations such as the loss of chromosome 3p has early been observed and has led to a genetic substratification of RCCs in the Heidelberg classification of renal cell tumors in 1997 (Kovacs et al. 1997). Mutations in the *VHL* gene that is located on the short arm of chromosome 3 (3p) cause the hereditary form of RCC associated with the VHL syndrome (Linehan 2012).

This syndrome is characterized by the development of tumors in different organs including hemangioblastomas of the central nervous system and retina, pheochromocytoma, pancreatic and inner ear tumors, as well as RCC of the clear cell type. It has become obvious that the *VHL* gene is also inactivated in over 90% of sporadic ccRCCs through mutation or epigenetic silencing (Gnarra et al. 1994, 1996). Since the VHL protein controls degradation of the hypoxia-inducible factors (HIFs), a genetic inactivation of *VHL* will lead to the stabilization of HIF proteins, a pseudo-hypoxic state, and transcriptional activation of genes involved in controlling oxygen tension, i.e., encoding pro-angiogenic (e.g., VEGF) and pro-survival factors (e.g., mTOR, BCL2, TGF-α) (Schödel et al. 2016). This knowledge was crucial for the implementation of novel therapeutic approaches to metastatic RCC and has heralded the era of targeted agents in ccRCC that, until recently, had largely replaced immunological treatment approaches (Motzer et al. 2007, 2015). A number of next-generation sequencing (NGS) studies have been performed in ccRCC, and recurrently mutated genes besides *VHL* have been detected. These include in particular genes encoding factors involved in chromatin remodeling such as *PBRM1*, *SETD2*, and *BAP1* (Cancer Genome Atlas Research Network 2013; Varela et al. 2011; Dalgliesh et al. 2010; Peña-Llopis et al. 2012; Sato et al. 2013). Remarkably, the genes are all located, together with *VHL*, on chromosome 3p, which has led to the proposal that ccRCC is not only a "metabolic disease" but at the same time a "disease of chromosome 3p loss" (Hakimi et al. 2013).

Besides the abovementioned three major subtypes of RCCs, the recently released WHO classification of renal cell tumors describes various other and newly defined RCC types (Moch et al. 2016).

Functional ITH

Transcriptomic analyses of human cancers have led to progress in the substratification of a number of entities, e.g., breast cancer (Nielsen and Perou 2015). This avenue has also been explored in ccRCC and has led to the discovery of two functional forms of ccRCC that may also correspond to certain genetic alterations.

Two subtypes of ccRCC (ccA and ccB) have been proposed based on gene expression patterns in which ccA was characterized by a transcriptional output to promote angiogenesis and fatty acid metabolism, while ccB tumors were

associated with epithelial to mesenchymal transition (EMT), cell differentiation, and cell cycle deregulation (Brannon et al. 2010). The subtype ccA was found to be associated with a significantly better prognosis than subtype ccB (median cancer-specific survival of 8.6 vs. 2.0 years). Similar results were reported by the TCGA consortium on ccRCC and others (Cancer Genome Atlas Research Network 2013; Haake et al. 2016).

Genomic ITH

Besides the remarkable intertumoral heterogeneity as outlined above, there is mounting evidence for extensive ITH in ccRCC. Morphological ITH has long been observed by pathologists in this tumor type. The true extent of genomic ITH, however, has only recently become more evident due to the application of NGS-based approaches.

Cytogenetic ITH

Intratumoral heterogeneity has long been recognized by conventional cytogenetics and loss of heterozygosity studies. In early studies, the DNA content of RCCs analyzed by flow cytometry has been reported to be heterogeneous with diploid, polyploidy, and aneuploid tumor cell clones coexisting in one tumor (Ljungberg et al. 1985). An investigation of chromosomal aberrations in cultured tumor cells from multiple RCC samples from a single tumor confirmed ITH on the chromosomal level (Nordenson et al. 1988). Being considered as the initial and the most common genetic alteration in ccRCC, the inactivation of *VHL* gene and deletion of chromosome 3p are highly prevalent in ccRCC; however, a high degree of ITH with respect to the *VHL* deletion status has also been reported (Moch et al. 1998).

Mutational ITH

NGS-based studies have expanded the spectrum of somatic mutations in ccRCC and have identified a number of driver genes that have the potential to characterize subgroups of ccRCC. One emerging molecular subtype based on driver gene mutations is based on the *PBRM1* and *BAP1* mutational status. One seminal study showed that combined approximately 70% of ccRCCs harbor inactivating mutations in *BAP1* (about 15%) or *PBRM1* (about 55%) and that these two mutations were mutually exclusive (Peña-Llopis et al. 2012). Clear cell RCCs could be segregated into *BAP1*- or *PBRM1*-deficient subtypes, with the *BAP1* loss being associated with a significantly worse prognosis (Kapur et al. 2013). It has been proposed that a *PBRM1* or *BAP1* mutation would set the course for ccRCCs with distinct properties, with *BAP1* loss being connected with mTORC1 activation and higher tumor grade (Kapur et al. 2013).

These results underscore that relatively simple genomic stratifiers can be applied to ccRCC patients. Both genes, *BAP1* and *PBRM1*, are considered truncal drivers. The inactivation of these genes is hence an early event during tumorigenesis and can be expected to be ubiquitously present. However, it has recently become clear that such truncal genomic alterations represent only a relatively small fraction of the genetic changes in ccRCC (Gerlinger et al. 2012).

Multiregion Genomic ITH

The concept of genomic ITH of ccRCC has been brought to a new and so far unexplored level by multiregion whole-exome sequencing studies. In two landmark papers by Gerlinger et al. (2012, 2014), multiregion whole-exome sequencing and DNA ploidy profiling were employed to characterize ITH in ccRCC. It was found that somatic mutational ITH is a common feature in ccRCC since 60–70% of mutations were not present in every region sequenced. Remarkably, approximately 25–50% of the mutations were unique for specific regions and referred to as "private" mutations. About 30% of the mutations were ubiquitous and present in all regions analyzed, and about 15–45% mutations are shared by several but not all regions. The frequency of mutations shared by metastatic sites was approximately 20%. Further analysis and

modeling revealed a branching rather than linear evolutionary pattern. Importantly, only *VHL* and *PBRM1* inactivations, out of 16 driver genes in total, were found to be truncal driver events in all or a subset of ccRCCs thus underscoring that many driver mutations are subclonal and spatially separated (Gerlinger et al. 2014).

It becomes obvious from this work that single-biopsy approaches lead to an underestimation of the somatic mutation rate. The authors illustrate this notion by showing that the prevalence of most driver mutations based on multiple sampling was higher than that based on single samples. For example, *TP53* mutations, which were detected in only 6% of patients in single biopsies of the TCGA study population, appeared in up to 40% of patients in their own study; similarly, mutations in genes of the PI3K–AKT–mTOR pathway were found in 28% of patients in the TCGA study cohort but in 60% of patients in their own study (Gerlinger et al. 2014).

Another key finding was that converging evolution is a common feature in ccRCC with multiple independently occurring mutations targeting the same genes including *MTOR* and other known driver genes (Gerlinger et al. 2012, 2014). This convergent evolutionary pattern underscores the strong selection pressure to maintain certain functions required by the malignant phenotype of ccRCC. This finding can open therapeutic opportunities as exemplified in a study using whole-exome sequence analysis of archived tumor tissue of five ccRCC patients in which rapalogs showed an exceptional clinical benefit and in which an mTOR pathway activation through direct or indirect genetic events was found (Voss et al. 2014).

The results by Gerlinger, Swanton, and colleagues are corroborated by sequence analyses of single cells from a ccRCC (Xu et al. 2012). By deep exome sequencing of 20 single cells from the tumor and 5 cells from adjacent non-cancer tissue, it was discovered that more than 70% of the mutations were cell specific.

There is compelling evidence that, similar to breast cancer, the genetic ITH of ccRCC becomes more and more evident the deeper the sequence analyses are carried out (Gerlinger et al. 2014; Fox and Loeb 2014). The rather daunting consequence of this notion is that tumors are highly complex and diverse systems in which the majority of cells differ from each other.

Molecular ITH in RCC with Sarcomatoid Differentiation

Morphological variations in the histopathological appearance are a frequent observation in RCC (Lopez et al. 2013). A prominent manifestation of this histomorphological heterogeneity is the sarcomatoid differentiation. Sarcomatoid differentiation can be found in all histologic subtypes of RCC and is commonly associated with an unfavorable prognosis (Delahunt et al. 2013). However, the molecular alterations underlying a sarcomatoid phenotype are poorly understood.

Whole-exome sequencing of matched normal, carcinomatous, and sarcomatoid tissue specimens showed a significantly higher burden of somatic single-nucleotide variants in the sarcomatoid component, and 42% shared mutations with the carcinomatous part including known ccRCC driver mutations. This indicates divergent clonal evolution of the sarcomatoid and carcinomatous parts from a common clonal precursor (Bi et al. 2016). Such a common origin has previously been proposed based on the analysis of X-chromosome inactivation (Jones et al. 2005). Mutations in A*RID1A* and BAP1 were significantly more frequent in sarcomatoid parts, and biallelic *TP53* mutations were found in 32% of the sarcomatoid specimens and not found in carcinomatous parts (Bi et al. 2016). Based on the observation that mutations in *TP53*, *ARID1A*, and *BAP1* were mutually exclusive, it has proposed that more than one route toward a sarcomatoid differentiation may exist (Bi et al. 2016).

Molecular Heterogeneity Associated with Metastatic Disease

The extent of intratumoral heterogeneity in metastatic lesions and the clonal relationship between the primary tumor and distant metastases are poorly characterized. However, such knowledge

is critical to develop strategies to suppress metastatic dissemination and lethal disease outcome. A comprehensive genomic, epigenetic, and transcriptomic analysis of a primary tumor, local invasion of the inferior vena cava (IVC), and distant metastasis to the brain in a ccRCC patient (Huang et al. 2014) found that the primary tumor was genetically and epigenetically more heterogeneous than the invasive or metastatic lesion. The overall spectrum of CNAs and DNA methylation profiles in the brain metastasis was distinct from that in primary tumor or IVC invasion suggesting that most of the tumor cells in the metastasis originated from rare founder subclones of the primary tumor. Another study also confirmed the origin of metastases of RCC from minor subclones in the primary tumor using the *TP53* mutational status (Bousquet et al. 2015).

Temporal Heterogeneity and Evolution in RCC

The significant molecular heterogeneity between spatially separated regions within individual tumors has spurred a renewed interest in the concept of Darwinian evolution of cancer proposed by Peter Nowell 40 years ago (Nowell 1976). Evidence for a dynamic change of malignant subclones during disease progression originated mostly from hematopoietic malignancies for its relative ease of longitudinal sampling. Solid tumors are rarely resampled and reanalyzed during the course of therapy in clinical practice for the lack of clinical indications or immediate accessibility. This makes the study of cancer evolution in solid tumors, including RCC, more challenging.

The basic principle of a Darwinian evolution includes stochastic genetic variation together with natural selection of the fittest variants (Greaves and Maley 2012). This evolutionary pattern is considered one of the main reasons of the emergence of anticancer drug resistance. How exactly the external selection pressures, i.e., cancer treatment, influence the molecular evolution of a tumor and what the critical characteristics of the drug-resistant subclones are remain yet to be understood.

The role of systemic treatment on RCC evolution has been investigated in a number of recent studies. For example, tumors with the lowest extent of mutational heterogeneity in a series of ccRCCs had been pretreated with the mTOR inhibitor everolimus prior to sample acquisition (Gerlinger et al. 2014). While a possible direct influence of the drug treatment on mutational heterogeneity remains to be tested, other studies on the effect of VEGF-targeted agents on the cancer evolution found in fact, and for reasons that are not completely understood, an increase of ITH (Stewart et al. 2015; Hatiboglu et al. 2017).

Recently, a number of studies challenged the prevailing model of a more or less linear cancer evolution over time. Instead, alternative models of punctuated evolution with bursts of genomic instability creating genetic variability followed by clonal selection are being reported (Baca et al. 2013; Gao et al. 2016). Whether such events also contribute to genomic ITH in RCC remains to be elucidated.

Spatial ITH

Despite the extensive ITH that is a hallmark of ccRCC, relatively little is known about the spatial distribution of tumor subclones within a tumor. In fact, until recently, tumor cells were thought to be heterogeneous but relatively evenly admixed inside a tumor nodule. A number of recent reports have challenged this notion in breast cancer (Almendro et al. 2014a, b), liver cancer, and a number of other malignancies (Waclaw et al. 2015) as well as ccRCC (Hoefflin et al. 2016). In the latter study, the initial question was whether the extent of functional ITH of a primary ccRCC confers prognostic information. In other words, are primary tumors with more aggressive features such as lymph node or distant metastases more heterogeneous than tumors without these features? The answer was no since small localized ccRCC and widely metastatic ccRCC basically showed a similar extent of functional ITH of the primary tumor. To reconcile this unexpected finding, a spatial analysis of ITH was performed that led to a definition of two tumor zones, i.e., tumor

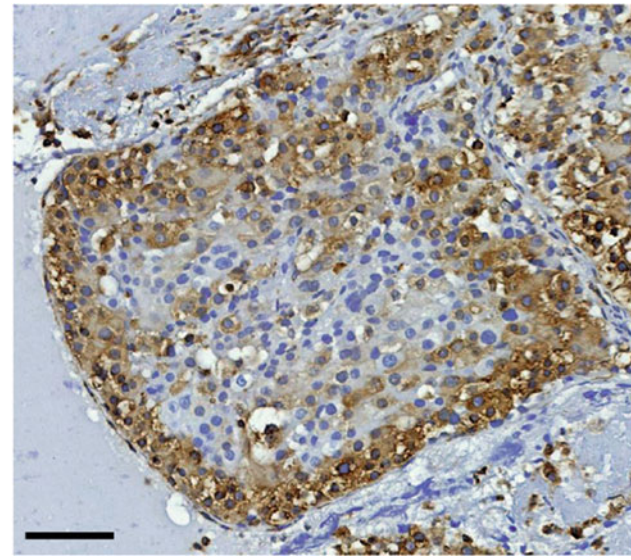

Fig. 1 Spatial and functional ITH in ccRCC. Immunohistochemical staining for phospho-S6RP S235/236, indicating activation of the PI3K/mTOR pathway, of an intrarenal metastasis of a ccRCC. Note the spatial separation of intracellular signaling activities between the center and periphery of the lesion. Scale bar = 100 μm

center and periphery, with very distinct functional properties in terms of proliferation and intracellular signaling (Fig. 1) as well as zone-specific mutations. Hence, the functional and genomic ITH of a tumor is shaped by topological niches, very likely under strong influence of the tumor microenvironment (Polyak et al. 2009).

Outlook and Clinical Implications

ITH is a hallmark of ccRCC besides metabolic alterations and chromosome 3p loss. The origin of ITH and how ITH is modulated by the microenvironment are important but so far poorly understood problems. Since about one quarter to half of all mutations in a ccRCC are ubiquitous, it will be important to focus on truncal driver aberrations and other ubiquitous mutations for future drug development. However, it cannot be ruled out that subclonal driver can replace truncal mutations leading to the emergence of drug resistance and disease progression. With new immunological treatment modalities such as immune checkpoint inhibitors on the horizon, an emerging question is how ITH will affect the patient outcome. Strategies to harness ITH in ccRCC to maximize the efficacy of these therapies should be considered.

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Histological (Sub)Classifications and Their Prognostic Impact in Renal Cell Carcinoma

35

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Abstract

Renal cell carcinoma (RCC) includes malignant epithelial tumors of the kidney with varying clinical and pathological presentation. RCC classification considers the originating cell type, histopathological features, staining characteristics, and unique molecular features. While data about the prognostic significance of RCC classification into certain subtypes remains inconsistent, there are several parameters which predict patients' survival independent of the RCC subtype. Among these, local tumor expansion, degree of infiltrative tumor growth, presence of lymph node or distant metastases, and histopathological grade of the tumor are general features routinely assessed as prognostic markers. Increasing knowledge about underlying molecular mechanisms has led to numerous molecular and immunohistochemical markers which developed as potential prognostic factors. In the following chapter, the basis of nomenclature, staging, and grading of RCC and prognostic biomarkers are discussed. Afterward, results regarding the prognostic relevance of histological classification are summarized, followed by detailed description of particular RCC subtypes. Histopathology, immunohistochemistry, and molecular pathology as well as its relevance for prognosis are presented for individual subtypes.

Introduction

Renal cell carcinoma accounts for approximately 4% of all diagnosed cancers in western countries (Siegel et al. 2016). While the majority of RCC are sporadic, several hereditary diseases are associated with higher incidences for the development of RCC. During the last decades, several morphological subtypes have been identified, and classification has been revised accordingly. Terminology to designate certain subtypes refers to characteristics such as cytological, architectural and staining features, and molecular alterations. While clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC) account for over 90% of renal cancers, other subtypes are very rare. Based on the observation that different subtypes are associated with certain clinical presentation and outcomes of patients, precise diagnosis is needed to predict disease progression and treatment response (Hsieh et al. 2017). In general, ccRCC is associated with worse prognosis compared to pRCC and chRCC; however, to date it remains unclear whether histological classification itself can be used as independent prognostic marker.

Due to intratumor and intertumor heterogeneity, RCC presents with heterogeneous clinical outcome of patients. Thus, numerous studies aimed to identify biomarkers with prognostic relevance, as well as with predictive value in order to improve clinical management. There are general prognostic parameters independent of the RCC subtype which have been supported by multiple independent studies. Among them, local tumor expansion, degree of infiltrative growth, and differentiation of the tumor are strong prognostic parameters which are routinely reported by pathologists. With the aim to improve prognostic stratification of patients, studies identified several molecular markers which associate with disease aggressiveness. Most molecules are involved in cell growth (e.g., proliferation and cell cycle markers such as Ki67 and cyclins), migration and invasion (e.g., cell adhesion molecules such as E-cadherin), and other pro-malignant processes. Although various studies supported the prognostic value of these molecules, to date there are no

biomarkers routinely used to predict disease progression. The main reason is the lack of independent prognostic significance when adjusting to known prognostic markers including T-stage and tumor grade (Holger Moch et al. 2016).

In addition to general factors, studies observed prognostic markers within individual subtypes. This includes morphological/architectural parameters, markers of differentiation, or further subclassification within individual subtypes. In this chapter, each subtype is introduced followed by summarizing the current knowledge about general as well as subtype-specific biomarkers.

General Classification of Renal Cell Carcinoma

Nomenclature and Classification

Nomenclature of RCC subtypes is based on histologic features, such as cytoplasmatic and/or architectural patterns (e.g., clear cell RCC or papillary RCC) and histochemical staining characteristics (e.g., in chromophobe RCC), in addition to their anatomical localization (e.g., collecting duct carcinoma and renal medullary carcinoma), resemblance to embryological structures, or association with a background renal disease (e.g., acquired cystic disease-associated RCC). Additionally, there are names referring to underlying molecular mechanisms (e.g., MiT family translocation carcinoma, succinate dehydrogenase-deficient renal carcinoma) or familial background (e.g., RCC-associated RCC).

The subtypes differ regarding the originating cell type and partially harbor unique molecular alterations. Histological classification has prognostic value as well as therapeutic relevance.

Staging

According to the current 2016 TNM staging system, there are two categories for renal-limited tumors: pT1a, pT1b, pT2a, and pT2b defined by sizes of $\leq$4, >4- $\leq$7, >7- $\leq$10, and >10 cm, respectively. Regional tumor expansion differentiates spread to peripheral perinephric and central sinus fat as well as renal sinus and vein invasion (pT3a), extension into inferior vena cava below the diaphragm (pT3b) or above the diaphragm or its infiltration (pT3c). Distant spread (pT4) includes direct extension into ipsilateral adrenal gland and invasion of the Gerota fascia (Holger Moch et al. 2016).

Grading

The WHO/International Society of Urological Pathology (ISUP) grading system is recommended for grading RCC (Table 1; see below) (Delahunt et al. 2013). It is a four-tiered grading system and defines grade 1–3 tumors on the basis of their nucleolar prominence. Basis for grading is a single high-power field representing the greatest degree of nucleolar pleomorphism. Presence of pronounced nuclear pleomorphism, tumor giant cells, rhabdoid and/or sarcomatoid differentiation defines a tumor as grade 4 (Holger Moch et al. 2016). Grade 1–4 tumors according to the WHO/ISUP grading system are shown in Fig. 1. The WHO/ISUP grading system is validated as an indicator of prognosis for clear cell and papillary renal cell carcinoma. Due to small numbers of other histological subtypes, it is not (yet) validated as an indicator for their prognosis, but can be applied for these to describe their morphological features.

Table 1 WHO/ISUP grading system for ccRCC and pRCC (Delahunt et al. 2013)

Grade	Description
Grade 1	Nucleoli are absent or inconspicuous and basophilic at ×400 magnification
Grade 2	Nucleoli are conspicuous and eosinophilic at ×400 magnification and visible but not prominent at 100× magnification
Grade 3	Nucleoli are conspicuous and eosinophilic at ×100 magnification
Grade 4	There is extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation

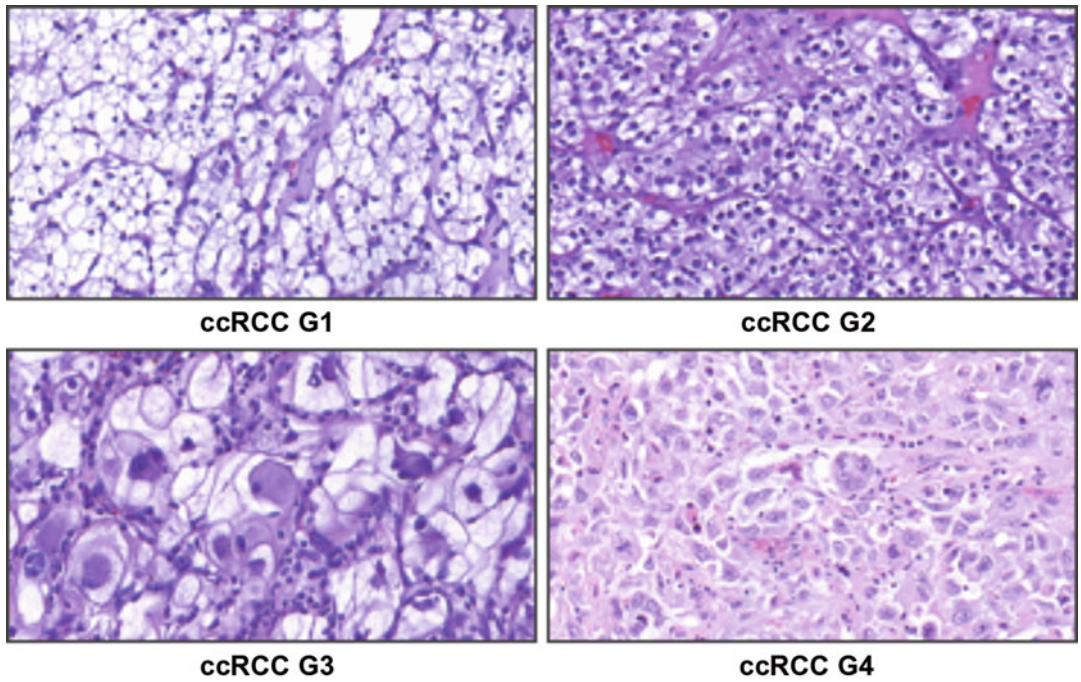

Fig. 1 Representative grade 1–4 tumors according to the WHO/ISUP grading system for renal cell carcinoma

General Prognostic Markers

The most important and routinely used prognostic markers for RCC include TNM stage and grading of the tumor.

Independent of the subtype, prognosis correlates with stage of disease and histopathological grade. Anatomical and histological information with prognostic relevance include tumor size, adrenal involvement, presence of lymph node or distant metastases, sarcomatoid features, (micro-)vascular invasion, tumor necrosis, as well as invasion of the collecting system and the venous system and into the perirenal fat (Holger Moch et al. 2016).

In general, the presence of sarcomatoid differentiation is associated with a dismal prognosis, meaning the tumor is undergoing dedifferentiation into spindle cells. Sarcomatoid differentiation is represented in the grading system as G4, and its presence should be reported for each subtype. Consequently, the separate category for "sarcomatoid renal cell carcinoma" is no longer part of the WHO classification (Hirsch et al. 2015).

Over the past years, the prognostic importance of renal sinus invasion has been established. Patients whose tumors invade the renal sinus have a significantly worse cancer-specific survival than patients with confined tumors. Involvement of the renal sinus increases with increasing tumor size (Lohse et al. 2015).

As mentioned above, WHO/ISUP grading system is validated as an indicator of prognosis for clear cell and papillary RCC, but not for other subtypes (Holger Moch et al. 2016) due to their low frequency.

Recently, the growing understanding of underlying molecular mechanisms of RCC has led to the identification of molecular markers to predict outcome and response to specific treatment approaches. Additionally, signaling pathways revealed to be critically involved in RCC pathogenesis enabled the development of targeted therapy for patients. There are numerous studies investigating the prognostic value of these molecules; however, so far there is no routinely used marker to predict outcome of patients.

Carbonic Anhydrase IX

Carbonic anhydrase IX (CAIX) is a VHL-dependent enzyme induced by hypoxia and critically involved in maintaining cellular pH balance (Neri and Supuran 2011). Loss of CAIC is associated with high-grade tumors, and underexpression in RCC tissue correlates with worse recurrence-free, disease-specific, and overall survival of patients (Genega et al. 2010; Ingels et al. 2017). In addition, high CAIX staining correlates with greater likelihood of response to systematic therapy for patients with metastasized RCC (Stillebroer et al. 2010). A recently published meta-analysis supported CAIX to be a useful prognostic parameter (van Kuijk et al. 2016). Until now, data show conflicting results regarding its significance as independent prognostic marker in multivariate analyses (Leibovich et al. 2007; Zhang et al. 2013); thus CAIX evaluation is not recommended as a useful biomarker.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor plays a crucial role in RCC tumorigenesis and has therefore been investigated as prognostic marker. Several studies observed a significant correlation between VEGF levels in tissues or serum and aggressive phenotypes; however, multivariate analysis could not support these results (Jacobsen et al. 2000; Phuoc et al. 2008).

Cell Cycle Proteins

Analysis of Ki67 and other cell cycle-regulating proteins such as cyclins or p53, reflecting proliferative behavior of the tumor, has been investigated to be used as prognostic factor for RCC. Several studies observed that the level of aberrantly expressed proliferation and cell cycle markers associates with aggressive phenotypes of RCC (Gayed et al. 2013; Haddad et al. 2017). High Ki67 independently predicts reduced disease-free survival time (Dudderidge et al. 2005) and has been suggested to improve clinical management of patients (Xie et al. 2017).

Cell Adhesion Proteins

The cell adhesion protein E-cadherin inversely correlates with the aggressive phenotype of various epithelial cancers. In RCC, loss of E-cadherin associates with increased incidence of metastasis (Katagiri et al. 1995). In ccRCC, aberrant nuclear E-cadherin has been suggested as prognostic marker in the background of VHL mutation (Gervais et al. 2007) and reduced expression has recently been identified to predict disease recurrence (Haddad et al. 2017). Recently, the adhesion molecule EpCAM (epithelial cell adhesion molecule) has renewed interest as independent studies revealed its positive expression as predictor for improved survival in both localized (Seligson et al. 2004; Eichelberg et al. 2013) as well as in metastasized RCC (Kim et al. 2005). While the majority of papillary and chromophore RCC samples showed an at least weak staining, in ccRCC EpCAM is lost in a subset of tumors which is associated with high-grade disease (Eichelberg et al. 2013; Zimpfer et al. 2014). Epithelial membrane antigen (EMA, MUC1) is a membrane-associated mucin reported to associate with poor prognosis in RCC (Langner et al. 2004) and to be expressed in carcinomas with sarcomatous differentiation (Yu et al. 2017).

Epithelial-Mesenchymal Transition (EMT) Markers

Vimentin as mesenchymal marker is widely used as diagnostic marker in various cancer types. ccRCC and most papillary RCCs are usually positive for vimentin, and high expression in ccRCC correlates independently with poor survival using different endpoints (Ingels et al. 2017; Shi et al. 2015). Among other epithelial-mesenchymal transition (EMT) markers, it has been shown that Clustering and Twist predict outcome in clinically localized RCCs (Harada et al. 2012). More studies are needed to validate

the independent prognostic value of EMT markers such as vimentin and proof their sensitivity and specificity for routine use.

Immune-Mediating Proteins

The preoperative measurement of circulating immune-mediating proteins such as C-reactive protein (CRP) or osteopontin has been suggested as prognostic markers for RCC patients (Sim et al. 2012). However, recommendations as routinely used marker are incongruent as CRP might not improve reductive accuracy (Bedke et al. 2012). In tissues, high CRP expression associates with poor survival in univariate analyses (Can et al. 2014). Overall, most studies focus on serum levels of CRP rather than intratumoral CRP expression, thus conclusion regarding assessment on tissues are limited.

Prognostic Relevance of Histological Classification

Numerous studies give evidence that prognosis is dependent on histological classification. Using large cohorts, several studies reported that ccRCC is generally associated with worse outcome of patients compared to papillary and chromophore CCC (Amin et al. 2002; Cheville et al. 2003; Patard et al. 2005). Observing an independent prognostic value, authors highlighted the need for accurate subtyping. As a representative example, Cheville et al. reported 5-year cancer-specific survival rates of 68.9%, 87.4%, and 86.7% for patients with clear cell, papillary, and chromophobe RCC, respectively, by including 2385 patients in their study. Additionally, several studies observed that ccRCC is associated with higher grades and advanced TNM stages compared to papillary RCC (Gudbjartsson et al. 2005). However, results are incongruent as multivariate analyses adjusting to tumor stage and differentiation partially failed to reveal significant differences in outcome between histological subtypes (Patard et al. 2005; Schrader et al. 2009).

Histological Subtypes of Renal Cell Carcinoma

Clear Cell Renal Cell Carcinoma (ccRCC)

Definition

Clear cell renal cell carcinoma (ccRCC) accounts for 65–70% of all renal cancers and occurs predominantly sporadically. In most cases, ccRCCs are solid tumors in the renal cortex, while multifocal and/or bilateral manifestation occurs in less than 5% of cases and is associated with hereditary cancer syndromes (Holger Moch et al. 2016).

Macroscopy

Macroscopically, tumors are well circumscribed and separated from the kidney by a pseudo capsule, while a real capsule is usually lacking. Diffuse infiltration in the renal parenchyma is untypical. The golden-yellow cut surface represents the high lipid content of tumor cells. Tumors harbor different grades of necrosis and hemorrhage and to a lesser extent calcifications and ossifications (Holger Moch et al. 2016).

Different metastatic spreads of ccRCCs lead to metastases on unusual sites. ccRCCs metastasize predominantly hematogenously via renal veins and the vena cava, resulting in pulmonary metastases. To a lesser extent, metastases in the central nervous system, head and neck region, and central and peripheral bones result from tumor spread into the lumbar veins. Lymphatic metastases can affect hilar, aortic, caval, and thoracic nodes (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

ccRCCs show diverse architectural growth patterns, mostly solid alveolar and acinar patterns which might appear micro- or macrocystic through dilatation of alveolar or acinar structures. Less often, tubular or pseudopapillary growth patterns as well as fibromyxoid stroma areas, calcification, and ossification might be seen. In more aggressive phenotypes, sarcomatous and rhabdoid changes have been described. Characteristically, tumors contain typical small, thin-walled vessel

formations as well as little inflammatory responses. Beside heterogenous morphologies, tumors are characterized by cells with clear or eosinophilic cytoplasm and distinct cell membranes. Eosinophilic cytoplasm is associated with high-grade tumors and predominantly present in necrosis or hemorrhage. Nuclei of tumor cells are mostly round with evenly distributed chromatin. In high-grade ccRCC, bizarre and large nuclei might be seen, and nucleoli range from small to large (Holger Moch et al. 2016).

PAX8 is a sensitive marker for the detection of renal epithelial neoplasms and is expressed in the nucleus of virtually all ccRCCs. Evaluation of PAX8 expression revealed higher intensity in RCC metastatic sites compared to the primary tumor (Barr et al. 2015). Additionally, ccRCCs show a positive reaction against epithelial markers such as AE1/AE3 or CAM5.2. Carbonic anhydrase IX (CAIX) is overexpressed in more than 75% of ccRCCs but lost in high-grade tumors. Concordantly, several studies observed that decreased CAIX levels are independently associated with poor survival of patients with advanced ccRCC, suggesting to use CAIX staining as a prognostic marker (Bui et al. 2003). However, other studies with long-term follow-up revealed conflicting results regarding CAIX as independent prognostic biomarker (Zhang et al. 2013). Comparing staining distribution, ccRCCs exhibit a membranous staining pattern of CAIX, while in pRCC, a basolateral staining can be observed. In contrast to chromophobe RCC, which exhibits diffuse CK7 expression, ccRCC lacks CK7, or CK7 is limited to isolated cells especially in high-grade ccRCCs. To distinguish ccRCC from other renal neoplasms, CD10 as a proximal tubule marker might be useful. The mesenchymal marker vimentin is higher expressed in tumors compared to paired normal renal tissue and shows the strongest levels in high-grade areas of ccRCCs. In line with this, vimentin has been suggested to predict survival of patients (Shi et al. 2015). Additionally, vimentin is a useful diagnostic marker to distinguish ccRCC from chromophobe RCC (Williams et al. 2009).

Besides having frequent molecular alterations, ccRCCs exhibit an inter- and intratumoral heterogeneity which hampers the development of gene-based molecular targets for therapy. ccRCCs possess characteristically loss of 3p promoting tumor initiation, progression, and metastasis. The most common genetic alterations involving the 3p locus are aberrations of the von Hippel-Lindau (VHL) tumor suppressor gene at 3p25–26 (Holger Moch et al. 2016). Different aberrations affecting VHL include promoter region methylation, loss of heterozygosity, and a large number of mutations leading to biallelic genetic alteration in both hereditary and sporadic ccRCCs. The von Hippel-Lindau protein is encoded by the VHL gene and plays a crucial role in the oxygen-dependent ubiquitin-mediated proteolytic degradation of several proteins. Studies show conflicting results regarding VHL gene aberration as prognostic or predictive biomarker (Cowey and Rathmell 2009). In addition to VHL, other genes on 3p frequently lost in ccRCC include epigenetic regulators and chromatin remodeling complexes such as SETD2, BAP1, and PBRM1, which are characterized as two-hit tumor suppressor genes. Among them, Polybromo 1 (PBRM1) is the second most frequently lost tumor suppressor gene in ccRCC with a mutation rate of approximately 45%. PBRM1 encodes BAF180 which is crucially involved in nucleosome remodeling and regulates oncogenic features of tumor cells (Brugarolas 2014). The BRCA1-associated protein-1 (BAP1) gene is mutated in approximately 15% of ccRCCs and encodes the protein BAP1, which is involved in the PI3K and mTOR signaling. BAP1 loss is associated with high-grade tumors and ccRCC-associated death of patients. In the majority of cases, PBRM1 and BAP1 mutation occur in a mutually exclusive manner, while tumors harboring mutations in both BAP1 and PBRM1 seem to possess an aggressive phenotype (Brugarolas 2014). Other molecular alterations comprise allelic losses on 14q partly resulting in loss of HIF1A, which has been suggested to be a molecular subtype of ccRCC and associates with poor prognosis (Monzon et al. 2011). A high proportion of ccRCCs harbors gain of 5q leading to amplification and subsequent overexpression of the SQSTM1 oncogene (Li et al. 2013).

The most precise prognostic and predictive factor for patients with ccRCC is the pathological stage, followed by tumor grade according to the WHO/ISUP grading system, and differentiation reflected by the presence of tumor necrosis, sarcomatoid, and rhabdoid features. Importantly, immunohistochemical and molecular markers described above are not routinely used in clinical practice.

Multilocular Cystic Renal Neoplasm of Low Malignant Potential

Definition

Multilocular cystic renal neoplasms of low malignant potential account for less than 1% of all renal tumors and characteristically do not recur or metastasize. Molecular analyses suggest that this neoplasm is genetically related to ccRCC. Most tumors are discovered incidentally and are associated with excellent prognosis (Holger Moch et al. 2016).

Macroscopy

The tumor is composed of numerous variably sized cysts and separated by thin septa, while solid tumor nodules are absent (Holger Moch et al. 2016).

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Multilocular cystic renal neoplasms of low malignant potential are morphologically not distinguishable from low-grade ccRCC. Cysts are lined by a single layer of clear cell tumor cells without prominent nucleoli, conform to WHO grade 1 or 2. Tumor cells express PAX8 and carbonic anhydrase IX. The septa between cysts consist of fibrous tissue characteristically with clusters of tumor cells. Tumor necrosis, vascular invasion or sarcomatous features are absent. Molecular alterations are similar to ccRCCs, including VHL mutations and 3p deletions (Holger Moch et al. 2016).

Papillary Renal Cell Carcinoma (pRCC)

Definition

Papillary renal cell carcinoma (pRCC) is a malignant tumor deriving from renal tubular epithelium. It is the second most common subtype of RCCs in adults and the most common subtype observed in pediatric RCC, accounting for approximately 10% of renal epithelial neoplasms (Fernandes and Lopes 2015). It occurs often in kidneys with end-stage renal disease and is rarely associated with hereditary syndromes. Traditionally, there are two types of pRCC: types 1 and 2 (Holger Moch et al. 2016).

Macroscopy

Most tumors are well circumscribed with a pseudo capsule and occur in the renal cortex, in part in association with renal scarring. If it occurs multiple and/or bilateral, an association with hereditary pRCC syndrome is possible (Holger Moch et al. 2016).

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pRCC shows papillary or tubulopapillary architecture with papillae formed by fine fibrovascular cores, often containing foamy macrophages and small calcifications (psammoma bodies).

Histologically, papillae of type 1 carcinoma show cells with nuclei in a single layer, with pale scanty cytoplasm. Cells of type 2 carcinoma show nuclear pseudostratification, abundant eosinophilic cytoplasm, and a lesser differentiation with a higher nuclear grade. Type 2 pRCC is usually larger and advanced and displays necrosis and lymphovascular invasion more frequently compared with type 1 pRCC. Type 2 pRCC can present with extensive nodal metastasis (Holger Moch et al. 2016). An example of pRCC types 1 and 2 is shown in Fig. 2.

The variant oncocytic pRCC (opRCC) shows eosinophilic, finely granular cytoplasm with prominent nuclei. There are statements that opRCC might be classified as an independent subtype of pRCC. It tends to be a favorable subtype mimicking type 1 pRCC with low malignant

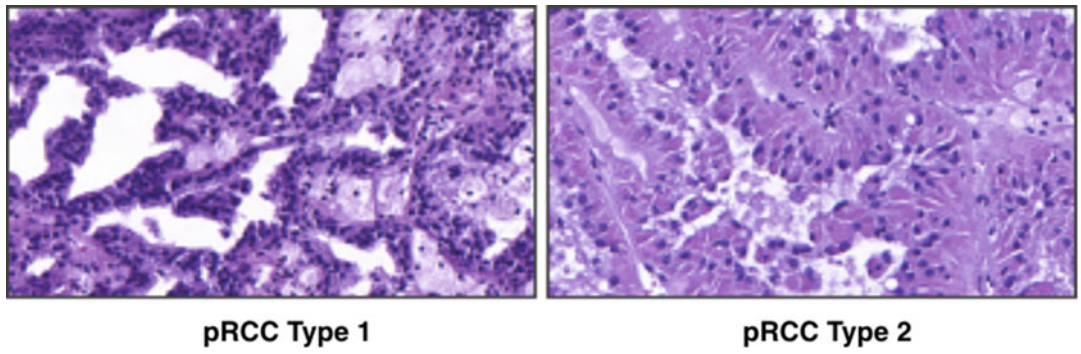

Fig. 2 Histology of papillary renal cell carcinoma type 1 and 2

potential and same genetic features (Han et al. 2017).

In both types, sarcomatous or rhabdoid differentiation is associated with dismal prognosis, while necrosis instead does not seem to predict survival of patients (Peckova et al. 2017).

Based on genomic analysis, there is evidence that type 1 and type 2 pRCC are individual diseases which differ biologically and clinically (Cancer Genome Atlas Research N et al. 2016). Therefore, pRCC subtyping is an independent predictor of outcome.

Type 1 tumors associate with significant better survival of patients as well as with lower stage and grade compared to type 2 pRCC. Type 1 frequently harbors gains of 7p and 17p, loss of the Y chromosome, and additional gains (3q, 8p, 12q, 16q, and 20q (Fernandes and Lopes 2015)) as well as alterations in the MET pathway (Cancer Genome Atlas Research N et al. 2016).

Type 2 pRCC instead shows allelic imbalance of one or more of 1p, 3p, 5p, 6p, 8p, 9p, 10p, 11p, 15p, 18p, and 22p. Losses of 8p, 9p, and 11q are associated with higher T stage and higher clinical stage, loss of 8p with positive M stage, and loss of 9p and gain of 3q with positive N stage (Fernandes and Lopes 2015). Molecular analysis could show that type 2 papillary RCC is a heterogeneous disease which can be divided in at least three further subgroups: tumors with CDKN2a alterations, TFE3/TFEB fusions, and CIMP hypermethylations. Tumors with CDKN2A loss and CpG island methylator phenotype (CIMP) are associated with a poor prognosis (Fernandes and Lopes 2015).

pRCC shows positive reactions for cytokeratin AE1/AE3, CAM5.2, high-molecular-weight cytokeratins, EMA, AMACR, RCC, vimentin, CD10, and CK7; CK7 is more in type 1 than in type 2.

Several genetic syndromes are associated with pRCC. Hereditary pRCC syndrome is an early-onset form which has recently been reported with multiple and/or bilateral Type 1 pRCC. It is based on the detection of germline mutations of the c-MET gene, associated with additional tumors in the breast, pancreas, lung, skin, and stomach (Fernandes and Lopes 2015). It is well accepted as a specific class of inherited renal cancer with an autosomal dominant pattern of inheritance and incomplete penetrance (Fernandes and Lopes 2015).

Hereditary Leiomyomatosis and Associated Renal Cell Carcinoma

Definition

Hereditary leiomyomatosis and associated renal cell carcinoma (hlRCC) is a genetic syndrome based on activating mutations in FH gene at 1q42.3-q43, which encodes the enzyme fumarate hydratase (Holger Moch et al. 2016).

Macroscopy

Renal tumors are predominantly localized in the cortex, but the medulla can be affected as well. It is associated with cutaneous leiomyomas, mostly located on arms or thorax, as well as uterine leiomyomas (Holger Moch et al. 2016).

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A renal tumor associated with hlRCC is mostly papillary, but there can also be a morphologic overlap with collecting duct carcinoma. Tumor cells show large nuclei with prominent inclusion-like eosinophilic nucleoli and abundant eosinophilic cytoplasm, resembling type 2 pRCC. The nucleoli are often surrounded by a clear halo, which imparts a "viropathic-like" appearance (Holger Moch et al. 2016).

Leiomyomas in context of hlRCC show atypical features with nuclei similar to those in renal tumors such as perinuclear halos (Przybycin et al. 2013).

Due to the underlying mutation of the FH gene, it shows a negative reaction for fumarate hydratase and positive reaction for modified cysteine-S-(2-succino)cysteine.

Prognosis is poor, and tumors frequently present at high stage with perinephric and/or venous invasion (Przybycin et al. 2013). There is a tendency toward early widespread dissemination, even with small tumors. hlRCC-associated renal tumors are estimated to be more aggressive than renal tumors of other hereditary renal cancer syndromes (Schmidt and Linehan 2014).

The subgroup of type 2 pRCC with CIMP hypermethylation patterns shows germline or somatic mutation of the FH gene, too, which could be one reason for poor prognosis of hlRCC (Cancer Genome Atlas Research N et al. 2016).

Chromophobe Renal Cell Carcinoma (chRCC)

Definition

Chromophobe renal cell carcinoma (chRCC) is a malignant renal tumor, arising from the distal nephron. It is characterized by cells with prominent cell membranes, wrinkled (raisinoid-like) nuclei with perinuclear halos, and pale to eosinophilic cytoplasm. It accounts for 5–7% of RCCs and is mostly sporadic. Hereditary forms are known, especially in the context of the Birt-Hogg-Dubé syndrome (Holger Moch et al. 2016).

Macroscopy

chRCC presents as well-circumscribed and unencapsulated tumor, light tan to brown in color, and sometimes with a central scar (Holger Moch et al. 2016).

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In its classic form, chRCC shows predominantly large pale cells (>80%) with a reticulated cytoplasm and distinctive cell membranes. This form is associated with necrosis and sarcomatous changes and presents as an aggressive tumor with a high potential for distant metastases (Holger Moch et al. 2016). An example of chRCC is shown in Fig. 3.

In its eosinophilic variant (> 80% eosinophilic cells), there are predominantly smaller, eosinophilic cells. This variant shows similarities to

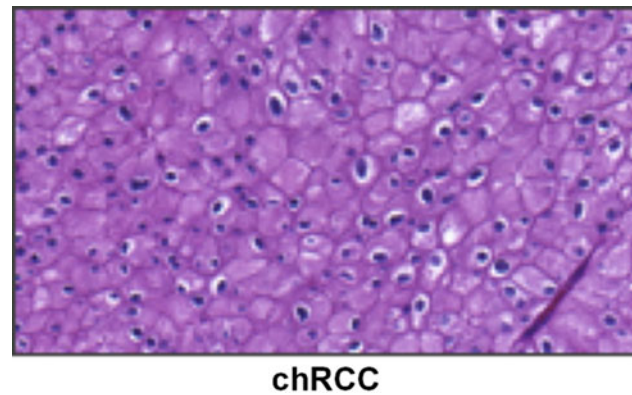

Fig. 3 Histology of chromophobe renal cell carcinoma

oncocytomas. It is often bilateral (11%) and multifocal (22%). Nuclei show an irregular wrinkled (raisinoid-like) appearance with perinuclear halos and a coarse chromatin; sometimes there is a binucleation. The growth pattern is solid, at times tubulocystic, with broad fibrotic septa (Vera-Badillo et al. 2012).

There are also mixed types. There is no evidence that the histologic variants show different molecular alterations.

Most cases are low grade and low stage (confined to the kidney) and show a favorable prognosis; the 5-year survival rate is estimated as 78–100%. Even in the setting of metastatic disease, chRCC has a better prognosis than pRCC and a similar prognosis to ccRCC, with a median survival of approximately 29 months compared with 5.5 months in pRCC (Motzer et al. 2002).

The small subset behaving aggressively is associated with a higher tumor stage, sarcomatous differentiation, necrosis, and small vessel invasion. Renal vein invasion is seen in approximately 5% of cases and incidence of metastatic disease is 6–7% (Vera-Badillo et al. 2012). Despite this more aggressive subset, there is no grading indicated (Hirsch et al. 2015).

Tumors show positive reactions for CD117 (KIT), parvalbumin, kidney-specific cadherin, and CK7. Hale colloidal iron staining is often diffused cytoplasmatically positive.

Cytogenetic studies revealed that chRCC is typically hypodiploid and contains a combination of monosomies involving chromosomes 1, 2, 6, 10, 13, and 21 (Hirsch et al. 2015). Losses of 2, 10, 13, 17, and 21 have been described in 93%, 93%, 87%, 90%, and 70% of chRCC, respectively, and might be useful as a diagnostic marker (Vera-Badillo et al. 2012).

There is a subset of tumors whose histology shows an overlap between chRCC and oncocytoma, leading to the name "hybrid oncocytoma/chromophobe RCC." Preferentially, this form is associated with the Birt-Hogg-Dubé (BHD) syndrome, a genetic syndrome which is characterized by inactivating mutations in the FLCN gene, which encodes for folliculin. FLCN is located on the short arm of chromosome 17. In FLCN −/− tumors, mTOR is upregulated resulting in activation of both mTORC1 and mTORC2 pathways. The PI3K-Akt-mTOR pathway seems to play a relevant role in preclinical models in this tumor type, and this could explain partial response observed with mTOR inhibitors. However, in sporadic chRCC, losses of chromosome 17 were reported but without associated FLCN mutations (Vera-Badillo et al. 2012).

Tubulocystic Renal Cell Carcinoma (tcRCC)

Definition

Tubulocystic renal cell carcinoma (tcRCC) is an uncommon cystic renal epithelial tumor, accounting for <1% of all RCCs. Less than 100 tcRCC cases have been documented to date in the literature (Holger Moch et al. 2016).

Macroscopy

It typically involves the renal cortex or corticomedullary junction. It probably originates from the proximal convoluted tubule or intercalated cells. The left kidney is more commonly (70%) affected. It mostly presents as a solitary, multicystic, and well-circumscribed mass with a spongy surface (Holger Moch et al. 2016).

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As the name implies, tcRCC is built up of numerous tubules of different size admixed with larger cysts which are lined by a single layer of flattened to cuboidal epithelium. The stroma is fibrotic. The nuclei are enlarged and irregular, their nucleoli intermediate to large (WHO grade 3). Cytoplasm sometimes shows oncocytoma-like aspects. It shows positive reaction for AMACR, CD10, CK19, and vimentin (Holger Moch et al. 2016).

Despite its high-grade cytology, most cases of tcRCC reported appear to have a favorable prognosis, usually being localized to the kidney at the time of diagnosis (pT1 and pT2) with <10% showing pT3 features (Zhao et al. 2015a) and with only rare cases of distant metastases (Bhullar et al. 2014), suggesting little value of grading in this neoplasm.

Because of its rarity, there is insufficient knowledge about the reasons for its indolent course.

Collecting Duct Carcinoma (cdCA)

Definition

Collecting duct carcinoma (cdCA) is a rare malignant epithelial tumor arising from the principal cells of the renal collecting ducts of Bellini, accounting for <1% of all RCC. It occurs more frequently in men (2:1) (Holger Moch et al. 2016).

Macroscopy

It is mostly located in the medulla with extension in the cortex or beyond the kidney with poorly defined tumor borders. If the tumor has grown large, the primary lesion can be difficult to identify. In these cases, identification of an infiltrative pattern that extends between nonneoplastic tubules in the cortex can be helpful (Hirsch et al. 2015). Both kidneys are affected equally (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

Histologically, it presents as a tubular, tubulopapillary, or tubulocystic tumor with irregular elongated and branching tubulus. There is a single layer of cells which are cuboidal to columnar or hobnail with pale to clear or eosinophilic cytoplasm. The nuclei are high grade, meaning large and pleomorphic with prominent nucleoli (Holger Moch et al. 2016). Further, there are numerous and abnormal mitoses as well as apoptotic bodies and coagulative necrosis. Sarcomatous and rhabdoid differentiation is commonly seen (Hirsch et al. 2015).

Diagnosis is a diagnosis of exclusion. Diagnostic criteria referred to WHO are (1) a medullary involvement, (2) a predominant tubular morphology, (3) desmoplastic stromal reaction, (4) high-grade cytology, (5) infiltrative growth pattern, and (6) the absence of other RCC subtypes or urothelial carcinoma.

Histological diagnosis is an adverse prognostic factor in itself. cdCA is per definition a high-grade tumor, and as a consequence, a grade should not be assigned (Srigley et al. 2013). The majority shows a highly aggressive clinical course with high prevalence (80%) of metastases and high tumor stage (>70% ≥pT3) at time of diagnosis. Three-year relative survival rates for localized, regional, and distant disease have been reported to be 93%, 45%, and 6%, respectively (Srigley et al. 2013).

Tumor cells show positive reactions for high-molecular-weight cytokeratins and CK7, sometimes a co-expression with vimentin. Immunohistochemical overlap with urothelial carcinoma shows positive reactions for PAX8 in the majority of cases and for p63 in 14% (Srigley et al. 2013).

Cytogenetic reports are limited due to the rarity of this tumor type. Most studies detect a combination of several monosomies, whereas others find more trisomies.

To date, conclusions based on genetic profile regarding prognosis cannot be drawn.

Mucinous Tubular and Spindle Cell Carcinoma (mtsRCC)

Definition

Mucinous tubular and spindle cell carcinoma (mtsRCC) is an uncommon renal epithelial neoplasm accounting for <1% of all RCCs with about 100 reported cases worldwide. It shows a female predominance with a ratio of 3:1. It is believed to be a low-grade malignant renal epithelial tumor based on low histological grade (Wu et al. 2013) with rarely described cases of lymph node metastasis and recurrence (Crumley et al. 2013). An association with nephrolithiasis is described (Holger Moch et al. 2016).

Macroscopy

In general, it occurs in the cortex, but localization in the medulla is possible. It exhibits as a well-circumscribed tumor with solid, shiny, and mucoid cut surface. An origin from proximal nephron has been suggested (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

Histologically, the tumor is characterized by a mixture of tubular and spindle cell components separated by variable amounts of mucinous stroma (Holger Moch et al. 2016).

Histologic features include mucin-poor variants, tumors with either tubular or spindle cell predominance, and oncocytic cytology (Hirsch et al. 2015).

Tumor cells are usually bland appearing with scant, pale to eosinophilic cytoplasm with round, and uniform nuclei that display low nuclear grade. Rare cases with sarcomatoid differentiation characterized by high-grade cytologic atypia, tumor necrosis, and increased mitotic activity have been reported (Zhao et al. 2015b). This dedifferentiation generally has a worse prognosis with shorter disease-free survival as well as early, more frequent metastasis (Arafah and Zaidi 2013). However, cases with classic, low-grade morphology with multiple distant metastases with both the primary tumor and metastases displaying identical morphology have also been reported (Zhao et al. 2015b). Tumor cells show positive reactions for CK7, PAX2, and AMACR and negative reactions for CK7 and AMACR in areas with sarcomatoid differentiation.

The immuno-profile suggests a proximal nephron origin and intimate relationship to pRCC, but unlike pRCC, it lacks gains on chromosomes 7 and 17 and losses of chromosome Y, showing that mtsRCC is a genetically distinctive entity different from pRCC (Zhao et al. 2015b).

Succinate Dehydrogenase-Deficient Renal Cell Carcinoma

Definition

Succinate dehydrogenase-deficient renal cell carcinomas (sdhRCCs) are hereditary malignant tumors defined by loss of succinate dehydrogenase (SDH) B (SDHB) expression, resulting in dysfunction of the mitochondrial complex II. sdhRCCs occur on the background of double-hit inactivation of the tumor suppressor gene SDH by germline mutations, which are associated with tumor syndromes causing paraganglioma, gastrointestinal stromal tumors, and pituitary adenoma. sdhRCCs account for approximately 0.05–0.2% of all renal cell carcinomas and present most commonly in young adult patients (Holger Moch et al. 2016).

Macroscopy

sdhRCCs are well-circumscribed solid or, to a lesser extent, multicystic tumors with a red-brown cut surface. Mostly, tumors are restricted to the kidney, while multifocal or bilateral manifestation occurs in approximately 30% of patients (Holger Moch et al. 2016).

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Microscopically, the tumor appears with lobulated or pushing margin and distributed cysts containing eosinophilic material. Malignant cells grow in a solid, nested, or tubular growth pattern. Characteristically, malignant cells have cytoplasmic vacuoles or inclusions that contain eosinophilic material which might appear bubbly. In high-grade tumors, these characteristics may be less prominent. The chromatin appears flocculent, nuclear contours are smooth, nucleoli are inconspicuous, and chromatin is evenly dispersed. With higher grades, increased nuclear atypia and eventually sarcomatoid features can be observed (Holger Moch et al. 2016).

The diagnosis of sdhRCC is defined by the loss of immunohistochemical staining for SDHB. Positive markers comprise CAM 5.2 and EMA and at least focal PAX8 expression (Williamson et al. 2015). In contrast, cytokeratin is present in only 30% of cases.

The underlying molecular alteration of sdhRCC is a double-hit inactivation of one of the SDH-genes through germline mutations (most commonly SDHB, less commonly SDHC, SDHA, and SDHD). This leads to dysfunctional assembling of the mitochondrial complex II at the inner mitochondrial membrane.

In most cases, sdhRCCs are low-grade tumors and associated with good prognosis of patients. Sarcomatoid features and high nuclear grade are predictive for metastatic spread of sdhRCCs.

Due to low case number and limited studies, there is currently no characteristic prognostic marker for sdhRCC.

MiT Family Translocation Renal Cell Carcinomas

Definition

MiT family translocation renal cell carcinomas are malignant tumors resulting from gene fusions involving members of the MiT family of transcription factors. The most common genetic alteration is Xp11 translocation, causing 40% of pediatric RCCs. t(6;11) translocation-associated RCCs are rare with approximately 50 published cases (Holger Moch et al. 2016).

Macroscopy

There are no macroscopic features characteristic for MiT family translocation RCCs (Holger Moch et al. 2016).

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MiT family translocation RCCs often show a papillary growth pattern and are composed of epithelial clear cells with abundant psammoma bodies. However, Xp11 translocation RCCs might also appear as other renal neoplasms. Characteristics of t(6;11) translocation RCCs involve a biphasic pattern, composed of large epithelial cells growing in nests as well as smaller cells clustered around basement membranes (Holger Moch et al. 2016).

MiT family translocation renal cell carcinomas characteristically harbor gene fusions between two members of the MiT family of transcription factors. There are Xp11 translocation RCCs with gene fusions involving the transcription TFE3 and one of multiple identified genes, accounting for approximately 40% of pediatric but only 1.6–4% of adult RCCs. The most common translocations are t(X;1)(p11.2;q21), resulting in the fusion of TFE3 and PRCC, and t(X;17)(p11.2;q25) resulting in the fusion between TFE3 and ASPSCR1. Less common are t(6;11) translocation RCCs harboring a gene fusion between MALAT1, a gene encoding a long non-coding RNA, and TFEB, resulting in TFEB overexpression (Holger Moch et al. 2016).

MiT family translocation RCCs consistently express PAX8 and other renal tubular markers but lack or underexpress epithelial markers. High nuclear TFE3 immunoreactivity and a TFE3 break-apart FISH assay are highly specific and sensitive for the detection of Xp11 translocation RCCs. t(6;11) translocation RCCs consistently express melanoma markers such as melan A and HMB45 and the cysteine protease cathepsin K. Nuclear TFEB expression and translocation detection by FISH are highly specific for t(6;11) translocation RCCs (Holger Moch et al. 2016).

Independent predictive markers for RCC-associated death are distant metastases and older age at time point of diagnosis (Ellis et al. 2014). Different fusion subtypes go along with different tumor manifestation, for example, patients with ASPSCR1-TF3 fusion tumors develop more often lymph node metastases compared to patients harboring other gene fusions.

Renal Medullary Carcinoma

Definition

Renal medullary carcinoma (rmCA) is a rare RCC subtype with approximately 200 described cases, predominantly in Blacks and associated with sickle cell trait or other hemoglobinopathies. These highly aggressive tumors occur mostly in young adults and have metastasized at time point of diagnosis in the majority of cases (Holger Moch et al. 2016).

Macroscopy

rmCA is a solid tumor located centrally on the renal medulla, is poorly circumscribed, and has as grayish/white cut surface (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

rmCA shares pathologic characteristics with collecting duct carcinoma and urothelial

carcinoma. Histological characteristics are features corresponding to high-grade adenocarcinoma histology including tubular, glandular, and tubulopapillary patterns with necrosis, inflammation, and desmoplasia. Tumor cells harbor prominent atypia and intracytoplasmic mucin. Stroma often appears myxoid in association with microabscesses and inflammatory infiltrates (Holger Moch et al. 2016).

Tumor cells consistently express PAX8; in about 50%, tumor cells are positive for polyclonal carcinoembryonic antigen, CK7, and CAM5.2. The stem cell marker Oct3/4 is expressed in the majority of renal medullary carcinoma and used as diagnostic marker (Rao et al. 2012).

Development of rmCA is associated with genetic alterations of hypoxia-inducible factor, p53, and vascular endothelial growth factor reflecting the underlying pathophysiological role of the hypoxic microenvironment of the renal medulla.

As rmCA is generally associated with poor survival of patients and account for less than 1% of all renal tumors, there are no independent prognostic markers routinely used to predict survival of patients.

Emerging New Tumor Entities

The 2013 ISUP Vancouver classification of renal neoplasia established a category of emerging new entities which include (Holger Moch et al. 2016):

- Thyroid-like follicular RCC
- Succinate dehydrogenase B mutation-associated RCC
- ALK rearrangement-associated RCC
- RCC MiT angioleiomyomatous stroma
- Oncocytic RCC occurring after neuroblastoma

To date, these emerging entities are not sufficiently characterized regarding morphology and molecular features. Additionally, due to rare case numbers and new definition of these subtypes, there are limited independent studies analyzing clinical course and outcome of patients. Thus, further studies are needed to characterize these new entities, to define diagnostic criteria and to increase knowledge about disease progression (Srigley et al. 2013). It remains uncertain if these tumors will be included as new entities in the WHO classification of tumors of the kidney.

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Treatment of Small Renal Masses

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Abstract

The incidence of renal cell carcinoma has been rising for years, particularly in industrial countries. It is very frequently diagnosed at the early stage of T1a, probably due to better early detection. At the same time, there is an increasing prevalence of chronic renal failure with higher morbidity and shorter life expectancy in those affected. Both factors underscore the urgent need for nephron-sparing treatments. The gold standard has thus shifted from radical to partial nephrectomy. Given good conditions, the intervention can be performed by laparoscopy, which offers the advantages of lower invasiveness. A treatment alternative can be advantageous for selected patients with high morbidity and an increased risk of anesthetic or surgical complications. Appropriate risk stratification requires prior histological confirmation of the small renal mass (cT1a) by assessment of biopsy specimens. Active surveillance represents a controlled delay in the initiation of treatment. Percutaneous radiofrequency ablation (RFA) and laparoscopic cryoablation are currently the most common treatment alternatives, though there are limitations particularly for central tumors near the renal

hilum. Newer ablation procedures such as high-intensity focused ultrasound (HIFU), irreversible electroporation, microwave ablation, percutaneous stereotactic ablative radiotherapy, and high-dose brachytherapy have high potential in some cases but are still considered experimental for the treatment of renal cell carcinoma.

Keywords

Small renal masses · Focal therapy · Active surveillance · Radiofrequency ablation (RFA) · Cryoablation · High-intensity focused ultrasound (HIFU) · Irreversible electroporation (IRE) · Microwave ablation (MWA) · Percutaneous radiotherapy · Surgery

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Introduction

Renal cell carcinoma is a relatively common disease in industrial countries like the German Federal Republic. Factors associated with affluence such as obesity probably play an essential role. In Germany, the Society of Epidemiological Cancer Registers (Gesellschaft der Epidemiologischen Krebsregister, GEKID) and the Robert Koch Institute (RKI) predict a continuous increase over the next few years (Robert Koch-Institut and und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. 2015).

Apart from the rising incidence of all types of cancer with increasing age, there is also an increase in the incidence of other diseases that can have a direct or indirect influence on the clinical course of cancer and particularly also on renal function. Especially chronic renal failure is associated a priori with a poorer life expectancy and a poorer quality of life (Kirchberger et al. 2012).

Radical nephrectomy was historically considered to be the treatment of choice for renal tumors. However, it offers no prognostic advantage over partial nephrectomy, at least for small tumors, and involves a markedly higher probability of consecutive renal failure. Organ-sparing therapy has therefore been established as the first treatment choice in the international guidelines during the last decades. Thus nephron-sparing or renal function-sparing surgery is regarded as the gold standard in the guidelines of the German Cancer Society, the German Urological Association, the European Association of Urology, and the American Urological Association (Olbert et al. 2015). In this context, however, a distinction is made between small renal masses (SRM $\leq$ 4 cm in diameter) and large ones. It is only at stage T2, i.e., over 7 cm in diameter, that removal of the entire kidney or radical nephrectomy is regarded as the standard treatment, especially since partial nephrectomy is generally no longer possible for tumors of this size (Ljungberg et al. 2016).

Imaging technology has vastly improved in the course of decades. CT and especially MRI now enable adequate differentiation between benign and malignant tumors as well as satisfactory

staging. This is paralleled by the development of new treatment techniques suitable for destroying renal tumors in a minimally invasive manner without requiring traditional surgery. In particular, radiofrequency ablation and cryoablation are already available as treatment alternatives. Numerous other ablation techniques still considered experimental are being investigated for their therapeutic advantage.

Confirming the Diagnosis: From Small Renal Masses to Renal Cell Carcinoma

Regardless of the clinical picture, patients should only be expected to endure additional morbidity if it has therapeutic consequences (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015). With reference to small renal tumors, this means that a biopsy to histologically confirm the image-based diagnosis of an uncertain mass is only necessary if it helps in selecting the appropriate therapy. For a surgical intervention such as radical or partial nephrectomy, however, imaging of a morphologically suspicious lesion without biopsy confirmation is considered an adequate indication if there are no serious contraindications for surgical exposure. For alternative treatments such as the ablations described in the following, a biopsy is absolutely necessary to compare initial and follow-up histology. It is unclear how preoperative biopsies with negative, i.e., nonmalignant, histology should be assessed. Basically, it would seem that surgery could be avoided in such cases. On the other hand, it is of course possible that the biopsy did not hit the intended target but only shows a central necrotic area, for example. The recommended procedure for solid tumors is a coaxial double-sleeve core biopsy (18-gauge needle) outside a possible central tumor necrosis with histological analysis (Ljungberg et al. 2016).

Cystic tumors are a special entity. They can already be malignant from category IIF (3–10%, most often papillary renal cell carcinomas) according to the morphological Bosniak classification system for CT evaluation (Graumann et al. 2015). Such a finding requires at least follow-up imaging (Visapää et al. 2013). Biopsy of cystic tumors harbors a high risk of false-negative results with a low cell density in fluid as well as the potential risk of a puncture-related needle tract seeding through cyst fluid leakage (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015). The procedure recommended to confirm the diagnosis here is a combination of coaxial core biopsy with histological analysis and fine-needle aspiration with cytological analysis (Ljungberg et al. 2016).

For suspected urothelial cancer of the collecting system, particularly if centrally located and/or invading the calyceal system (with or without hematuria), percutaneous biopsy is considered contraindicated because of the increased risk of metastases in the puncture canal (Robertson and Baxter 2011). In such cases, it is essential to attempt endoscopic confirmation of the findings on the condition that this will have therapeutic consequences, as stated above.

Despite the relatively high sensitivity (94–98%) and specificity (100%) of biopsy for accurately diagnosing a renal cell carcinoma, there is a high rate (up to 20%) of false-negative or inconclusive samples. A negative biopsy (normal parenchyma) is therefore an indication for repeat biopsy. A 90% success rate has been described for such a procedure (Ljungberg et al. 2016; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015).

Another limitation of biopsy-based diagnosis with precise determination of the tumor entity is the intratumoral biological heterogeneity of renal

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cell carcinomas (Höfflin et al. 2015). It is difficult in some cases to distinguish between basically benign oncocytomas and oncocytic renal cell carcinomas. Besides, the potential of such tumors to degenerate into cancer is being discussed. Biopsy of small renal masses usually correlates with the initiation of therapy (Maurice et al. 2015).

Active Surveillance and Watchful Waiting

Active Surveillance

The concept of active surveillance (AS) involves regular follow-up imaging for small localized asymptomatic renal tumors (SRM, cT1a, ≤4 cm) that grow slowly and show a low metastatic tendency. This risk is defined by the tumor size and the pathological subtype after histological confirmation by punch biopsy. Curatively intended treatment should only be initiated if the tumor size increases or at the patient's request. Thus the active surveillance strategy is directly dependent on the tumor biology and the diagnostic certainty. There are no objective criteria for selecting appropriate patients, and no uniform definition of the precise way in which AS should be carried out. To correctly determine whether AS is indicated, it is therefore necessary to consider comprehensive information obtained in an interdisciplinary setting involving urologists, radiologists, pathologists, and possibly other specialists. Numerous studies on the progression of small cT1a renal tumors have revealed a relatively slow growth rate of 0.2–0.4 cm per year and a very low metastatic rate of 1–2% in the first 2–4 years of follow-up. However, these data include a considerable number of histologically unconfirmed tumors or even tumors histologically classified as benign and also comprise substantial heterogeneity within renal cell carcinoma subtypes (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015). From a meta-analysis for the subgroup of biopsy-confirmed pT1a renal cell carcinomas (n = 120) with a median tumor size of 2.48 cm (1.7 to 4.0 cm), Chawla et al. calculated a median growth rate of 0.35 cm per year (0.42 to 1.6 cm per year) after a mean follow-up period of 30 months (25 to 39 months), although the initial tumor size did not correlate significantly with the growth rate (Chawla et al. 2006). Thompson et al. described a metastatic rate of 0.13% for renal cell carcinoma < 3 cm (1/178), although the metastatic risk increased by 24% per centimeter of additional growth (Thompson et al. 2009).

Visualization of vascular, capsular, adrenal, and calyceal invasion is a prognostically unfavorable factor and thus a contraindication for AS. Another adverse factor is biopsy histology revealing Fuhrman nuclear grade 3–4 (high-grade) clear cell or non-clear cell renal cell carcinoma. Anatomical classification systems like the PADUA score (preoperative aspects and dimensions used for anatomical classification), the R.E.N.A.L. score (radius, exophytic/endophytic, nearness to collecting systems or sinus, anterior/posterior, and location relative to polar lines), or the C-index can also provide early indications for surgery or the type of surgery and can thus be helpful in making the decision for or against AS (Camacho et al. 2015).

There is no tumor marker for monitoring renal masses; the concept of repeat biopsy to monitor renal tumors during AS has not been established either. Therefore, AS is generally performed only with follow-up imaging (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015).

Unfortunately, there is also no recommended scheme for the imaging modality or time interval. Depending on the risk of progression, it may be expedient to adapt the follow-up scheme to the schemes recommended by current guidelines for postoperative care after successful surgical treatment of renal cell carcinoma (Ljungberg et al. 2016; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015).

In staging the upper body, conventional non-contrast computed tomography (CT) tends to be advantageous for diagnosing abdominal conditions, while magnetic resonance imaging (MRI) tends to be the better for further differentiating malignancy and grading (Vargas et al. 2013;

Hallscheidt et al. 2004). Image-based monitoring during active surveillance should be carried out at least once a year. Retrospective studies and meta-analyses, but no prospective randomized study data, are available on AS of small renal masses and pT1a renal cell carcinomas. Moreover, no large series or meta-analyses have been performed to investigate biopsy-confirmed pT1a renal cell carcinomas during AS (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015).

Jewett at al. analyzed a progression rate of 0.13 cm per year and a metastatic rate of 1.1% in 101 biopsy-confirmed pT1a renal cell carcinomas over a median follow-up of 28 months (Jewett et al. 2011). Lane et al. found no significant survival difference between AS and surgical treatment with partial or radical nephrectomy for small renal masses in 537 patients with a mean age $\geq$75 years. However, only 4% of 148 deaths during a median follow-up of 3.9 years were attributed to clinical progression of renal cell carcinoma (Lane et al. 2010). Pierorazio et al. found that quality of life did not differ between immediate treatment and active surveillance groups after one year of follow-up (Pierorazio et al. 2013). In general, AS is not recommended for renal tumors >4cm with ill-defined margins and/or marked inhomogeneity or for biopsy-confirmed aggressive renal cell carcinoma or nonmorbid patients with a long life expectancy and morphologically suspicious imaging findings. In clinical use, however, active surveillance is now retreating more and more into the background in view of the alternative procedures for local ablation described in the following.

Watchful Waiting

In patients with a low life expectancy (e.g., due to old age or very high comorbidity), follow-up of an incidentally detected asymptomatic tumor would cause unnecessary psychological stress without having therapeutic consequences. Therefore, a wait-and-see strategy without targeted diagnostic or therapeutic measures should be considered in such cases. This watchful waiting or wait-and-see approach differs fundamentally from active surveillance. Factors that can lead to diagnostic procedures and/or therapy include symptoms such as bone pain caused by bone metastasis or hematuria caused by collecting system invasion. The aim here should be purely palliative treatment – for example, radiotherapy for pain relief or embolization/local ablation of the abnormality causing the symptoms. Such a watchful waiting strategy should be accompanied by a procedure known as best supportive care. This includes general support measures such as nutrition counseling, physiotherapy, or targeted pain therapy. Since by definition there are no follow-up imaging examinations or objectifiable quality-of-life parameters, such a procedure cannot be substantiated by large published series.

Ablation

Guideline-Based Ablation Procedures

Radiofrequency ablation (RFA) and cryoablation (CA) are evaluated as alternative curative treatment options for small renal tumors in the guidelines of the German, European, and American urological and radiological associations. The greatest amount of data is available here because these techniques have been used for such a long time; however, there are no data from prospective studies or even randomized controlled trials (Whitson et al. 2012). Apart from effectiveness for tumor control, assessment of the complication rates and quality of life plays an important role. Direct comparison of RFA and CA revealed no superiority of one procedure over the other in terms of disease-specific, relapse-free, or overall survival (Ljungberg et al. 2016). Decisive for the success and complication rate is the location and size of the renal tumor. Camacho et al. demonstrated that an R.E.N.A.L. score > 8 results in a higher local relapse and complication rate with RFA and CA (Camacho et al. 2015).

A definitive assessment of the two procedures as treatment alternatives cannot be made in the

current data situation. Therefore, this treatment option is not recommended at present for non-central T1a renal tumors in older patients with high morbidity and corresponding surgical or anesthetic risks and contraindications (Ljungberg et al. 2016; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2015).

Radiofrequency Ablation (RFA)

RFA is a hyperthermal ablation technique in which a high-frequency alternating current (375–400 kHz) causes ionic agitation via active electrodes with resultant frictional heat (Joule effect) reaching 100 °C and consecutive coagulation necrosis in the target tissue. This frictional heat is conducted radially outward from the electrode into the tissue (conduction principle). On the whole, temperatures of 50–105 °C are reached with a multivarying effect. At low temperatures, there will be protein denaturation, chromosomal alterations, damage to cellular membranes and organelles, and damage to the vascular system. High temperatures of around 100 °C lead to coagulation, vaporization, and carbonization of tissue (Duffey and Kyle Anderson 2010). Electrodes applied are monopolar or bipolar probes, compact single, cluster, or preferentially expandable guard electrodes of various sizes.

RFA was first applied in 1997 (Zlotta et al. 1997). The probe type, application time, and temperature level influence the size and homogeneity of the ablation zone. Zones ranging up to 7 cm can be achieved. A safety margin of 5–10 mm around the visualized mass is recommended. RFA has limited applicability for central renal cell carcinomas because of their proximity to the hilum and the associated risk of perforation. Heat loss through blood and urine flow (heat-sink convection) should also be taken into account. Prior transarterial embolization of the target and margin tissue can serve to reduce the heat-sink effect through renal arteries.

Open-surgical, percutaneous, and laparoscopic RFA approaches have been described. Percutaneous RFA is the energy-based ablation method most commonly applied for alternative treatment of renal cell carcinoma. It is technically easy to perform and takes relatively little time (10–20 min).

RFA applicators can be monitored by CT or MRI real-time scanning. RFA is performed primarily under local anesthesia with analgesia and sedation. Target temperatures of about 80 °C for 8–10 min are required within the operating temperature range to hyperthermally destroy tissue as completely as possible.

The occasional inhomogeneity and varying vascularity of renal tumors can sometimes lead to incomplete ablation (skipped lesions) through the above-described heat-sink effect with consecutive impedance jumps in the energy flow (Klingler et al. 2007). Thus, despite formally adequate application of the technique, the primary success rate is not 100% but only 90–100%, depending on the size and location of the tumor (Zagoria et al. 2011). The prospects of success are greater for smaller tumors (SRM $<$ 3 cm) and especially for those located in the cortex. Diverse studies describe a progression/local relapse rate of 2–12% for pT1a renal cell carcinomas in the first 5 years (Kunkle and Uzzo 2008).

An advantage of ablation techniques in general is that they can be repeated. A secondary success rate of nearly 100% has been described. The probability of metastatic spread after RFA is comparable to that associated with an active surveillance strategy (metastasis-free and disease-specific survival rates of 95–99%) (T racy et al. 2010). Mostly only minor complications occur after renal RFA and are expected in 0–20%. As mentioned above, proximity to the renal collecting system or large vessels poses a risk, and therefore RFA is not recommended in these cases because it can result in perforations, fistulas, or strictures (Wah et al. 2014). Outcomes of RFA are comparable to those of partial nephrectomy with the reservation that there have been no prospective randomized controlled trials (Takaki et al. 2010). However, expansion of the indications for RFA, possibly even beyond T1a tumors, is to be expected as more and more long-term data become available.

Cryoablation

Cryoablation (CA) is the only hypothermal ablation procedure and was first applied in 1995 as the oldest of the procedures discussed here (Uchida et al. 1995). A cryoprobe is inserted to carry out active freeze-thaw processes with temperatures dropping to -70°C and rising above 0 °C. Subsequent cell dehydration and mechanical disruption through ice crystal formation in the tissue are accompanied by hypoperfusion-related ischemia that ultimately leads to coagulation necrosis in the target area. In contrast to hyperthermal ablation, CA does not provide adequate hemostasis and thus involves an increased risk of bleeding. Like RFA, CA has only limited applicability for centrally located renal cell carcinoma because of its proximity to the renal hilum and the collecting system. Thermoregulation takes place via gas-filled cryoprobes with a thermally insulated shaft and noninsulated tip, utilizing the so-called Joule-Thomson effect (density- and pressure-related temperature change). Argon gas (−180 °C) is used for freezing and helium gas for thawing. Depending on the tumor size, 3–5 cryoablation needles and 2 thermal sensors are placed under image guidance. A safety margin of 5–10 mm is recommended. As described for RFA, the cold-sink effect can compromise the treatment success here too through impedance jumps (Berger et al. 2009). The cold-sink effect can also be reduced for CA by prior transarterial embolization (Duffey and Kyle Anderson 2010).

Like RFA, CA has also been applied using open-surgical, percutaneous, and laparoscopic as well as transluminal and endoscopic approaches. In contrast to RFA, the laparoscopic intervention under general anesthesia is the most widespread technique, though the procedure is currently very rarely performed in Europe. The surgical complexity is high because, like in laparoscopic partial nephrectomy, the kidney has to be surgically exposed so that the needles can be precisely placed in the tumor. After CA has been performed, the ice ball is mechanically compressed for 5–10 min and then visually monitored for another 5–10 min under reduced intra-abdominal gas pressure. Hemostasis can be achieved using liquid or solid hemostyptics or glue; persistent bleeding can also be treated with other surgical procedures such as circular suturing (Gill et al. 2003).

The primary success rate of CA ranges between 90% and 100% for small renal masses (Atwell et al. 2008). For technical reasons, the success rate depends on the tumor size and location; in analogy to RFA, the best results are obtained for tumors < 3 cm and located in the peripheral cortex (Georgiades et al. 2008). Diverse studies have described a progression or local relapse rate ranging between 3% and 17% for T1a tumors in the first 5 years (Atwell et al. 2008; Georgiades et al. 2008; Pirasteh et al. 2011). Thus, in terms of metastasis-free or disease-specific survival, CA also does not differ substantially from purely conservative treatment methods such as active surveillance. The complication rate is low at 2–19%, and mostly only minor complications occur here as well (Gill et al. 2005). The technical and surgical complexity is much greater than with percutaneous radiofrequency ablation. Moreover, the materials are far more expensive, so that the technique is now performed in only very few centers.

Other Potential Alternative Ablation Techniques

High-Intensity Focused Ultrasound (HIFU)

High-intensity focused ultrasound (HIFU) is a hyperthermal ablation procedure with temperatures of over 80 °C. A parabolic reflector is used to focus ultrasound waves of a piezoelectric crystal (1–4 MHz, pulse duration 4–6 s, peak energy 2000 kJ/cm (Kirchberger et al. 2012)) on the target tissue. This subsequently leads to coagulation necrosis as with radiofrequency ablation. Percutaneous HIFU therapy uses the so-called split-beam technology (external HIFU probe with integrated ultrasound coupling) for ablation at a penetration depth of 3.5–8.0 cm. Such a measure usually requires general anesthesia. Percutaneous HIFU is technically difficult to apply, however,

due to factors such as respiration-induced kidney motions, acoustic window limitations through signal loss across bone, and dynamic manual ultrasound control (Wu et al. 2003; Ritchie et al. 2010).

Laparoscopic HIFU therapy may circumvent this problem. In analogy to laparoscopic cryoablation, however, this requires laparoscopic exposure of the entire kidney. The HIFU transducer is relatively large (18 mm in diameter). We are dealing here with a HIFU probe ("side firing dual focal length," Misonix, Inc., USA). During a 10–40 min procedure, the tumor is ablated at a temperature of > 90 °C under real-time ultrasound monitoring. Klingler et al. performed surgical resection of the ablated tumor after laparoscopic HIFU. Ablation was found to be complete in four and incomplete in three of seven patients (Klingler et al. 2008). The HIFU procedure was uneventful in these seven patients. Ritchie et al. analyzed 12 patients with small renal masses (median 3.8 cm, 2.0–4.7 cm, 2 endophytic tumors, 10 exophytic cortical tumors, 4 oncocytomas, and 8 renal cell carcinomas) after uneventful laparoscopic HIFU followed by laparoscopic partial nephrectomy. In eight cases, ablation was incomplete with primarily subcapsular residues (skipped lesions) (Ritchie et al. 2010). The data situation for high-intensity focused ultrasound as a therapy for small renal masses is very limited, and there is a high rate of incomplete ablations in this small series.

Irreversible Electroporation

Irreversible electroporation (IRE) is a relatively new minimally invasive nonthermal technique for tissue ablation. Here a local critical electrically induced disturbance of the cell membrane dipole potential causes irreversible membrane pore formation. This leads to a permanent increase in cell membrane permeability and a loss of cell homeostasis with consecutive cytolysis within 1–7 days. Via 2–6 needles, 90–100 high-energy ultrashort rectangular high-voltage pulses per electrode pair (at least 90 per pair, 1.500–3.000 V, current strength 30–50 A, pulse duration 70–100 μs) are locally applied under endotracheal anesthesia with complete muscle relaxation and ECG triggering. Through the postulated all-or-none reaction starting at a "critical" induced transmembrane potential and the cellular effect (sparing the matrix), the ablated area should exhibit a very small transition zone and sharp delineation between treated and surrounding tissue (Rubinsky 2010). In 2007, IRE (NanoKnife® system; AngioDynamics Inc, 2–6 needle electrodes) was granted approval for clinical application (general approval for soft tissue tumors). Previous experimental and phase-1 publications were able to demonstrate safe application with sparing of the collecting system and renal vessels. In seven patients submitted to CT-guided IRE for pT1a renal cell carcinoma (1.6–3.1 cm), Thomson et al. found five cases of complete ablation and two cases of tumor progression (29%) by follow-up CT after 3 months (Thomson et al. 2011). After CT-guided IRE of 20 peripheral T1a renal tumors (1.5–2.9 cm; including 13 biopsy-confirmed renal cell carcinomas), Trimmer et al. identified residual tumors by CT or MRI morphology in 2 of 20 cases after 6 weeks (10%) as well as a biopsy-confirmed relapse in one of 6 cases after one year (17%) (Trimmer et al. 2015).

First post-resection histological results 4 weeks after IRE of biopsy-confirmed solid pT1a renal cell carcinomas were presented in a phase 2a trial by Wendler et al. Resected tumor samples after IRE showed massive tumor damage without evidence of viable tumor remnants. However, in contrast to previous assumptions, affected nontumorous renal tissue displays side effects such as intimal hyperplasia with large-vessel occlusions in the perifocal area and renal papillary necrosis (Wendler et al. 2015a, 2015b). These first preliminary study results suggest that percutaneous ablation of solid renal cell carcinomas by IRE requires further technical optimation but is basically possible and also favorable as a nephron-sparing therapy for central tumors.

Microwave Ablation

In microwave ablation (MWA), energy is delivered to target tissue by induction of frictional heat.

Through its dipole moment, rotational motion is caused by dielectric hysteresis (rotating dipoles) at a frequency of 915–2,450 MHz via a microwave generator (45–200 watts) and appropriate antennas. This generates local temperatures of at least 100 °C and ranging above 150 °C over 10–15 min.

Hyperthermia results in coagulation necrosis with a radius of damage that varies according to the antenna geometry. The literature contains numerous experimental animal studies on in vivo renal tissue but only a few clinical studies on microwave therapy of small renal masses (Floridi et al. 2014). After percutaneous ultrasound-guided MWA in 98 patients with pT1a renal cell carcinomas (0.6–4 cm), Yu et al. found a success rate of 97% over a median period of 26 months and progression in only one case after 32 months. The major complication rate was 1.7% (Yu et al. 2015).

Moreland et al. treated 53 patients with biopsy-confirmed pT1a renal cell carcinoma (0.8–4.0 cm) by percutaneous ultrasound-guided MWA. Follow-up CT or MRI examinations were carried out in 38 patients after 8 months. None of the cases showed a local relapse. The clinical examination revealed a significant change in renal function in six cases (11.3%) (Moreland et al. 2014). Due to its specific mode of action in stimulating water molecules, MWA may be a particularly suitable ablation method for cystic renal tumors or complicated/malignant renal cysts. Carrafiello et al. found an ablation rate of 100% and no relapses over a period of 24 months after percutaneous CT- or ultrasound-guided MWA in seven patients with Bosniak III or IV cysts (1.4–2.7 cm) (Carrafiello et al. 2013). Given the high technical complexity and the relatively large antennas, MWA has thus far been unable to prevail over other percutaneous hyperthermal ablation techniques, particularly RFA.

Percutaneous Radiotherapy

Primary percutaneous radiotherapy for focal treatment of localized renal cell carcinoma is historically regarded as ineffective and thus useless. The basis for this is the relatively high radiation resistance of renal cell carcinoma and the high toxicity in radiosensitive adjacent organs (small and large bowel) due to the lack of tissue-sparing potential. Technological advances enable more precise hypofractionated irradiation (radiosurgery) known as stereotactic ablative radiotherapy. Treatment is delivered in one fraction or only a few fractions (24–40 Gy in 1–5 fractions with 4–25 Gy per fraction). Robot-assisted linear accelerators are applied as well as modern immobilization measures and new computer-based radiation geometry with 3D and 4D simulation, respiratory triggering, fiducial markers, cone beam imaging, intensity-modulated radiotherapy (IMRT), etc.

As opposed to conventional radiotherapy, which induces apoptosis by DNA damage, stereotactic radiotherapy acts on various cellular structures and signaling pathways with consecutive lethal nonthermal damage. Campbell et al. summarized the results of 14 studies published from 2003 to 2015 in which stereotactic ablative radiotherapy (SABR) of localized renal cell carcinomas was performed in 138 patients with 166 T1a-T1b tumors (Campbell et al. 2015). A conclusive uniform assessment, however, is strongly limited by the great heterogeneity of the tumor data and treatment regimens as well as the assessment criteria. The authors conclude that primary SABR may be a future treatment option for local renal cell carcinoma.

Brachytherapy

Brachytherapy (BT) delivers very high radiation doses to target tissue via temporarily implanted radiation sources. The typical steep dose reduction can prevent high and unwanted radiation exposure of surrounding tissue. In image-guided afterloading, initially inactive applicators are placed under CT scan real-time monitoring und then secondarily loaded with the divergent radiation source via the afterloader. An exact radiation therapy plan (dose distribution) is calculated via the position and dwell time of the applicators. High-dose rate brachytherapy (HDR-BT) is

characterized by a continuous high-dose rate (HDR > 12 Gy/h), Iridium-192 currently being the isotope most commonly used for beta therapy. This leads to lethal nonthermal cell damage by acting on various cellular structures and signaling pathways.

After positioning the brachytherapy catheter via fixed valve introducers (e.g., angiography introducers) inserted by the Seldinger technique under intravenous analgesia and sedation, a contrast-enhanced planning CT or MRI scan (breath-hold technique, section thickness ≤ 5mm) is acquired to determine the exact location in relation to tumor extension (coordinates x, y, z). The irradiation time of about 20–90 min is dependent on the tumor volume (TV); ideally 100% (D 100) of the target volume (TV + safety margin of a few millimeters) should be covered by the intended dose. If necessary, underexposed tumor areas are treated again in a second session.

This technique enables treatment of irregularly shaped tumors without size limitation and regardless of respiratory motion. No clinical data have as yet been published on percutaneous HDR-BT for treatment of localized renal cell carcinoma. The irradiation of renal cell carcinomas and the tolerance dose of nontumorous renal parenchyma are currently being investigated in a prospective phase I/II trial (Ricke et al., University of Magdeburg, Germany) (Bretschneider et al. 2012).The as yet unpublished interim results show good controllability and a good response of renal cell carcinomas.

Surgery

Partial Nephrectomy and Renal Tumor Enucleation

Renal tumor resection is regarded as the treatment of choice, but partial nephrectomy (PN, nephron-sparing surgery) should be performed whenever possible. In experienced centers, laparoscopic and open interventions do not differ with regard to overall or cancer-specific survival. However, laparoscopy is associated with a smaller intraoperative blood loss and a shorter hospital stay than open surgery (Ljungberg et al. 2016; Gill et al. 2007).

The indication with regard to the access path strongly depends on the patient's constitution, the location of the tumor (R.E.N.A.L. score), and, above all, the surgeon's experience with laparoscopic nephrectomy. Consecutive urine output is not dependent on the access. Despite shorter operation and ischemia times with open PN with a less marked postoperative decrease in GFR and, on the other hand, lower morbidity with laparoscopic PN, no difference in the degree of renal failure was found after a follow-up period of 3.6 years (Muramaki et al. 2012).

The most important outcome parameter is the ischemia time of healthy renal parenchyma spared, which has to be as short as possible for maximum preservation of renal function. Cooling (cold ischemia) is recommended for an expected ischemia time of more than 25 min. Zero ischemia partial nephrectomy can be performed when a tumor is more favorably, especially peripherally, located and heavy bleeding is not expected (Gill et al. 2011). Furthermore, a maximum of healthy parenchyma should be spared in the sense of a possible tumor enucleation (nephron-sparing surgery).

Meta-analyses after partial nephrectomies or tumor enucleations show a rate of 0–7% for positive resection margins, most of which appear to have no influence on the relapse rate or the cancer-specific or overall survival rate (Marszalek et al. 2012). Therefore, current guidelines recommend a simple follow-up rather than repeat surgery. Comparative studies have not yet been conducted to assess the value of laparoscopic single-port PN or other laparoscopic techniques such as robot-assisted PN.

Conclusions for Clinical Practice

1. Partial nephrectomy is the gold standard for small renal tumors if there is no contraindication.
2. With good image accessibility, active surveillance with or without histological monitoring is also a possible alternative. This is

recommended only for selected patients with low-risk renal cell carcinoma < 3 cm.
3. As a "non-therapy," watchful waiting is a viable option for older and comorbid patients whose renal tumor will probably have no consequences.
4. There are numerous alternative ablation procedures, but only radiofrequency ablation and cryotherapy are guideline approved.
5. All other procedures, as, for example, IRE, are currently considered experimental.

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Partial Versus Total Nephrectomy: Indications, Limitations, and Advantages

37

Riccardo Autorino, B. Mayer Grob, Georgi Guruli, and Lance J. Hampton

Contents

Abstract

The choice between partial nephrectomy (PN) and radical nephrectomy (RN) remains a clinical challenge. In the era of "precision-surgery," we are asked to offer the best treatment possible, which is the one with the best risk-benefit ratio. In this equation we include patient's characteristics (overall physical health, frailty, distress, body habitus, comorbidities, renal function) and tumor characteristics (mostly location and size). Moreover, the decision process is necessarily influenced by surgeon's factors (own surgical expertise and prior outcomes, as well as comfort with various surgical procedures, especially in the case of minimally invasive techniques). Despite being far from optimal, current evidence suggests that PN does not universally translate into a clinical benefit for all patients with renal masses where this surgery is technically feasible. Overall, PN has gained a consolidated role and it represents the way to go for simple renal masses of lower stage and limited size whenever. Efforts should be made to remove barriers limiting its implementation. PN can represent a viable option also for larger renal tumors, as it seems to offer acceptable surgical morbidity,

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equivalent cancer control, and better preservation of renal function, with a potential for better long-term survival. For T2 tumors, while RN remains the standard, the use of PN should be selectively considered on a case-by-case basis.

Introduction

Since its description in the late 1960s, radical (total) nephrectomy (RN) has represented, for three decades, the main surgical treatment of renal tumors (Robson et al. 2002). The procedure was based on few key principles, including early ligation of the renal vessels to minimize the risk of vascular tumor emboli, excision of Gerota's fascia including the kidney and adrenal gland, and extensive lymph node dissection.

In the early 1990s, the concept of nephron-sparing surgery (NSS) for elective indications (patients with normal contralateral kidney) was introduced and popularized (Van Poppel et al. 1991; Campbell and Novick 1995; Steinbach et al. 1995; D'Armiento et al. 1997; Herr 1994). This conservative approach was mainly fostered by the widespread use of cross-sectional imaging, which led to a stage migration with consistent decrease in renal tumor size at presentation (Nguyen et al. 2006). Convincing evidence showed similar long-term outcomes compared to RN (Herr 1999; Pahernik et al. 2006). Moreover, an increasing awareness toward health-related quality of life fueled the concept of maximal functional preservation, along the already established paradigm of cancer control (Clark et al. 2001; Poulakis et al. 2003). With maturing data and refinements in surgical techniques, partial nephrectomy (PN) has gradually become the gold standard surgical treatment for localized kidney cancer, as recommended by current guidelines (Ljungberg et al. 2015; Campbell et al. 2009; Finelli et al. 2017) (Table 1).

Nevertheless, the intrinsic complexity of PN carries a specific risk of perioperative complications, especially in patients with advanced age and significant comorbidities (Tomaszewski et al. 2014). In addition, the largely awaited results of the EORTC randomized control trial 30,904 failed to demonstrate a survival advantage in favor of PN (Scosyrev et al. 2014). Thus, the debate radical versus conservative kidney cancer surgery is still ongoing as we realize that recommending PN to all patients for whom the operation is technically feasible cannot represent a perfect solution and the challenge is to identify for each patient the right balance between perioperative risks and potential advantages of nephron preservation.

Aim of this chapter is to summarize the current evidence on comparative outcomes of RN and PN

Table 1 Overview of current guidelines of kidney surgery for localized renal cancer

	PN	RN
EAU (Ljungberg et al. 2015)	NSS recommended in patients with T1a tumors It should be favored over RN in patients with T1b tumor, whenever technically feasible	Laparoscopic RN recommended for patients with T2 tumors and localized renal masses not treatable by NSS Laparoscopic RN should not be performed in patients with T1 tumors for whom PN is indicated
AUA (Campbell et al. 2009)	NSS should be considered in all patients with a clinical T1 renal mass	RN is still a viable option when necessary based on tumor size, location, or radiographic appearance if the surgeon judges that NSS is not feasible or advisable. A laparoscopic approach to RN is now an established standard
ASCO (Finelli et al. 2017)	Standard treatment should be offered to all patients in whom an intervention is indicated and with a tumor amenable to this approach	Should only be reserved only for patients with a tumor of significant complexity that is not amenable to PN or for whom PN may result in unacceptable morbidity

EAU European Association of Urology, *AUA* American Urological Association, *ASCO* American Society of Clinical Oncology, *NSS* nephron-sparing surgery, *PN* partial nephrectomy, *RN* radical nephrectomy

for localized renal tumors, to review current established and expanding indications of PN, and to analyze its advantages and limitations compared to RN.

Contemporary Trends in the Use of PN

There is no doubt that dissemination of PN into clinical practice has increased over the past two decades. Moreover, the use of PN has been regarded by many as quality-of-care indicator, and therefore concerns have been raised as NSS still remains underused. Hollenbeck et al. reported one of the early studies looking into this issue by using the NIS administrative database from 1998 to 2002; they found a PN rate increase from 3.7% to 12.3%, with an overall PN rate of 7.5% (Hollenbeck et al. 2006). Several other studies from both the USA and Europe have been reported on trends in the use of PN for the management of (Zini et al. 2009; Thompson et al. 2009; Dulabon et al. 2010; Sun et al. 2012; Colli et al. 2012; Patel et al. 2012, 2013; Liss et al. 2014; Hadjipavlou et al. 2016; Tan et al. 2016; Simone et al. 2016) (Table 2). Overall, despite a significant increase over the past few years, especially for small renal masses (clinical T1a tumors), there is still room for further implementation of PN, especially in smaller (lower volume) and nonacademic community hospitals. Another important aspect is the impact that minimally invasive techniques have played in kidney cancer surgery. There is a body of literature suggesting that the slow adoption of PN might in part be explained by the rise in laparoscopic RN for localized tumors (Abouassaly et al. 2010). On the other side, evidence suggests that in adoption of robotic technology is likely to translate into higher use of PN (Patel et al. 2013).

Table 2 Contemporary trends in the use of PN: overview of relevant studies worldwide

Reference	Dataset (origin)	Study period	N of procedures	Clinical tumor stage	PN rate, %	Increase in PN use during study period
Zini	Multicenter registry (Europe)	1987–2007	1,883	T1–2	31.7	4.5-fold
Thompson	MSKCC database	2000–2007	1,533	T1	56%	From 69 to 89% (T1a) From 20 to 60% (T1b)
Dulabon	SEER (USA)	1999–2006	18,330	T1a	35	From 21 to 45%
Sun	SEER (USA)	1998–2008	26,468	T1a	34	From 5 to 40%
Colli	NCD	2000–2008	142,194	T1	na	From 17 to 31%
Patel	NIS (USA)	2002–2008	226,419	na	19.8	From 15 to 25%
Patel	Maryland HSCRC	2000–2011	14,260	na	18.4	From 9 to 27%
Liss	NIS (USA)	2007–2011	95,711	T1	32.3	From 29 to 35%
Hadjipavlou	BAUS (UK)	2012	1,768	T1	38.8	na
Benegas	SEER (USA)	2004–2009	835	T1	27.6	From 43 to 55% (T1a) From 9 to 18% (T1b)
Tan	SEER (USA)	2000–2009	11,678	T1	25.3	From 14.6 to 41.4%
Simone	Multicenter registry (Europe)	2004–2014	2,526	T1	56.9	na

PN partial nephrectomy, *na* not available, *SEER* Surveillance, Epidemiology, and End Results Program, *NCD* National Cancer Database, *NIS* National Inpatient Sample, *HSCRC* Health Services Cost Review Commission, *BAUS* British Association of Urological Surgeons

PN Versus RN for Small Renal Mass

The inclusion of PN in current clinical guidelines had been supported by evidence coming from a plethora of large institutional or population-based studies suggesting equivalent oncological outcomes, better functional outcomes, and ultimately superior overall survival compared to RN (Thompson et al. 2008; Huang et al. 2009; Weight et al. 2010). However, more recent evidence generated much controversy on these arguments, fostering the idea that the "protective" benefit of NSS might in fact not be universal across all groups of patients.

The EORTC 30904 represents the only prospective randomized trial to test the hypothesis that PN s is indeed batter than RN for the treatment of patient with small (<5 cm) renal mass and normal contralateral kidney (Table 3) (Scosyrev et al. 2014; Van Poppel et al. 2007, 2011). Three reports from this trial have been published. The first one on surgical outcomes showed that perioperative complications requiring reoperation, although fairly rare in both arms, were slightly more common after PN compared with RN (4.4% vs. 2.4%) (Van Poppel et al. 2007). In 2011, the analysis on survival outcomes was reported (Van Poppel et al. 2011), and this showed an unanticipated 10-yr. overall survival benefit favoring RN (81.1%) over PN (81.1% vs. 75.7%; HR 1.5; 95% CI, 1.03–2.16; $p = 0.03$). This survival difference was not significant when including only patients with RCC ($p = 0.07$). Regardless, patients undergoing PN were not found to have improved survival. Only 12 of 117 deaths were the result of renal cancer (1.5% of RN patients and 3% of PN patients; $p = 0.23$). The most recent analysis was on kidney function (Scosyrev et al. 2014). With a median time to last eGFR measurement of 6.7 years, PN was found to substantially reduce the incidence of at least moderate renal dysfunction (eGFR <60) compared to RN (64.7% vs. 85.7%), although the incidence of advanced kidney disease (eGFR <30) was similar between groups (RN, 10%, and PN, 6.3%) and the incidence of kidney failure (eGFR <15) was nearly identical (RN, 1.5%, and PN, 1.6%). While this trial represents the only level I evidence to date, it does have several notable limitations. Initially designed as a non-inferiority study and powered to show a 10% difference in overall survival at 5 years between groups, trial completion was delayed and the trial was closed before the accrual goals were met. Considerable disparities in baseline comorbidities, loss to follow-up, and significant crossover were observed. Limitations notwithstanding, findings from the EORTC trial should not be ignored, also considering that likelihood that a similar randomized trial will ever be repeated is low.

Table 3 A snapshot of the EORTC 30904 trial (Scosyrev et al. 2014; Weight et al. 2010; Van Poppel et al. 2007)

Study design	Randomized, non-inferiority, multicenter, phase 3 study
Study period	1992–2003
End points	Primary end point: overall survival Secondary end points: disease-specific survival, progression, and surgical side effects
Inclusion criteria	Patients with a solitary, T1–T2 N0 M0 renal tumor ≤5 cm suspicious for RCC, a normal contralateral kidney, and WHO-PS 0–2
Number of enrolled patients	541 (RN = 273; PN = 268)
Main findings	Slightly higher complication rate in PN group
	Overall, NSS is worse than RN in terms of 10 year overall survival In RCC patients only, trend in favor of RN is no longer significant
	NSS substantially reduced the incidence of at least moderate renal dysfunction (eGFR <60) Incidence of advanced kidney disease (eGFR <30) is similar in the two treatment arms, and incidence of kidney failure (eGFR <15) is nearly identical
Study limitations/ flaws	Study prematurely closed because of poor accrual Disparities in baseline comorbidities Considerable crossover between treatment arms

Another important contribution to the field was given by Kim et al., who performed a systematic review and meta-analysis of 36 eligible studies including over 41,000 patients undergoing PN (23%) or RN (77%) (Kim et al. 2012). Most of the studies were on clinical T1a (<4 cm) tumors. In a pooled estimate including the abovementioned EORTC 30904 and 20 additional retrospective studies, PN correlated with a 19% reduction in all-cause mortality (HR 0.81; p <0.00001). Moreover, PN was associated with a 29% reduction in cancer-specific mortality (HR 0.71; $p = 0.0002$) compared with RN. This last finding is likely to be related to the large selection bias, as tumors selected for PN were also those with lower tumor complexity and lower associated oncologic risk. Another finding of the meta-analysis was a 61% risk reduction of severe chronic kidney disease for PN patients (HR 0.39; p <0.0001), when considering the nine studies where this outcome was reported. Overall the authors concluded by warning that their findings should be considered within the context of the low quality of included studies and their significant heterogeneity.

More recently, another two meta-analyses were reported. Gu et al. included 14 cohort studies involving 28,764 patients and found that PN had a superior overall survival (HR: 0.81; p <0.001), whereas cancer-specific survival (HR: 0.85; P <0.060) and recurrence-free survival (HR: 0.66; $p = 0.239$) were similar between PN and RN (Gu et al. 2016). Notably, compared with the previous study by Kim et al.(2012), this meta-analysis tried to minimize overestimating the treatment effect from pooled estimates by excluding studies from overlapping dataset, such as those using population-based SEER data. In the other analysis by Wang et al. (2016), 26 studies were pooled for new-onset chronic kidney disease, and 6 studies were pooled for cardiovascular outcomes. PN correlated with a 73% risk reduction of new-onset chronic kidney disease in all included patients (HR = 0.27; p <0.0001) compared with RN. On the other end, there were no significant differences between groups regarding cardiovascular events (HR = 0.86; $p = 0.238$) and death (HR = 0.79; $p = 0.196$).

Analyses of retrospective administrative datasets present significant limitations undermining their validity. Selection biases contribute to profound measured and unmeasured differences in these datasets, and pretreatment characteristics associated with treatment type and management decisions are poorly captured. Studies using advanced statistical methods to overcome these limitations have recently become available. One of these was reported by Tan et al. who investigated the long-term survival after PN versus RN using "instrumental variable analysis," a statistical method that relies on an "instrument" that is strongly associated with the treatment of interest. They assessed patients with clinical T1a renal masses and found that all-cause mortality was 15.5% better following PN at 8 years of follow-up, which translates into one life saved for every seven patients undergoing PN instead of RN (Tan et al. 2012).

PN Versus RN for more Complex Renal Mass

While current guidelines recommend elective PN (over RN) as the standard surgical treatment for clinical T1a renal tumors and T1b ones whenever technically feasible (Ljungberg et al. 2015), RN is still regarded as the reference standard for larger (clinical T2) masses. NSS for anatomically complex masses can carry perioperative and oncologic risks that would be avoided if a RN were performed. Thus, the decision-making process in regarding the optimal treatment for these masses is more challenging. Nevertheless, emerging data seem to suggest a potential role for PN in this setting (Fig. 1).

Robust population-based analyses showed that PN for T1b tumors provides equivalent cancer control relative to RN (Crépel et al. 2010; Badalato et al. 2012). It has also been suggested that even in patients with higher-risk (> 7 cm) masses, PN does not compromise cancer-specific mortality (Kopp et al. 2014; Long et al. 2012; Becker et al. 2011; Bigot et al. 2014). Mir et al. recently reported a meta-analysis of comparative functional, oncological, and surgical outcomes of PN versus RN specifically in larger (cT1b-2) renal

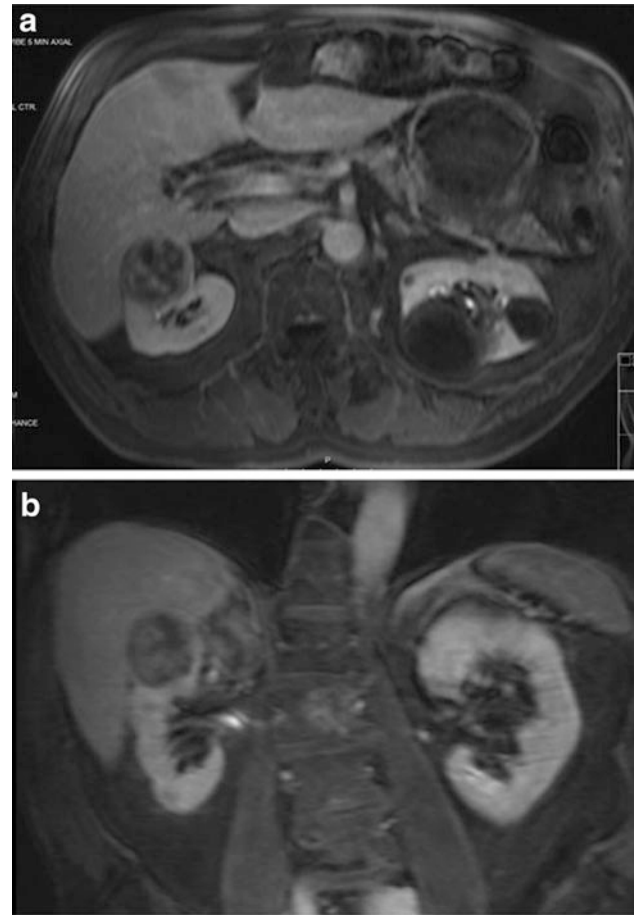

Fig. 1 Kidney MRI (a = transversal section; b = coronal section) showing a complex cystic mass measuring at 5 × 4 cm arising from the anterior/superior pole of the right kidney. Given high anatomic complexity (RENAL score 8a) and patient age of 72, in a case like this, a risk trade-off between PN and RN should be considered. This patient successfully underwent a robotic partial nephrectomy. Pathology showed renal cell carcinoma with negative surgical margins. After 2 years, post-surgery is free from disease and with stable renal function

masses (Mir et al. 2017). Overall, 21 case-control studies including 11,204 patients (RN = 8620; PN = 2584) were deemed eligible and included in the analysis, with most studies being on open PN. A lower likelihood of postoperative complications was found for RN (RR: 1.74; $p < 0.001$). PN was associated with better postoperative renal function, as shown by higher postoperative eGFR (WMD: 12.4 ml/min; CI, 9.8, 14.9; $p < 0.001$), lower likelihood of onset of postoperative CKD (RR, 0.36; CI, 0.52, 0.76; $p < 0.001$), and lower decline of eGFR (WMD, −8.6; CI, −12.6, −4.7; $p < 0.001$). Likelihood of tumor recurrence was lower for PN (OR: 0.6; $p < 0.001$), as well as cancer-specific (OR: 0.58; $p = 0.001$) and all-cause mortality (OR: 0.67; $p = 0.005$). Four studies compared PN ($n = 212$) to RN ($n = 1,792$) in the specific case of T2 (> 7 cm) tumors. Again, a higher likelihood of complications was recorded for PN (RR: 2.0; $p < 0.001$). Higher recurrence rate was found for RN group (RR: 0.61; $p = 0.004$), as well as a higher cancer-specific mortality (RR: 0.65; $p = 0.03$). Notwithstanding the intrinsic limitations of this type of analysis, these findings suggest that PN in these cases becomes a more technically demanding procedure, as demonstrated by higher odds of worse surgical outcomes. However, this increased surgical risk is counterbalanced by a similar efficacy of PN (vs. RN) in providing effective cancer control, with the notable advantage of allowing a better preservation of renal function. Unfortunately, it was not possible to perform a pooled analysis of more reliable parameters assessing patient surgical risk, and also, it was not possible to perform a pooled analysis of tumor complexity scores, such

as the RENAL or the PADUA score. Kopp et al. reported the only available series specifically looking at comparative outcomes of PN and RN for clinical T2 renal masses after adjusting for tumor complexity as based on the RENAL score (Kopp et al. 2014). They found that patients with RENAL score > 10 are the ones at higher risk of tumor progression and where the functional benefit of PN versus RN might disappear. Intuitively, PN carries a higher risk of bleeding and of urine leak compared to RN, as it implies tumor resection, vascular manipulation, and renal reconstruction. This was the case in the abovementioned EORTC trial, where there was an increased incidence of hemorrhage (3.1% vs. 1.2%), urinary fistulae (4.4% vs. 0%), and reoperation (4.4% vs. 2.4%) in those undergoing PN (Van Poppel et al. 2007). This becomes even more intuitive when more extensive parenchyma resection is needed, as in the case of larger masses.

PN Versus RN in the Elderly

The issues of additional surgical complexity and subsequent potential higher risk of complications become even more relevant in elderly patients, who present more comorbidities and limited life expectancy. Sun et al. used the SEER data to quantify the effect of PN versus RN on other-cause mortality in this specific patient population (patients with T1 tumor, aged ≥75 years, with ≥2 comorbidities). No difference was recorded between PN and RN in patients who were aged ≥75 years (HR: 0.83; $p = 0.2$) and those with ≥2 baseline comorbidities at diagnosis (HR: 0.83; $p = 0.1$). Therefore the authors suggested that elderly patients and/or those with multiple comorbidities at diagnosis may not benefit from PN with respect to other-cause mortality (Sun et al. 2013). In another analysis of 14,186 nephrectomy procedures performed within the VA healthcare system between 2002 and 2014, Leppert et al. found that PN utilization increased for all groups over time, but older patients showed the least increase in odds of PN (Leppert et al. 2017). On the other hand, Kim et al. used the National Cancer Database to determine the treatment of older patients (≥70y) diagnosed with T1 renal tumors, and they recorded an increasing use of PN over the study period 2002–2011 (Kim et al. 2017). An et al. queried their institutional renal mass registry for patients 65 and older with solitary cT1/T2 renal mass resected by PN or RN. Of these, 437 (55.5%) underwent PN and 350 (44.5%) underwent RN. Perioperative outcomes were similar between PN and RN groups as were complications (37.8% vs. 38.9%). Estimated change in eGFR was less in PN versus RN (6.4 vs. 19.7, $P < 0.001$), and overall and cancer-specific survival were equivalent between modalities. Thus, the authors concluded that elderly patients are not harmed and may potentially benefit from PN, and therefore age alone should not be a contraindication to NSS (An et al. 2017).

PN Versus RN: Emerging Concepts in the Decision-Making Process

The above findings should be interpreted under the light of recent evidence supporting the concept that chronic kidney disease (CKD) "is not created equal" (Lane et al. 2014). According to recent data, the annual decline in kidney function for patients with preexisting CKD (CKD-M) versus de novo CKD postsurgical (CKD-S) would be close to 5% versus 0.7%. Moreover, the survival curves for patients with surgical CKD approximate the survival curves of overall population (Lane et al. 2013). In a study of 4300 patients with a median follow-up of 9.4 years, Lane et al. found CKD-S is associated with more stable renal function and better overall survival than CKD-M. Thus, the authors concluded that select patients with cT1/T2 kidney cancer might be better managed with RN, in contralateral kidney is normal, and eGFR is >45 ml/min, whereas patients with CKD should be offered a NSS approach (Lane et al. 2015). These emerging data regarding the lack of harm resulting from RN procedure are supported by long-term data from donor nephrectomy patients (Ibrahim et al. 2009).

PN has been regarded as a higher-risk procedure with increased risk of urinary fistulae and procedure-specific complications. This paradigm may be shifting however, with the increasing adoption of the robotic platform (Kaouk et al.

2012). As mentioned above, robotic technology may enable surgeons across different practice settings to perform NSS more frequently (Patel et al. 2013). With increasing surgical experience, indications for robotic PN have significantly expanded to include more demanding clinical scenarios, such as completely intraparenchymal tumors (Autorino et al. 2014), hilar tumors (Eyraud et al. 2013), and patients with previous ipsilateral NSS procedure (Autorino et al. 2013).

Moreover, current evidence suggests that robotic PN can translate into better outcomes than conventional laparoscopic PN. A recent meta-analysis of 25 studies (including almost 5000 patients) showed that patients treated with robotics presented larger (WMD 0.17 cm, $p = 0.001$) and more complex (WMD 0.59 RENAL score, $p = 0.002$) tumors. Nevertheless, robotic surgery was associated with a decreased likelihood of conversion (RR 0.36, $p < 0.001$), lower risk of complications (RR 0.84, $p = 0.007$) and positive margins (RR 0.53, $p < 0.001$), and shorter warm ischemia time (WMD 4.3 min, $p < 0.001$) (Leow et al. 2016). Thus, robotics might replace laparoscopy as the most common minimally invasive approach for PN whenever the necessary technology is available (Ghani et al. 2014).

Conclusions

The choice between PN and RN remains a clinical challenge. In the era of "precision surgery" (Autorino et al. 2017), we are asked to offer the best treatment possible, which is the one with the best risk-benefit ratio (Fig. 2). In this equation, we include patient's characteristics (overall physical health, frailty, distress, body habitus, comorbidities, renal function) and tumor characteristics (mostly location and size). Moreover, the decision process is necessarily influenced by surgeon's factors (own surgical expertise and prior outcomes, as well as comfort with various surgical procedures, especially in the case of minimally invasive techniques).

Despite being far from optimal, current evidence suggests that PN does not universally translate into a clinical benefit for all patients with renal masses where this surgery is technically feasible. Overall, PN has gained a consolidated role, and it represents the way to go for simple renal masses of lower stage and limited size whenever. Efforts should be made to remove barriers limiting its implementation. PN can represent a viable option also for larger renal tumors, as it seems to offer acceptable surgical morbidity, equivalent cancer control, and better preservation of renal function, with a potential for better long-term survival. For

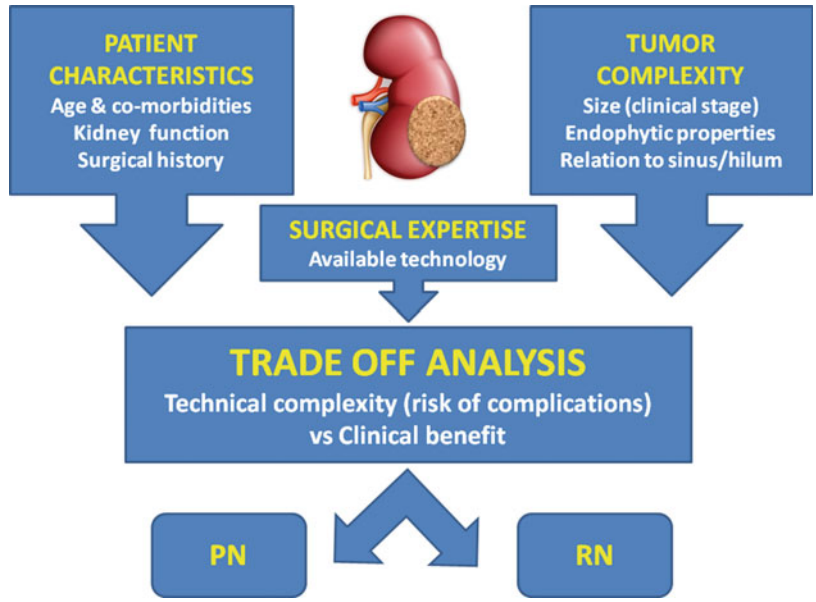

Fig. 2 PN or RN for the surgical management of localized renal tumors: factors involved in the decision process

T2 tumors, while RN remains the standard, the use of PN should be selectively considered on a case-by-case basis.

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Surgical Methods in Treatment of Kidney Tumors: Open Surgery Versus Laparoscopy Versus Robotic Surgery

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Contents

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Abstract

Localized kidney tumors are mainly treated with surgery to cure renal cell cancer. Kidney tumors can be treated in various surgical fashions such as open, laparoscopic, or robot-assisted surgery. No randomized, controlled trials have assessed oncological outcomes of laparoscopic vs. open radical nephrectomy (ORN). Among available nephron-sparing surgical modalities, the open partial nephrectomy (OPN) is considered as standard of care in the treatment of localized RCC. However, with rapid and progressive improvements in minimally invasive technologies and expanding laparoscopic surgical expertise, laparoscopic partial nephrectomy (LPN) continues to develop as a viable alternative. Nevertheless, also for comparison of OPN vs. LPN, there is a lack of randomized clinical trials, and the available evidence is based largely on reported nonrandomized and retrospective comparative studies. Regarding oncologic safety, data from large published series have demonstrated comparable oncological outcomes for LPN and OPN, with a 5-year overall and cancer-specific survival rate of 86% and 100%, respectively. Also, in centers with laparoscopic expertise, no difference in PFS was found between OPN and LPN. Also, the rate of positive margin (0–3.6%) and local recurrence rates (0–2%) seem to be quite comparable to those reported in open series ranging from 0% to 14% and 0% to 10%, respectively. A randomized clinical trial is needed to validate and compare the advantages and disadvantages of LPN over OPN. In the meantime, the potential benefits of minimally invasive surgery must be weighed against the possible higher risk of complications and the possibility of longer periods of ischemia.

Introduction

Kidney tumors (KT) are a heterogeneous group of tumors ranging from benign renal masses to various types of cancers. In the European Union, more than 80,000 new cases of renal cell carcinomas (RCC) were detected in 2012. For localized disease, several surgical options besides active surveillance and thermal ablation exist. The basic principles of how kidney sparing surgery is performed and who are best candidates will be discussed in a different chapter. The intention of this chapter is to give an overview of the different surgical methods, open/laparoscopic/robot-assisted surgery, on kidney tumors. There will also be a focus on RCC-associated vena cava thrombus disease.

General Patient Selection and Indications

Prior to laparoscopy and robotic surgery, open radical nephrectomy (ORN) and later on open partial nephrectomy (OPN) had been the gold standard in the surgical treatment of RCC. With the evolution of minimally invasive techniques, open surgery was only subjected to patients with locally advanced tumor growth in which these new techniques were not feasible. Today limited lung capacity and anticoagulants that cannot be stopped are the only nonsurgical contraindications for performing laparoscopy. A tumor with vena cava (VC) involvement is the only indication reserved for an open approach.

Open Renal Surgery

For simple (partial) nephrectomy, a lateral approach (subcostal or supracostal) is most commonly used. The patient is placed on the operating table in a

45°–90° position with flank exposure over the 12th rib. The upper leg lies straight, whereas the lower leg is flexed. The operating table is flexed until the flank muscles become tense. In cases when difficulties of approaching the main renal vessels or pronounced adhesions of the tumor with its surroundings are expected, the anterior approach is often preferred. The anterior approach can be either transverse, subcostal, or midline and provides best exposure to the vascular pedicle. The advantage of the anterior approach provides better visibility of the renal vessels. Disadvantages are the risk of bowel injury, later formation of adhesions, and contamination of the peritoneal cavity. Although the lateral approach is quicker and easier, it provides more limited exposure.

Using the lateral approach, an incision over the twelfth or eleventh rib is made. After having gone through the external and internal oblique muscle, as well as the transversalis muscle, the Gerota fascia is bluntly pushed medially of the psoas muscle. In case of nephrectomy, one may keep the Gerota fascia intact. In this case, the kidney with its Gerota fascia is completely mobilized before vessel ligation. Alternatively, the Gerota fascia is longitudinally opened. The perirenal fat is bluntly and sharply dissected by keeping the capsule intact. The early identification of the ureter is helpful for using it as a leading structure. There are two options of vessel ligation. One option is to ligate the pedicle. However, this can create an arteriovenous fistula. The other option is to separately ligate the renal vein and artery. One should keep in mind that anatomic alterations (e.g., two arteries, lower pol artery, etc.) are frequent. Preoperative CT or MRI scans are helpful in surgery planning.

Laparoscopic Renal Surgery

Patient Selection and Indications

Since the first laparoscopic nephrectomy by Clayman et al. in 1991, the method of minimally invasive surgery has become the preferred standard of treatment in most patients with localized kidney tumors (Clayman et al. 1991). Initial indications for laparoscopic nephrectomy included benign and malignant diseases of the kidney, as well as donor nephrectomy for living donor transplantation. In the case of malignant diseases, the principal indication for laparoscopic radical nephrectomy (LRN) is renal mass up to a size of $\leq$10 cm, which cannot be treated with partial nephrectomy. The European Association of Urology (EAU) Guidelines from 2017 underlines that laparoscopic nephrectomy is the standard of care for cT_2 tumors (and cT_1 tumors that cannot be operated by the nephron-sparing surgery), with low morbidity and good tumor control equivalent to open tumor nephrectomy (Ljungberg et al. 2017). This also points out the possible relative contraindications for LRN, namely, smaller tumors with a good possibility of nephron-sparing partial nephrectomy and large renal tumors with lymph node metastases or venous thrombus. Currently, LRN can be performed by intraperitoneal, extraperitoneal, or hand-assisted approaches, as well as single-portal (LESS) and mini-laparoscopic techniques. The choice of type of the surgery (open or laparoscopic or LESS) is largely made by surgeon's training background and the availability of equipment in hospital along with consideration of patient-related factors, which may include tumor location and size, comorbidities, body habitus, and history of prior abdominal surgeries. However, given that clinical safety and oncologic efficacy appears to be equivalent between open and LRN, a minimally invasive approach should be preferred whenever feasible. Nevertheless, one question that must be faced in virtue of ever-increasing experience in urological laparoscopy is whether the size of the renal tumor really relevant to laparoscopy. Currently, LRN is best documented for cT_1 ($\leq$7 cm) or cT_2 (>7 cm, limited to the kidney) tumors. However, some reports show that in the hands of an experienced laparoscopic surgeon, larger renal masses can also be removed laparoscopically (Hemal et al. 2007). Also, an invasion of the renal vein does not appear to be an absolute contraindication, as long as a safe tumor-free distance from the junction with the vena cava exists (Martin et al. 2008). Individual reports have also been available for the laparoscopic resection of large renal tumors in patients with

advanced diseases who were planned to receive adjuvant immunotherapy (Mattar and Finelli 2007).

Due to the wide use of imaging methods, the number of small, asymptomatic, and randomly discovered kidney tumors is constantly increasing. As of result of the above, smaller and hence low-stage renal masses are more amenable to nephron-sparing surgery (NSS) in terms of partial nephrectomy (PN) as the surgical treatment of choice. Principally, nephron-sparing surgery is performed either as open partial nephrectomy (OPN) or laparoscopic partial nephrectomy (LPN). While OPN remains as the reference standard, LPN is now widely accepted as a feasible and safe alternative. The classic surgical approach of radical nephrectomy (RN) is widely considered excessive in the surgical excision of small renal masses. Factors that have led many urologists to reconsider the routine use of RN for the management of localized renal masses may include equal oncological outcomes for renal tumors of less than 7 cm whether RN or PN is performed, the fact that approximately 20% of clinical T1 renal tumors are benign neoplasms and 60–70% are indolent tumors with limited metastatic potential, and, most importantly, emerging evidence that RN is an independent risk factor for the development of chronic kidney disease (CKD) (Dash et al. 2006). Hence, NSS is specially indicated in patients with a high risk of postoperative renal insufficiency. These patients include those with bilateral renal tumors, with tumors in a solitary functioning kidney, or with a compromised contralateral kidney. Therefore, surgical management of renal tumors, wherever possible, should be aimed at organ preservation, whether by conventional laparoscopy, robot-assisted, or open surgery. Recent reports from larger series have shown a clear advantage of NSS (open, laparoscopic, or robot assisted) with respect to the functional results with equivalent oncological and clinical outcomes for cT_{1a} tumors (Sun et al. 2012; Van Poppel et al. 2011a). The fact that also cT_{1b} tumors can be safely operated laparoscopically in terms of LPN has been shown by several reports, and in many centers with adequate expertise, LPN is the treatment of choice for cT_{1b} tumors as it preserves kidney function (Sprenkle et al. 2012). However, some renal tumors may not be suitable for LPN due to their unfavorable location, e.g., adherence to renal helium, insufficient volume of remaining parenchyma to maintain proper organ function, the use of anticoagulants that can be discontinued, or the presence of renal vein thrombosis.

Surgical Techniques

Laparoscopic radical nephrectomy can be performed transperitoneally, peritoneoscopically, or hand assisted. The **transperitoneal approach** is currently the most frequent performed technique, as urologists are more familiar with anatomical conditions and it offers a much larger field of work. The procedure of transperitoneal laparoscopic radical nephrectomy begins with the thoracoabdominal positioning of the patient on a vacuum mattress and fixation in order to allow the patient to tilt in all directions. Thereafter, a supraumbilical incision (approx. 2 cm) and the establishment of the pneumoperitoneum are performed via a Veress needle with a pressure of 10–15 mmHg. The first trocar (10 mm) is then inserted over the same incision, and an endoscopic inspection of the abdominal cavity is carried out. Alternatively, if the use of a Veress needle is not preferred, a paraumbilical incision of approximately 2 cm is performed, and the camera port is inserted under direct view after incision of posterior rectal fascia. In the nephrectomy, on the right side, two additional trocars (10 mm and 5 mm) are inserted in the right middle clavicular line 4 cm below and above the umbilicus level. A fourth trocar is then inserted a few centimeters below the xyphoid where a liver retractor can be applied. The operating table is tilted by 30°, and the Toldt line is incised. The colon is mobilized and pushed off medially. Next the psoas muscle is identified. The ureter is then identified underneath and medially of the lower renal pole and used as a guide structure to the renal hilum. The kidney hilum is to be exposed by means of partly sharp, partly blunt dissection technique, and the renal vein(s) and artery(s) are separated. The main renal artery is ligated with four endoclips or Hem-o-loks and transected between the 2 and 3 clips. The renal vein is also ligated and transected in the same manner or alternatively with an

Endo GIA. Finally, the ureter is transected between two clips. The kidney with the intact Gerota fascia is then detached from the lateral and proximal adhesions and retrieved from the abdominal cavity by means of an endobag via an extended trocar incision. After the reduction of the intra-abdominal pressure to 5 mmHg, the surgical field will be inspected for bleeding, which will be coagulated using bipolar cautery. A drain can be used optionally. Postoperative management includes the usual monitoring of the circulatory parameters, laboratory control, mobilization, and removal of the bladder catheter on the first postoperative day. Postoperative infusion and analgesic therapy were designed according to the individual needs of the patients.

The advantages of **retroperitoneal LRN** include faster access to the renal hilum, avoiding intraperitoneal irritation and less interference with ventilation and hemodynamic functions (Linhui et al. 2010). Disadvantages are difficulty in salvaging the kidney in the sack in the smaller work space as well as longer learning curve. The retroperitoneal LRN starts with the patient in lumbotomy position with a 2 cm incision in the posterior axillary line approx. 3 cm below the rib. After dissection of the fascia, the retroperitoneal space will be developed with the index finger, thereafter placing the balloon trocar and expanding the retroperitoneal space under view with the inserted camera and then removing the balloon and gas insufflation. After identification of the psoas muscle, the peritoneum will be pushed to medial. Hereafter, two additional ports in the midaxillary line above the iliac crest (12 mm) and below the tip of the 12th rib are inserted. The ureter is medial to the psoas muscle identified and afterwards dissected. Also in this technique, the ureter is used as a guide structure to the renal hilum. The kidney hilum is identified easily as dissection is continued proximally; however, the renal artery is exposed first, followed by the renal vein. Next, the renal artery is clipped by means of Hem-o-lok clips (four clips each) and transected between the clips. The renal vein is also clipped with Hem-o-lok and cut between the clips. Thereafter the following steps are taken: mobilization of the kidney on all sides, clipping of the ureter in the middle part, and retrieval of the kidney by means of an endobag via an extended trocar incision.

In the **hand-assisted technique (HALN)**, a special hand port is inserted over the extension of the distal trocar section. Possible reported advantages of the HALN lie in the better tractile function and better control on the hilus. A disadvantage is higher costs. HALN is used for donor nephrectomy in some clinics as a HALDN. In doing so, the incision for the hand-held sport is then used for organ retrieval.

After the establishment of laparoscopy in the surgical treatment of renal tumors, more and more authors are now presenting their results using various modified techniques such as single-site laparoscopy (LESS), natural orifice transluminal endoscopy surgery (NOTES), or robot-assisted radical or partial nephrectomy. LESS and NOTES have their first steps behind them and are now reported with increasing frequency in smaller series of tumor and partial nephrectomies (Greco et al. 2012; Porpiglia et al. 2011). The main advantage is still to be seen in cosmetics. Morbidity and oncological safety must be assessed on the basis of larger reports.

Laparoscopic Partial Nephrectomy

Laparoscopic partial nephrectomy (LPN) is technically more challenging, and the technique is still evolving, particularly as the surgical indications are expanding. As in LRN, LPN can also be performed either transperitoneal, retroperitoneal, or hand assisted. However, as already mentioned above, the final choice of the type of approach is dictated by the tumor location and the surgeon preference. However, the **transperitoneal approach** is currently applied mainly for anterior and laterally located tumors as well as for larger or infiltrating tumors requiring heminephrectomy. While the obvious advantage of the **retroperitoneal approach** is direct access to the posterior and posteromedial renal masses, the limited retroperitoneal space and reduced triangulation make this approach technically more demanding. Further, in patients with previous abdominal surgery, the retroperitoneal approach for LPN might be considered (Breda et al. 2009). The operation room setup and the positioning of the patient are principally the same as in LRN. Also, the insertion and

position of the trocar ports and the access to the kidney and its vessels are similar to the steps already described above for LRN. Following inspection of the abdominal cavity for concomitant pathology, the peritoneum is incised along the line of Toldt and the colon reflected medially. After preparation of the renal hilum, the renal vessels are identified, and the warm ischemia is established by cross-clamping of the renal artery with a laparoscopic bulldog clamp. In selected cases with small exophytic peripheral tumors, a wedge resection can be performed. Then, the kidney is mobilized completely to allow exposure of the tumor lesion. If available, a laparoscopic ultrasound probe should be used to determine the line of incision and depth of tumor involvement. Tumor excision might be performed with monopolar scissor or a harmonic scalpel with a security margin of 3–5 mm. However, similar to the open partial nephrectomy, complete removal of entire malignant tissue with free resection boundaries is of utmost importance for the final oncological outcome. Therefore, the resection site is usually evaluated by means of frozen section analysis (FSA). The specimen will be entrapped into an endoscopic bag and retrieved later via a muscle-splitting incision at a former port site in the lower abdomen. For hemostasis, the tumor bed is coagulated with an argon beamer and compression of the resection site can be achieved by renorrhaphy over a prefashioned bolster. Also, various methods of tissue sealing, for example, a gelatin matrix thrombin tissue sealant (Flowseal), can be applied. However, the achievement of hemostasis and closure of the renal parenchyma during an LPN continue to be important steps during the procedure. On the one hand, the laparoscopist is keen to reduce warm ischemia time (WIT) and, on the other hand, to secure adequate hemostasis and integrity of the collecting system. Clamping of the renal hilum with prolonged warm ischemia carries a potential risk for ischemic renal damage; hence, a WIT "cutoff point" of 30 min has conventionally been accepted as a safe limit for NSS (Desai et al. 2005a). Nevertheless, the true impact of warm ischemia on the long-term renal function continues to be evaluated, and the reported safe mean WIT from so far published series varies from 20 min to 60 min (Wille et al. 2006; Haseebuddin et al. 2010). However, in small and peripherally located tumors, LPN can be accomplished in the absence of hilar control by novel mechanical and biological hemostatic aids.

Some centers with adequate expertise prefer to perform LPN in hand-assisted technique. **Hand-assisted partial nephrectomy (HALPN)** represents an attempt to combine the surgical advantages of laparoscopy with the hand control offered by open surgery. Hand-assisted laparoscopic partial nephrectomy allows the surgeon to place one hand in the abdomen while maintaining the pneumoperitoneum required for laparoscopy. The potential advantages of HALPN are better control of the renal pedicle, easier compression of renal parenchyma, hemostasis, as well as faster dissection and suturing while maintaining a less morbid incision.

Clinical Performance

Laparoscopic Radical Nephrectomy

In principle, laparoscopic radical nephrectomy has the same spectrum of complications as in open tumor nephrectomy. However, the functional advantages of minimally invasive surgery in renal surgery are particularly evident. In addition to cosmetics, reduced morbidity is also seen as a benefit of laparoscopic technology in comparison to open surgery (Burgess et al. 2007; Raghuram et al. 2005; Borin 2008). The avoidance of traumatic access is an advantage for patients; comparable perioperative data as well as the functional and oncological equivalence to open procedures are found abundantly in the literature (Hoda and Fornara 2012; Golombos et al. 2017). Data from the large series show that after laparoscopic nephrectomy, patients benefit from early mobilization, fewer painkillers, shorter hospitalization, and an early return to normal activities (Heuer et al. 2010; Liu et al. 2017). Many patients appreciate the faster convalescence with early return to home. Gabr et al. found in an analysis of their data from a series of 255 patients

with LRN that the morbidity (complications and duration of hospitalization) of the LRN is not related to tumor characteristics (tumor size, etc.) but from general patient-related factors such as "body mass index" (BMI), age, and ASA score (Gabr et al. 2009a). The clinical-immunological advantages of laparoscopic nephrectomy have been demonstrated in the animal experiments and in-patient series (Sáenz et al. 2007; Duchene et al. 2008). It has been shown that the extent of operative trauma can significantly influence the systemic response of the organism (Duchene et al. 2008). The known humoral factors include immunological parameters (inflammatory and anti-inflammatory cytokines, stress factors, C-reactive proteins), hormonal parameters (cortisol, cytokines), and neurotransmitters (serotonin) (Fornara et al. 2000; Matsumoto et al. 2005).

Laparoscopic Partial Nephrectomy

Laparoscopic partial nephrectomy can be associated with some major urological complications including hemorrhage, urinary leak, and impaired renal function. Potential risk factors for complications during LPN may include patient's age and condition, increased blood loss, prolonged WIT, tumor location, and the presence of solitary functioning kidney (Eisenberg et al. 2010). As shown by several large prospective and retrospective series, the overall complication rate of LPN varies from 8% to 35%, which is in fact quite comparable to those from published open partial nephrectomy series (5%–38%) (Dominguez-Escrig et al. 2011). In particular, the rate of urinary leakage after LPN has been reported in a range from 2% to 9% (Choi et al. 2015; Stephenson et al. 2004). However, the tumor location and the impact of surgeon's experience have to be considered when reporting data on urinary leakage after LPN. For instance, a higher incidence of urinary leakage is reported for endophytic (26.3%) and hilar (50%) tumors compared with 6.1% in exophytic masses (Venkatesh et al. 2006). Further, the reported hemorrhagic complication rates after LPN range from 2% to 9%, with a reported blood transfusion rate ranging from 6% to 8%, respectively (Yin et al. 2009; Simmons 2007). With growing experience in surgical technique as well as the routine use of hilar clamping and renorrhaphic stiches, a positive impact on perioperative hemostasis during LPN is noticeable. However, the real impact of novel biological hemostatic agents still remains controversial. For instance, as Gill et al. compared the outcomes of LPN using Flowseal as sealant agent, they demonstrated a reduction in the overall (16% vs. 36.8%, $P = 0.008$) and hemorrhagic (3.2% vs. 11.8%, $P = 0.08$) complication rates (Breda et al. 2007a; Gill et al. 2005). There is also controversial discussion about the impact of tumor size on the incidence of complications during LPN. Data from large retrospective multicenter series demonstrated for LPN in tumors >4 cm significantly higher mean operative time, blood loss, blood transfusion rate, and urinary leakage rate (Patard et al. 2007). However, in the same retrospective study, no significant differences were found in the overall complication rates or length of hospital stay (Patard et al. 2007) for tumors >4 cm. On the other hand, Porpiglia et al. showed in an assessment of the risk factors in tumors ranging from 1 cm to 6 cm that there is no correlation of tumor size with complications of LPN (Porpiglia et al. 2008a). The LPN is considered as nephron-sparing surgery, and the renal functional outcome after this procedure is of upmost importance (Volpe et al. 2015). Acute renal failure after LPN has been reported in the range of around 1% of the cases by large prospective and retrospective series (Scosyrev et al. 2014; Hung et al. 2013). Risk factors for poor renal functional outcomes following LPN, as measured by calculation of estimated glomerular filtration rate (eGFR) obtained from the Modification of Diet in Renal Disease formula, include preoperative chronic kidney disease, advanced age with WIT >30 min, reclamping of the renal artery, and a WIT >60 min (Zhang et al. 2016; Mir et al. 2015). Furthermore, when comparing the clinical results of retroperitoneal and transperitoneal approaches, the retroperitoneal approach was associated with a shorter warm ischemia and operating time, as well as shorter hospital stay

(Ng et al. 2005). However, no differences were reported in terms of blood loss, perioperative complications, and postoperative functional and histological outcomes.

Oncological Outcome

Laparoscopic Radical Nephrectomy

Laparoscopic tumor nephrectomy is considered an oncologically unproblematic procedure. It can be deduced from several studies that the local tumor control is as good as that of open surgery with tumor-specific 5-year survival rates of 88–98% (Colombo et al. 2008). In addition, the relapse-free and tumor-specific survival rates are comparable with those of open surgery (MacLennan et al. 2012a). Long-term observations show that perioperative and patient-related factors do not affect oncological results in either open or laparoscopic nephrectomy. Rather, the relapse-free and tumor-specific survival seem to depend on the status of pathologic parameters (histology, stage, grading, resection status) (Breda et al. 2007b). In the pioneering period of laparoscopy, when a significant endocavitary traumatization of the tumor occurred in the initial learning phase of the surgeon, a high incidence (20%) of port metastases was reported after laparoscopic interventions in visceral surgical and gynecological malignomas (Fornara et al. 2003). This complication has been significantly reduced with the accumulation of experience and improvement of the equipment such as the use of endoscopic bag and abandonment of intracorporeal morcellation. An increased hematogenic tumor cell scattering due to laparoscopy has not been demonstrated so far. However, it is presumed that tumor cell scattering in the context of oncological operations is essentially due to a mechanical tumor cell entrainment, which occurs only when the instruments come into direct contact with the tumor (Wind et al. 2009). Special care must be taken in laparoscopy for the removal of the tumor from the abdominal cavity, where an endoscopic bag should be used carefully and should not be broken during the maneuver. Taking into account all precautions, the rate of implantation metastases can be reduced to the level which is also known from open surgery.

Laparoscopic Partial Nephrectomy

For cT1N0M0 renal tumors, LPN has similar oncologic outcomes in terms of positive surgical margins, local or distant recurrence rates, and cancer-specific survival to the OPN (Tan et al. 2011; Lane and Gill 2010; Gong et al. 2008). Also regarding the tumor size, a large retrospective analysis showed that positive surgical margins, local or distant recurrence rates, and cancer-specific survival were not significantly different in tumors $\leq$4 cm and >4 cm (Patard et al. 2007).

Robotic Renal Surgery

After the establishment of laparoscopy in the surgical treatment of renal tumors, reports of experiences with various modified techniques are now also increasing. The robot-assisted laparoscopy appears to offer a technical advantage in organ-preserving interventions such as LPN or in reconstructive operations due to tridimensional vision, computer-aided elimination of tremor, and six degrees of freedom at the distal ends of instruments, which supposedly facilitate intracorporeal suturing and might potentially reduce the WIT. Although the previously reported experience with robot-assisted laparoscopy postulates an advantage with regard to reconstructive interventions, there are also some reports on **robot-assisted radical nephrectomy (RRN)** available. For instance, Klingler et al. reported already in 2005 about the feasibility of the RRN for a small group of five patients (Klingler et al. 2005). In another study, this group compared RRN in six patients with laparoscopic (n = 33) and open (n = 18) radical nephrectomy (Nazemi et al. 2006). The robot group showed a relatively lower blood loss, but the operating time was significantly longer (345 min vs. 265 min). There was no statistically significant difference in operative parameters between robot-assisted and

laparoscopic method. Thus, from the reported experience with robot-assisted radical nephrectomy, it can be concluded that RRN offers no substantial significant advantage compared to laparoscopic standard nephrectomy. However, also the problem of the high costs in acquisition and maintenance remains unchanged. On the other hand, the **robot-assisted laparoscopic partial nephrectomy (RLPN)** has recently taken root. Long-term data on oncological as well as functional results are still pending, but the present short- and midterm data correspond to those which we know from open and conventional laparoscopic partial nephrectomy (Spana et al. 2011; Wu et al. 2014; Xia et al. 2017; Choi et al. 2015).

Comparison of Surgical Methods

Unfortunately, randomized clinical trials (RCT) that directly compared open vs. laparoscopic vs. robotic-assisted approaches for renal surgery for their clinical efficacy and/or oncological safety are rarely available. In the literature, however, we would find mostly cohort studies and retrospective database reviews with low methodological quality.

ORN vs. LRN

No RCTs have so far assessed long-term oncological outcomes of laparoscopic vs. open radical nephrectomy. In the available cohort studies and retrospective database reviews, comparable oncological outcomes for LRN vs. ORN were found (Hemal et al. 2007; Jeon et al. 2011). In particular, no significant differences in CSS, PFS, and OS were found between LRN and ORN, not even for renal tumors $\geq$T2 (Hattori et al. 2009; Steinberg et al. 2004; Laird et al. 2015). Regarding the clinical efficacy, the available data from one RCT and some few retrospective studies showed significantly less perioperative blood loss, shorter duration of hospitalization, shorter convalescence time, and reduced analgesic use for the LRN group as compared with the ORN group (Hattori et al. 2009; Golombos et al. 2017; Gratzke et al. 2009). On the other hand, operation time was significantly shorter in the ORN groups. However, in all published studies, no difference was observed in the number of patients receiving blood transfusions, as well as in overall rate of complications. Further, very few studies have evaluated the postoperative QoL scores and found no difference between ORN and LRN (Gratzke et al. 2009). Furthermore, concerning the surgical technique, two RTCs compared the retroperitoneal vs. transperitoneal approach for RN and found similar oncological outcomes and no difference in patients' reported quality of life variables (Desai et al. 2005b; Nambirajan et al. 2004). Also, conventional LRN was compared to HALRN in one RCT, which showed shorter surgery time in the HALRN group, while length of hospitalization was shorter for the standard LRN cohort (Nadler et al. 2006). However, no difference was found in oncologic outcome parameters.

RN vs. PN

For comparison of oncological safety or clinical efficacy of RN vs. PN, irrespective of the surgical technique used, only one prospective RCT including patients with T1 stage RCC and some few retrospective series are available so far (Butler et al. 1995; D'Armiento et al. 1997; Lee et al. 2007; Van Poppel et al. 2011b). The main conclusion from these studies is that while there is no significant difference in survival parameters (CSS or OS) between the two methods, PN have demonstrated to better preserve general kidney function, thereby lowering the risk of development of metabolic or cardiovascular disorders. As a matter of fact, partial nephrectomy, particularly OPN, is associated with the most robust data regarding preservation of filtration function and the lowest risk of CKD (Patel et al. 2017; Minervini et al. 2014). Hence, in patients with preexisting CKD, PN is the treatment of choice to limit the risk of development of end-stage kidney failure which requires hemodialysis. In terms of clinical safety, one randomized study by the EORTC comparing RN to OPN for T1a stage RCC found a slightly higher rate of severe hemorrhage for OPN (3.1%

vs. 1.2%) and in addition a urinary leakage rate of 4.4% in OPN group (Van Poppel et al. 2007). Nevertheless, the overall complication differences were minimal between these two surgical techniques. However, other studies, mostly retrospective data reviews, found no difference in the length of hospital stay, mean intraoperative blood loss, or the transfusion rate (An et al. 2017; Shekarriz et al. 2002). Further, one study reported a longer operation time for OPN compared to RN, but this was not confirmed by others (Gabr et al. 2009b; MacLennan et al. 2012b).

OPN vs. LPN

Among available nephron-sparing surgical modalities, the open partial nephrectomy is considered as standard of care in the treatment of localized RCC given its broad application and the most substantial supporting body of data. However, with rapid and progressive improvements in minimally invasive technologies and expanding laparoscopic surgical expertise, LPN continues to develop as a viable alternative to OPN. Nevertheless, also for comparison of OPN vs. LPN, there is a lack of randomized clinical trials and the available evidence is based largely on reported nonrandomized and retrospective comparative studies. Regarding oncologic safety, data from large published series have demonstrated comparable oncological outcomes for LPN and OPN, with a 5-year overall and cancer-specific survival rate of 86% and 100%, respectively (Gong et al. 2008; Marszalek et al. 2009; Lane and Gill 2007). Also, in centers with laparoscopic expertise, no difference in PFS was found between OPN and LPN (Lane and Gill 2007; Gill et al. 2007). Also, the rate of positive margin (0–3.6%) and local recurrence rates (0–2%) seem to be quite comparable to those reported in open series ranging from 0% to 14% and 0% to 10%, respectively (Porpiglia et al. 2008b; Aron and Gill 2007; Marszalek et al. 2012). As for clinical safety, reports from large series showed that the mean estimated blood loss was lower with the LPN group, while surgical time was generally longer in the LPN group and warm ischemia time is shorter in the OPN group (Marszalek et al. 2009; Gill et al. 2007; Porpiglia et al. 2016; Muramaki et al. 2013). Further, as reported by Gill et al. from a comparative series of 1800 patients with a single renal tumor ≤ 7 cm undergoing OPN ($n = 1028$) or LPN ($n = 771$), the incidence of intraoperative complications was comparable in both groups (Gill et al. 2007). However, LPN was associated with more immediate postoperative complications, particularly urological, and an increased number of subsequent procedures. In conclusion, a randomized clinical trial is needed to validate and compare the advantages and disadvantages of LPN over OPN. In the meantime, the potential benefits of minimally invasive surgery must be weighed against the possible higher risk of complications and the possibility of longer periods of ischemia.

Vena Cava Tumor Thrombus

Background

A special feature of renal cell carcinoma is the potential to grow into the renal vein and inferior vena cava (IVC). This accounts for approx. 4–10% of RCC at presentation (Ferlay et al. 2013). The treatment of choice has been radical nephrectomy with thrombectomy. The aggressive surgical approach is widely accepted as the default management option as systemic therapy has shown limited effect on tumor thrombus growth. There is a variety of surgical strategies depending on the level of tumor thrombus extension. Regarding tumor thrombus extension, several stratification systems exist (Bissada et al. 2003). Table 1 gives an overview of the most frequently used classification systems.

Surgical Techniques

Based on expert opinion, for tumor thrombus limited to the renal vein, minimal modifications of the standard surgical approach are required. The tumor can be milked easily deeper into the renal vein and a vascular clamp be applied. Usually, the IVC is

Table 1 Various classification systems

	Renal vein	Infrahepatic		Above the liver edge but below the hepatic vein	Hepatic IVC	Suprahepatic infradiaphragmatic	Suprahepatic supradiaphragmatic	Atrium
		IVC <2 cm above the renal vein	IVC >2 cm above the renal vein					
Ciancio	I	II		IIIa	IIIb	IIIc	IIId	IV
Moinzadeh		I					II	III
Neves	0	I	II			III	IV	
Novick	I	II					III	IV
Hinman	I	II					III	
AJCC, UICC 2010	T3a	T3b					T3c	

IVC inferior vena cava, *AJCC* American Joint Committee on Cancer, *UICC* Union Internationale Contre le Cancer
References: Ciancio et al. (2010), Moinzadeh and Libertino (2004), Neves and Zincke (1987), Novick et al. (1989), and Hinman (1998)

kept intact. In case the tumor verges on the IVC, a Satinsky clamp is applied embedding the complete renal vein. After excision, the caval defect is oversewn with running sutures.

Proximal and distal VCI control is required on level II tumors. In addition, the contralateral renal vein must be controlled with tourniquets during resection. After tumor thrombus removal, the CVI lumen is flushed and should be inspected for residual tumor fragments. In most cases, the CVI can be closed by running suture. In case of bigger defects, caval patches must be used. Importantly, as the last suture is tightened, the distal clamp is released to remove retained air.

Class III tumors usually require vascular bypass although conventional techniques are described (Mandhani et al. 2015). Veno-venous bypass is usually sufficient, but cardiopulmonary bypass with circulatory arrest and profound hypothermia can also be used. A mobilization of the liver is mostly required to gain additional exposure. Once adequate vascular control is obtained, cavotomy and vena caval reconstruction are completed as described for level II tumors.

A carciopulmonary bypass and circulatory arrest during resection is necessary when treating level IV tumor thrombus. The approach is challenging and requires a multidisciplinary team of thoracic and abdominal surgeons as well as urologists. The abdominal part of the surgery is as described for level III tumors.

Prognostic Factors

Various prognostic factors have been identified:

- Tumor Thrombus Level

Pathological stage has been shown to be the most important prognostic factor in RCC, but the impact of the tumor thrombus level on survival remains under debate. In an attempt to evaluate the survival prediction accuracy of the AJCC/UICC staging system (version 2009), the tumor thrombus level was reported to be an independent predictor of survival (pT3a 43.2 months vs. pT3b 37.3 months vs. pT3c 22.2 months) (Blute et al. 2004).

- Metastasis

The presence of metastasis has been reported to be strong predictor of survival in RCC with venous extension regardless of tumor thrombus level (Mandhani et al. 2015; Martinez-Salamanca et al. 2011; Gettman et al. 2003).

- Histological RCC Subtypes

Data is sparse in respect of survival outcomes in correlation with histological subtypes and additional tumor thrombus. One study showed that patients with papillary histology had significant worse outcomes and higher tumor thrombus levels when compared to other subtypes (Spiess et al. 2012). The 5-year cancer-specific survival was 59.5%, 54.8%, and 36.8% for chromophobe, clear-cell, and papillary subtypes.

Perioperative Complications

Radical nephrectomy in combination with tumor thrombectomy has been shown to be associated with high morbidity (up to 70%) and mortality (up to 16%) rates depending on the extent of tumor thrombus (Gettman et al. 2003; Tilki et al. 2014; Sosa et al. 1984). Some factors seem to increase perioperative morbidity: patient comorbid conditions, performance status, distant metastatic spread, and tumor thrombus extension above the diaphragm.

Survival

There is limited data on survival. Disease-free 5-year survival was reported between 35% and 55% influenced by stage and grade of tumor rather than level of thrombus (Almgard et al. 1973; Zielinski et al. 2000). Five-year overall survival rates range between 47% and 63% not affected by tumor thrombus extent (Almgard et al. 1973; Zielinski et al. 2000; Hatcher et al. 1991).

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Systemic and Sequential Therapy in Advanced Renal Cell Carcinoma

39

Viktor Grünwald and Mareike Hornig

Contents

Abstract

The systemic and sequential therapy of locally advanced or metastatic renal cell carcinoma (mRCC) was revolutionized in the past decade with the introduction of specific targeted agents, directed against pathways crucial for tumor growth and metastatic activity.

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Randomized controlled clinical trials testing specific inhibitors, i.e., for the vascular endothelial growth factor (VEGF)/VEGF receptor or mechanistic (mammalian) target of rapamycin (mTOR) pathway, showed superior efficacy for these novel agents in mRCC patients, but its effect on overall survival (OS) has been questioned because only few studies showed OS improvement.

The introduction of several agents to the repertory of accessible drugs in mRCC led to the establishment of a sequential therapy consisting of VEGF-antibody bevacizumab; tyrosine kinase inhibitors (TKIs) pazopanib, sunitinib, axitinib, and sorafenib; and mTOR inhibitors temsirolimus and everolimus. Several studies addressed the issue of how best to arrange the available agents depending on tumor histology, former treatment response, as well as individual patient status and comorbidities. However, no specific sequence could be identified, and the continuous treatment with the sequential use of these agents remains the standard of care (SOC).

Nowadays, another set of new agents, namely, nivolumab, as immune checkpoint inhibitor, and cabozantinib and lenvatinib as third-generation TKIs, enrich the field of cancer therapeutics. Interestingly, the introduction of these novel agents to the field of mRCC was associated with an increase of overall survival in these studies – an observation which rarely occurred during the past.

Introduction

The systemic treatment of renal cell carcinoma (RCC) was subject to major changes in the past decade, not to talk about a revolution in this field. For a long time, locally advanced (la) and/or metastatic (m)RCC was considered an incurable disease with no or low chances for median or long-term survival. In fact, in some clinical studies, the overall survival of mRCC patients still remains lower than expected, yet there is a clear success in terms of prolonging progression-free survival in mRCC patients, thanks to sequential therapeutic options. For some patients, life expectancy could probably be doubled or even tripled by sequential use of currently available agents.

Only one decade ago, systemic therapy in mRCC consisted mainly of immune stimulation via application of interleukin (IL)-2 or interferon (IFN)-alpha (α) (Negrier et al. 2002). With the use of cytokines as palliative treatment, an improvement of the median OS to 13.3 months was achieved (Coppin et al. 2004). However, despite the 3-month improvement in median OS, the response rate remained limited, and most benefit was derived in asymptomatic patients with favorable metastatic sites. But patients who achieved a tumor response were associated with long-term disease control and survival, respectively (Hughes et al. 2015).

The role of chemotherapy in the context of cytokine treatment was explored in numerous studies. But it was not until recently that randomized clinical trial with proper statistics was able to clarify that chemoimmunotherapy does not provide additional benefit and should not be used in clinical practice (Gore et al. 2010). Twenty-eight percent of these patients received targeted therapies in subsequent lines of therapy, which may have led to a median OS of 19 months in this study, which is higher compared to historical control from the cytokine era.

Only recently, laboratory studies about tumor biology and mechanisms of growth and metastatic activity led to the development of a whole new world of therapeutic weapons against specific tumor targets. The so-called targeted therapy consists of a range of agents, designed to specifically inhibit cellular pathways crucial for tumor growth and survival.

RCC is a highly vascularized tumor, its growth and survival crucially depending on neovascularization and endothelial activation in the tumor milieu. This activation is mainly based on receptor tyrosine kinase activity on endothelial cells. The identification of the vascular endothelial growth factor receptor (VEGFR) as a key driver in RCC was made on the basis of disruption of the von Hippel-Lindau (vHL) function via the hypoxia-inducible factor (HIF) in clear cell RCC (CWM et al. 2007). Based on this molecular

event, overexpression of VEGF occurs in the tumor and drives the characteristic highly vascular tumor. This observation has led to the clinical development of VEGFR inhibitors, mainly as tyrosine kinase inhibitors (TKIs) blocking a spectrum of tyrosine kinases, including the VEGFR (Coppin et al. 2008). Besides, the mTOR pathway could be identified, also triggering HIF-induced secretion of VEGF as well as genetic modifications inducing cell growth, proliferation, and survival of cancer cells. Inhibition of the mTOR pathway is clinically relevant yet ranging below the efficacy of VEGF-targeting therapies. Combining and sequentially using both mechanisms of action were since then assessed in clinical trials and routine clinical practice, since recommendations for treatment in la/mRCC are still subject to uncertainties and regularly remodeled based on actual clinical trials and mechanistic insights into tumor survival, development, and resistance mechanisms.

Of note though, these agents were able to improve efficacy of systemic treatment with median progression-free survival (PFS) in the range of 8–11 months (Motzer et al. 2009, 2013a), encouraging the pharmaceutical and clinical world to remain on the track of targeted therapy while improving individual patient's outcome by defining the best sequence and choice of agent in clinical studies. The optimal placement and long-term effect of immunotherapy (i.e., programmed cell death protein (PD)-1 inhibition) remain to be determined, as this option is thought to induce long-term response and possible cure in a fraction of metastatic patients. Whether this might be best achieved via combinations with other immunotherapeutics or targeted agents is a main focus of current research and might become clinical reality in the near future.

Treatment recommendations are regularly updated and published by international committees and cancer societies. Knowledge about basic molecular findings in RCC, treatment-related remodeling of tumor gene expression, and especially modifications in the initiation of neovascularization, as well as clinical evidence about durations of response, cases of primary resistance, and response to differing sequences of treatment with targeting agents, continuously improve or at least change our view and understanding of treatment and biology of RCC.

The General Approach to a Patient with Advanced Renal Cell Carcinoma

With the invasion into the Gerota fascia and/or presence of distant metastasis, renal cell carcinoma is classified as stage IV. Primary treatment options for stage IV include systemic therapy as well as cytoreductive therapeutic advances, i.e., surgical resection of primary tumor and/or metastases. An individual approach should be made in order to address the best treatment option for the patient, which may consist of local therapy and/or medical treatment.

Surgical Treatment

In patients with oligometastatic disease or advanced renal cell carcinoma, nephrectomy and surgical metastasectomy should always be discussed if patients are symptomatic or the intervention is possibly conferring to a better prognosis. Especially in those patients relapsing >1 year after initial surgical intervention and/or patients with good/intermediate prognostic features, nephrectomy remains a relevant treatment option (Choueiri et al. 2011). Isolated oligometastatic lymphonodal and/or lung metastases should always be discussed interdisciplinary for indication of surgical management.

Histology

Of note, clinical trials almost exclusively include patients with clear cell histology (ccRCC), which represents the most common subtype of RCC (80–90%), thus leaving the clinician with little evidence on how to treat patients with less frequent histologic subsets such as papillary (pRCC, 6–15%) and chromophobe (ch) RCC (2–5%) (Lopez-Beltran et al. 2006).

Despite a morphology-based diagnosis, increasing evidence supports the notion that RCC remains a heterogenic disease (The Cancer Genome Atlas Research Network 2016; Becht et al. 2015; Durinck et al. 2015; Gerlinger et al. 2014), indicating that distinct therapeutic approaches may be justified in the future. The latest update of the pathological classification addresses this issue by opening a more diverse field of RCC pathology with a number of distinct entities (Shuch et al. 2015).

Adjuvant Therapy

After the first resection and histologic classification of a localized RCC, patients and professionals often deal with the question of if or when to apply adjuvant chemotherapy. Of note, there is clear evidence that RCC is not susceptible to standard chemotherapy regimens. During the past decades, immunotherapies have been explored as adjuvant treatment options, but none of them was able to deliver survival benefit (Chamie et al. 2016; Wood et al. 2008).

The boost in efficacy of the targeted therapies in metastatic RCC has raised the question whether these agents will be able to cure patients by adjuvant treatment. A number of studies are underway to address this question, of which two have already reported results (see Table 1).

Recent studies delivered evidence as for the rationale of an adjuvant systemic treatment for postsurgery locally advanced RCC patients with targeted agents. The ASSURE trial compared 1 year treatment with either sunitinib or sorafenib to placebo (Haas et al. 2016). The primary endpoint was median disease-free survival (DFS), which did not reach significance for any of the groups (sunitinib, 5.8 years; sorafenib, 6.1 years; placebo, 6.6 years). More interestingly, five treatment-related deaths and poor tolerability of full-dose targeted treatment were reported, which led to a dose decrease after the inclusion of 1323 patients.

S-TRAC tested whether 1 year of treatment with either sunitinib or placebo was able to improve DFS in high-risk patients (Casey et al. 2016). The primary endpoint of the study was met for sunitinib (DFS: 6.8 vs. 5.6 year; HR 0.761, $p = 0.03$) and has raised a debate whether or not adjuvant treatment is justified. After 5 years, 59.3% (sunitinib) and 51.3% (placebo) of patients remained disease-free, respectively. However, no mature OS data is currently available for either trial and leaves the current judgment for adjuvant treatment based on intermediate surrogate endpoints (i.e., DFS) and tolerability.

Interestingly, the treatment was associated with a substantial number of severe toxicities in both studies. S-TRAC reported grade 3–4 adverse events (AE) in 62% (sunitinib) and 21% (placebo), respectively. In concordance, ASSURE reported ≥grade 3 AEs of 63% (sunitinib), 72% (sorafenib), and 25% (placebo). In addition to the five reported treatment-related deaths from ASSURE, the role of targeted therapies needs to be assessed critically, as effects have to outweigh risks associated with treatment.

Table 1 Phase III trials for adjuvant treatment with targeted agents (ClinicalTrials.gov)

Trial	Primary endpoint	Status	ClinicalTrials.gov identifier
ASSURE (sunitinib/sorafenib vs. placebo)	DFS	Reported DFS inferior to placebo (Haas et al. 2016)	NCT00326898
S-TRAC (sunitinib vs. placebo)	DFS	Reported DFS superior to placebo (Casey et al. 2016)	NCT00375674
ATLAS (axitinib vs. placebo)	DFS	Active, not recruiting	NCT01599754
EVEREST (everolimus vs. placebo)	DFS	Active, not recruiting	NCT01120249
SORCE (sorafenib vs. placebo)	DFS	Closed	NCT00492258
PROTECT (pazopanib vs. placebo)	DFS	Active, not recruiting	NCT01235962

Currently, adjuvant treatment cannot be recommended and should be assessed in light of the ongoing trials with targeted therapies (ATLAS, EVEREST, SORCE, PROTECT) (see Table 1). Current clinical studies investigate the role of immunotherapies in this setting. Given their mode of action, expectations for an improvement of OS are high, and ongoing trials may draw a different picture of adjuvant treatment in the future.

Metastatic Disease: Systemic Treatment

The treatment of patients with metastatic or irresectable local disease should be individualized to the patient's needs and aims. In order to pick the most appropriate choice of therapy, the assessment of the disease status and the patient's risk are a prerequisite to come to a conclusion. Local therapy is in principle offered if patients have completely resectable disease or palliation of symptoms might be achieved. Furthermore, local therapies are applied in light of patient's prognosis. In this chapter, we do focus on medical treatment, which is one option in the armamentarium of RCC treatment.

Prognostic Scores

Current treatment guidelines are mostly based on Memorial Sloan Kettering Cancer Center (MSKCC) scoring for risk assessment of patients. This risk assessment contains Karnofsky performance status (PS) <80%, the absence of prior nephrectomy, hemoglobin less than the lower limit of normal, lactate dehydrogenase >1.5 times the upper limit of normal, and corrected serum calcium >10 mg/dl. A score of 0 means favorable risk, 1–2 risk factors means intermediate risk, and >3 risk factors means poor risk for survival (Motzer et al. 1999). With the introduction of targeted therapies, additional parameters have been included in order to improve prediction. The International Metastatic RCC Database Consortium (IMDC) score extended the known factors to a total of six: Karnofsky PS <80%, hemoglobin <lower limit of normal, time from diagnosis to treatment <1 year, corrected calcium above the upper limit of normal, platelets greater than the upper limit of normal, and neutrophils greater than the upper limit of normal (Heng et al. 2013). The major advantage of the IMDC score is its better discrimination of high- and intermediate-risk patients on targeted therapies (see Table 2).

Table 2 MSKCC and IMDC score (Motzer et al. 1999; Heng et al. 2013). A score of 0 means favorable risk, 1–2 risk factors means intermediate risk, and ≥3 risk factors means poor risk for survival

MSKCC score	IMDC score
Karnofsky performance status (PS) <80%	Karnofsky PS <80%
Time from diagnosis to treatment <1 year	Time from diagnosis to treatment <1 year
Hemoglobin less than the lower limit of normal	Hemoglobin less than the lower limit of normal
Lactate dehydrogenase >1.5 times the upper limit of normal	
Corrected serum calcium >10 mg/dl	Corrected calcium above the upper limit of normal
	Neutrophils greater than the upper limit of normal
	Platelets greater than the upper limit of normal

IMDC The International Metastatic Renal Cell Carcinoma Database, *MSKCC* Memorial Sloan Kettering Cancer Center

Start of Medical Treatment

For patients with relapse or stage IV and surgically unresectable disease, systemic treatment is recommended in principle. The aim of the treatment is to palliate symptoms and postpone progression or the onset of symptomatic disease. The major disadvantage of targeted therapies is its high burden of toxicity, with an incidence of grade ≥ 3 in 60–70% and all grade AEs in 95–98% of patients (Motzer et al. 2007, 2013a; Haas et al. 2016; Choueiri et al. 2016). As many RCC patients come in good general conditions without tumor-related symptoms, treatment offers them a substantial drop in quality of life (Cella et al. 2008). Hence, the start of therapy has to be

balanced against toxicity and renders a distinct approach more feasible in selected patients. The aim is to expose only patients in need for therapy to toxic treatment and spare adverse events in patients with indolent disease. So far, no clear-cut criteria exist to identify these patients, and assessment is subjective to the physician and the patient.

Low tumor burden and asymptomatic disease or specific metastatic locations (Grassi et al. 2016) or histology (Rini et al. 2016a) may drive the process for the decision. Data from placebo-controlled phase III trials indirectly support this option, as well as other clinical studies (Choueiri et al. 2016; Sternberg et al. 2013; Nosov et al. 2012). Despite not reaching significance, there is a trend to inferior outcome in patients on placebo (Sternberg et al. 2013), indicating that patient selection is a key in order to offer such an approach and there is a remaining risk for early progression or death in these patients. A prospective study assessed an expert-based selection as a potential tool, which showed that tumor burden, IMDC risk category, sarcomatoid differentiation, and performance status have impact on active surveillance (Rini et al. 2016a). However, the overall benefit and the individual risks associated with active surveillance need to be further assessed. At the current state, active surveillance should be offered by experienced physicians with expertise in RCC treatment only.

Guidelines for Medical Treatment

Numerous groups addressed the treatment algorithm for RCC on national and international level. In Europe, guidelines of the European Society of Medical Oncology (ESMO) (see Table 3) and European Association of Urology (EAU) (Table 1) (EAU guidelines on renal cell carcinoma, limited text update March 2016) prevail and are updated periodically. In the United States (USA), the National Comprehensive Cancer Network (NCCN) provides recent guidelines for cancer treatment. In all guidelines, recommendations for the sequential use of medical agents are given. However, no recommendation for a specific, prespecified sequence can be given. Instead the best choice of a drug at a time should be made, in order to accommodate patient's needs at the decision time point accordingly.

National guidelines are tailored to the specific needs of a given country and might be more applicable in countries with limited access to treatment.

As addressed before, the decision on when to start treatment depends on various factors such as localization, histology, tumor burden, time to metastatic state, MSKCC score, and patient will, which can only be partially addressed in guidelines. Of note, patients included in clinical phase III trials mostly belong to low- or intermediate-risk groups and limit therefore the generalizability of the reported evidence.

Treatment Algorithms

As the current standard of care in mRCC consists of continuous exposure of patients to therapy, this implies a therapy sequence rather than just one line of therapy. There is no recommendation on a specific sequence; therefore the choice of an agent is bound to different therapeutic scenarios, for which physician and patient are seeking the best solution. Given the fact that even in clinical studies, about half of the patients do not receive subsequent line of therapy, it gives some weight to the choice of agent given. Today, the first-line therapy mainly consists of tyrosine kinase inhibitors (TKIs), which exert every activity in mRCC. However, during the past, the treatment consisted of cytokines, which today may be given in conjunction with bevacizumab, a VEGF-monoclonal antibody (mAb). We summarize historical and contemporary approaches in the next paragraphs.

Cytokines

Since RCC was found to be a tumor with resistance to conventional chemotherapeutic agents (about 30 years ago), the concept of immunotherapy was introduced to advanced stage RCC therapy rather early. In the 1980s, the principle antitumor activity of cytokines has been reported. IL-2 administration in murine models could prove to confer to tumor shrinkage via activation of resting lymphocytes capable to be turned into activated killer cells (Rosenberg et al. 1985). These results and the observation that patients

with mRCC may acquire spontaneous remissions have led to the development of immunotherapies in mRCC. At that time given, immune stimulation was the hotspot of antitumor therapy. Interleukin (IL)2 and interferon-alpha (IFN-α) were given either subcutaneously (s.c.) or intravenously (i.v.) to mRCC patients. About 10–20% of mRCC patients did respond to this therapy, with low numbers of complete responders, though (Motzer et al. 2009; McDermott et al. 2005). However, sustained clinical benefit was attained in patients with tumor response to cytokine treatment (Hughes et al. 2015). This has kept i.v. IL-2 treatment in business bound to specialized centers, as toxicity is high and life-threatening with this type of treatment. Especially in the United States,

Table 3 Treatment options for mRCC (based on NCCN/ESMO/EAU 2016 guidelines)

Therapy	NCCN [categories][a]	ESMO [LE, GR][b]	EAU [LE][c]
First line Clear cell histology *Good/intermediate prognosis*	Pazopanib (Negrier et al. 2002) Sunitinib (Negrier et al. 2002) Bevacizumab + IFN-α (Negrier et al. 2002) Axitinib [2A] High-dose IL-2 [2A] (selected patients) Sorafenib [2A] (selected patients)	*Standard:* Sunitinib [1, A] Bevacizumab (+IFN-α) [1, A] Pazopanib [1, A] *Option:* HD IL-2 [III, C] Sorafenib [II, B] Bevacizumab + low-dose IFN [III, B]	Sunitinib [1b] Pazopanib [1b] Bevacizumab + IFN-α [1b]
Non-clear cell histology	Sunitinib Axitinib Bevacizumab Cabozantinib Erlotinib Everolimus Lenvatinib + everolimus Nivolumab Pazopanib Sorafenib Temsirolimus [All 2A]	*Standard:* Sunitinib [II, B] *Option:* Temsirolimus [III, B] Sunitinib [III, B] Pazopanib [III, B] Everolimus [III, B]	Sunitinib [2a] Everolimus [2b] Temsirolimus [2b]
Poor risk	Temsirolimus (Negrier et al. 2002)	*Standard:* Temsirolimus [II, A] *Option:* Sunitinib [II, B] Sorafenib [III, B] Pazopanib [III, B]	Temsirolimus [1b]
Second line Clear cell histology	Cabozantinib (Negrier et al. 2002) Nivolumab (Negrier et al. 2002) Axitinib (Negrier et al. 2002) Lenvatinib + Everolimus (Negrier et al. 2002) Everolimus [2A] Pazopanib [2A] Sorafenib [2A] Sunitinib [2A] Bevacizumab [2B] High-dose IL-2 [2B] (selected patients) Temsirolimus [2B]	Post-cytokines: *Standard:* Axitinib [II, A] Sorafenib [I, A] Pazopanib [II, A] *Option:* Sunitinib [III, A] Post-TKI: *Standard:* Nivolumab [I, A] Cabozantinib [I, A] *Option:* Axitinib [II, B] Everolimus [II, B] Sorafenib [III, B]	After VEGF therapy: *Based on OS:* Nivolumab [2a] *Based on PFS:* Cabozantinib [2a] Axitinib [2a] Sorafenib [2a] Everolimus [2a]
Non-clear cell histology			Any targeted agent (Gore et al. 2010)

(*continued*)

Table 3 (continued)

Therapy	NCCN [categories][a]	ESMO [LE, GR][b]	EAU [LE][c]
Third line		Post 2 TKI: *Standard:* Nivolumab Cabozantinib [II, A] *Option:* Everolimus [II, B] Post-TKI and mTOR: Sorafenib [I, B] Nivolumab or cabozantinib [V, A] *Option:* Another TKI or TKI-rechallenge [IV, B] Post-TKI/nivolumab: *Standard:* Cabozantinib [V, A] *Option:* Axitinib [IV, C] Everolimus [IV, C] Post-TKI/cabozantinib: *Standard:* Nivolumab [IV, A] *Option:* Everolimus [V, B] Axitinib [V, B]	After VEGF therapy: Nivolumab [2a] Cabozantinib [2a] Everolimus [2a] After VEGF and mTOR therapy: Sorafenib [1b] After VEGF and nivolumab: Cabozantinib (Gore et al. 2010) Axitinib (Gore et al. 2010) Everolimus (Gore et al. 2010)

EAU European Association of Urology, *ESMO* European Society of Medical Oncology, *GR* grade of recommendation, *IFN-α* interferon-alpha, *IL* interleukin, *LE* level of evidence, *mTOR* mechanistic target of rapamycin, *NCCN* National Comprehensive Cancer Network, *TKI* tyrosine kinase inhibitor, *VEGF* vascular endothelial growth factor

[a]Grading based on NCCN standards

[b]LE and GR adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System

[c]LE based on Oxford Centre for Evidence-Based Medicine (CEBM) rating system

patients with oligometastatic disease and very good performance status are still considered eligible for application of high-dose IL-2.

Much more common is the less aggressive and palliative treatment approach by subcutaneously applied cytokines, which nowadays remains a part of the combination of bevacizumab and IFN-α. We use bevacizumab and IFN-α as a treatment option in low-risk patients such as patients with glandular metastases (i.e., thyroid gland, pancreas, etc.) or favorable risk (Escudier et al. 2007). Irrespective of the risk group or dose of IFN-α, the median progression-free survival (PFS) was significantly longer in the bevacizumab plus IFN-α group than it was in the control group with placebo+IFN-α (10.2 months vs. 5.4 months), underscoring the boost of efficacy that has been seen in mRCC with the introduction with VEGF inhibitors to the treatment algorithm.

Targeted Therapies

Growing insights into cellular pathways responsible for tumor growth and metastasis led to the development of therapeutic agents aiming at specific cellular targets. Those include the vascular endothelial growth factor (VEGF) and its receptor (VEGFR), which contribute to tumor growth via stimulation of angiogenesis, as well as mechanistic target of rapamycin (mTOR), a serine/threonine protein kinase regulating cell growth, proliferation, and motility.

Inhibition of the VEGF pathways via antibodies or tyrosine kinase inhibitors (TKIs) targeting the VEGFR, as well as mTOR inhibition via mTOR inhibitors (mTORi), successfully

blocks tumor growth and even confers to necrosis.

A common concept of oncogenesis is the acquisition of mutations conferring to survival advantage, uncontrolled cell growth, and immune evasion. In clear cell RCC development, a major effector was found to be the von Hippel-Lindau (VHL) gene that shows responsible for the degradation of the hypoxia-inducible factor (HIF) via proteasome activity. The VHL gene is mutated or silenced in up to 75% of RCC, predominantly those of clear cell histology (Patel et al. 2006). HIF increase in the cell is directly stimulating the VEGF pathway. Knowing that RCC is a highly vascularized tumor depending on rapid growth of tumor vessels, the inhibition of VEGFR via targeted agents had a strong rationale (see Fig. 1).

Since 2005, five VEGF-targeting agents were approved for clinical use in mRCC: multi-TKI pazopanib, sunitinib, and sorafenib, as well as bevacizumab, an anti-VEGF-antibody, in combination with IFN-α. Phase III clinical trials could prove all substances to confer to prolonged PFS.

The range of adverse events (AE) of VEGF-targeting agents treatment is broad, ranging from skin toxicity (e.g., hand-foot syndrome), fatigue, and hypertension to gastrointestinal toxicity (e.g., diarrhea, bleeding) and/or stomatitis, yet only about 10% of patients will discontinue therapy due to side effects (Grünwald et al. 2007).

Both everolimus and temsirolimus are so-called rapalogues, due to their evolution from rapamycin, also called sirolimus, a potent antitumor effector inhibiting the mTOR pathway. mTOR is an intracellular serine/threonine kinase that regulates cell size and proliferation, its activation conferring to cell-cycle progression and tumor growth. RCC frequently shows alterations in this signaling pathway, with increase in mTOR activity. Of note, activation of mTOR confers to elevated intracellular HIF levels, which is known to play a key role in RCC

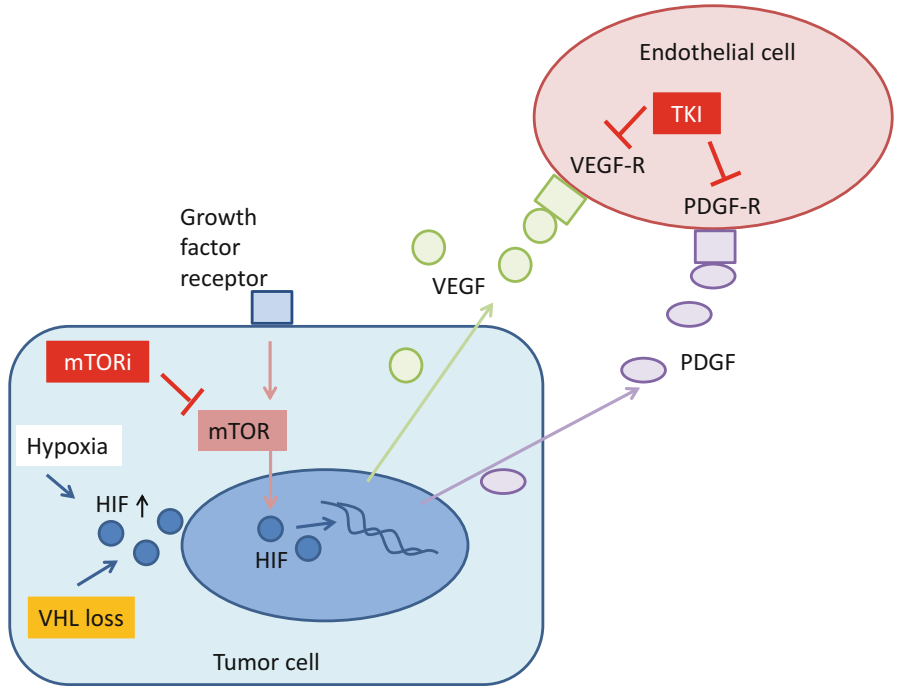

Fig. 1 Mechanisms of vascularization and inhibition of tumor growth in RCC (*HIF* hypoxia-inducible factor, *mTOR* mechanistic target of rapamycin, *mTORi* mTOR inhibitor, *PDGF* platelet-derived growth factor, *PDGFR* platelet-derived growth factor receptor, *TKI* tyrosine kinase inhibitor, *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptor, *VHL* von Hippel-Lindau (gene))

development, due to stimulation of VEGF transcription (Voss et al. 2011).

mTOR inhibitors temsirolimus and everolimus have been approved in locally advanced or metastatic RCC. Of note, treatment of advanced RCC was the first approved indication for mTOR inhibitors in clinical oncology. Their major advantage is their tolerability, but they offer objective response to a much lesser degree than VEGF-targeting agents.

The most common adverse events were found to be metabolic abnormalities (hyperglycemia and hypercholesterolemia), hematological toxicity, asthenia, rash, fatigue, nausea, infections, and stomatitis. Of note, interstitial pneumonitis, a rare but potentially serious AE, occurred in up to 25% (everolimus) and/or 8% (temsirolimus) of patients, respectively (Motzer et al. 2010; Hudes et al. 2008).

Nowadays, the molecular diversity of RCC was reported to be more complex than anticipated. Distinct entities with its own molecular background were recently reported and may open novel avenues for further drug development in mRCC (The Cancer Genome Atlas Research Network 2016; Evelönn et al. 2016; Malouf et al. 2014).

First Line (See Tables 3 and 4)

Tyrosine Kinase Inhibitors

Pazopanib

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR-1, VEGFR-2, and VEGFR-3, platelet-derived growth factor (PDGFR)-alpha and PDGFR-beta, and stem cell factor receptor (c-KIT). In a placebo-controlled phase III trial comparing pazopanib and placebo, PFS benefit was 5 months (9.2 vs. 4.2 months) with an objective response rate (ORR) of 30% vs. 3%. Most common AEs (10–50%) were diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting, fatigue, weakness, abdominal pain, and headache. Before and during treatment, monitoring of liver function is crucial, since the most notable grade 3 toxicity was found to be hepatotoxicity (20–30%). Of note, the final analysis of OS did not show an effect of pazopanib, yet this might be due to the frequently used crossover to the open-label extension with pazopanib (Sternberg et al. 2013; Motzer et al. 2014a).

Sunitinib

The multikinase inhibitor (targeting, e.g., PDGFR-alpha, PDGFR-beta, VEGFR-1, VEGFR-2, VEGFR-3, c-KIT, FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor (CSF)-1R, and neurotrophic factor receptor (RET)) is suggested to confer to inhibition of both angiogenesis and cell proliferation, established as first-line therapy in a large phase III trial compared to treatment with IFN-α. PFS benefit was 6 months (11 vs. 5 months), with an ORR of 31%, comparable to that of pazopanib. Severe AEs (5–12%) were neutropenia, thrombocytopenia, hyperamylasemia, diarrhea, hand-foot syndrome, and hypertension (Motzer et al. 2007).

Data analyses in a retrospective study did reveal non-inferiority in OS and PFS for pazopanib and sunitinib (Ruiz-Morales et al. 2016). The COMPARZ trial did directly compare efficacy and safety of pazopanib and sunitinib in the first-line setting, revealing a comparable PFS (8.4 vs. 9.5 months) and ORR (31% vs. 25%). Of note, pazopanib was associated with less toxicity

Table 4 Study results for FDA-approved agents in first-line treatment

Agent	Comparator	Median PFS (months)	Median OS (months)	Reference
Pazopanib	Placebo	11.1 vs. 2.8[a]	22.9 vs. 20.5	Motzer et al. (2013a)
Sunitinib	IFN-α	11 vs. 5[a]	26.4 vs. 21.8	Motzer et al. (2009)
Bev + IFN-α	IFN-α	10.2 vs. 5.4[a] 8.5 vs. 5.2[a]	23.3 vs. 21.3 18.3 vs. 17.4	Escudier et al. (2010) Rini et al. (2010)
Sorafenib	IFN-α	5.7 vs. 5.6	na	Escudier et al. (2009b)
Temsirolimus	IFN-α	5.5 vs. 3.1	10.9 vs. 7.3[a]	Hudes et al. (2008)

Bev bevacizumab, *FDA* Food and Drug Administration, *IFN-α* interferon-alpha, *na* not available, *OS* overall survival, *PFS* progression-free survival

[a]Statistically significant

of certain AEs (fatigue, hand-foot syndrome, taste alteration, thrombocytopenia) yet more hepatotoxicity. The final results did show similar OS expectations for both drugs (28.3 vs. 29.1 months) (Motzer et al. 2013a).

The smaller phase III PISCES trial did compare blinded randomization of patients to receive either pazopanib or sunitinib as first-line therapy for 10 weeks before switching to the other agent, in order to determine patient preference. Of note, 70% of patients did prefer pazopanib due to better quality of life, in some instances despite an objective increase or similar incidences of such toxicities (Escudier et al. 2012). The results of these studies have been questioned by some, as the differences remained small in many categories and PISCES is prone to bias, given the study size and setup. However, these studies indicate the key role of TKI to attain prolonged survival in mRCC and also underscore the importance of patient-based assessment of toxicity. It becomes clear that a substantial improvement of outcome will have to be provided by novel therapeutic avenues in mRCC, rather than from more of the same mechanisms of action.

Sorafenib

Sorafenib is a first-generation TKI, which mostly is recommended as an alternative approach in first line given the lower possibility for response compared to other TKIs. Comparison of sorafenib versus IFN-α in treatment-naïve patients in a randomized phase II trial did show efficacy in the first line only through ORR improvement (69% vs. 39% tumor regression), yet there was no PFS benefit. Since patients crossing over from IFN-α to sorafenib did have progression-free intervals, a clinical benefit for sorafenib as second-line therapy after IFN-α and TKI was presumed (Escudier et al. 2009a). The SWITCH study underscored the inferior activity in mRCC when comparing sorafenib with sunitinib in first line (Eichelberg et al. 2015).

Axitinib

Axitinib is a selective, second-generation inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3. Axitinib offers lower IC-50 rates for VEGFR-2 inhibition, which offers a pharmacological advantage. Based on results from a phase III trial comparing axitinib versus sorafenib in treatment-naïve patients, axitinib did confer to PFS increase (10.1 vs. 6.5 months, not significant) with acceptable toxicity. Most common adverse events for axitinib (>10% difference compared to sorafenib) were diarrhea, hypertension, weight loss, and decreased appetite (Hutson et al. 2013). In a recent randomized phase II trial, double-blinded dose-escalated axitinib was tested in treatment-naïve patients. Dose-increased axitinib improved the ORR (54% vs. 34%), which was the primary endpoint (Rini et al. 2013a). As a secondary endpoint, the OS of dose-escalated axitinib with 42.7 months was very promising and in favor to standard dose axitinib (30.4 months) (Rini et al. 2016b). However, the difference was not significant and mirrored the small PFS advantage for axitinib dose titration (HR 0.85; $p = 0.24$) (Rini et al. 2013a). Patients who had adverse events that prevented dose escalation also achieved a remarkable result with an OS of 41.6 months, indicating that for axitinib treatment with a tolerable and sub-toxic dose is a key element of its therapeutic management – which may be achieved by standard dose or dose titration. This study also showed in a prospective fashion including pharmacokinetics that the relationship between TKI treatment and hypertension is much more complex than previously anticipated. It therefore does not support the use of blood pressure as a surrogate marker of efficacy (Rini et al. 2014).

Based on this data, axitinib is not recommended for first-line use in mRCC but is used by some on a global scale.

Monoclonal Antibodies

Bevacizumab

VEGF-A-binding recombinant human monoclonal antibody bevacizumab was introduced as first-line therapy based on phase III findings (AVOREN and CALBG trial) comparing bevacizumab plus IFN-α versus IFN-α alone. Addition of bevacizumab did confer to an increase in PFS (3–5 months benefit, total of 10.2 and 8.5 months, respectively) as well as better ORR (30.6% and 25.5%, respectively) (Escudier et al. 2007; Rini et al. 2010).

Bevacizumab is recommended in first-line therapy in good- or intermediate-risk patients.

mTOR Inhibitors

Temsirolimus

Temsirolimus, an intravenously applied mTORi, was approved based on findings from the phase III, multicenter, randomized, open-label ARCC trial in previously untreated patients with advanced RCC and three or more of six unfavorable prognostic factors comparing temsirolimus ± IFN-α and IFN-α alone. Hudes et al. introduced a selection of predictors conferring to short survival in order to select patients eligible for use of temsirolimus in the first-line setting: LDH level >1.5 time UNL, hemoglobin level <LLN, corrected calcium level >10 mg/dl (2.5 mmol/l), interval of <1 year from original diagnosis to start of systemic therapy, Karnofsky PS <70, and ≥2 sites of organ metastasis. Results did show a significant improvement in OS (10.3 vs. 7.3 months) for temsirolimus alone. Of note, combination of temsirolimus and IFN-α led to an increase in AE (including grade 3 or 4) (Hudes et al. 2008). Based on this study, temsirolimus is only indicated as first-line therapy in patients with poor-risk features.

Of note, despite its appearance in official guidelines and the phase III evidence including survival benefit, temsirolimus is not generally used in the first-line setting for high-risk patients.

Second Line (See Tables 3 and 5)

After the failure of first-line therapy, approximately 50% of patients do receive second-line treatment. Based on the previous exposure, the drug for the next line of treatment is chosen. As the first-line therapy is dominated by TKIs, only a fraction of patients receives cytokines or mTORi. The current recommendations were recently updated according to emerging data for treatment after TKI failure with next-generation TKIs: lenvatinib, cabozantinib, or the PD-1 inhibitor nivolumab. Historically, the TKI axitinib and mTORi everolimus were considered standard options as second-line therapies.

Tyrosine Kinase Inhibitors

Axitinib

A multicenter, randomized phase III trial (AXIS) did compare axitinib versus sorafenib in the second-line setting after exactly one prior systemic therapy (mostly cytokines or sunitinib), showing PFS advantage of 2 months for axitinib (6.7 vs. 4.7 months), with a doubled ORR (19% vs. 9%). However, when focusing on the predominant patient population in the real-world setting, efficacy after the failure of sunitinib dropped to 3.4 vs. 4.8 months (HR 0.741, p = 0.0107), and ORR was 11% (Rini et al. 2011). Based on the response rate, axitinib remained at that time the most active second-line treatment. However, overall activity remained modest after all and indicated need for further improvement.

Most common AEs with axitinib were hypertension, fatigue, dysphonia, and hypothyroidism (Motzer et al. 2013b). Of note, a recent phase II study in patients with cytokine refractory mRCC reported 5-year survival rates for axitinib of 20.6% in median (Rini et al. 2013b).

Table 5 Study results for FDA-approved agents in second-line treatment

Agent	Comparator	Median PFS (months)	Median OS (months)	Reference
Nivolumab	Everolimus	4.6 vs. 4.4	25 vs. 19.6[a]	Motzer et al. (2015b)
Cabozantinib	Everolimus	7.4 vs. 3.8	na	Choueiri et al. (2015)
Axitinib	Sorafenib	6.7 vs. 4.7[a]	na	Rini et al. (2011)
Everolimus	Placebo	4.9 vs. 1.9	14.8 vs. 14.4	Motzer et al. (2010)

FDA Food and Drug Administration, *na* not available, *PFS* progression-free survival, *OS* overall survival
[a]Statistically significant

Sorafenib

Placement of sorafenib as second-line treatment is based on results of a phase III placebo-controlled trial (TARGET) including patients progressive after prior cytokine therapy. PFS was significantly higher (5.5 vs. 2.8 months), OS was not significant due to the crossover to the sorafenib arm, after censoring the net benefit for median OS is 3.5 months (17.8 vs. 14.3 months) (Escudier et al. 2009b). There is also data about treatment with sorafenib in the post-sunitinib or post-bevacizumab setting, showing a median PFS of 4.4 months (Garcia et al. 2010). The SWITCH study investigated whether sorafenib was superior to sunitinib in regard to the cumulative PFS of two lines of therapy (Eichelberg et al. 2015). The study did not meet its primary endpoint, and efficacy of sorafenib was inferior in the first and second line. However, the OS remained similar between both treatment arms.

Sunitinib

Sunitinib has shown efficacy in previously treated patients. As a second-line option, sunitinib demonstrated efficacy after failure of cytokines and/or TKI with a PFS of 8.7 months after first-line cytokine therapy (Motzer et al. 2006) or 5 months in direct sequence after sorafenib (vs. 4.7 months with sorafenib after sunitinib) (Dudek et al. 2009).

Third-Generation TKIs

Only recently, two next-generation TKIs have been approved by FDA and EMA, cabozantinib and lenvatinib, in 2016. Both are multi-tyrosine kinase inhibitors, blocking not only VEGFR but also MET and AXL signaling cascades (cabozantinib) or multiple VEGF pathways like VEGFR2 and VEGFR3 (lenvatinib). Of note, both MET and AXL seem to be associated with tumor progression, but more importantly, animal models showed that the development of resistance to mere VEGFR inhibitors can be mediated through AXL and MET (Zhou et al. 2016). In ccRCC loss of the VHL tumor suppressor gene is known to not only upregulate the VEGF pathway but also expression of AXL and MET tyrosine kinase receptors, resulting in the rationale to treat VEGFR-targeting TKI-resistant patients with AXL inhibitors (Escudier et al. 2016).

Both, cabozantinib and lenvatinib (in combination with everolimus), could induce not only prolonged PFS but also increased OS.

Cabozantinib

Cabozantinib has very recently been tested in the second-line setting in a phase III trial (METEOR) in patients after previous TKI therapy. Patients with one to three prior therapies were included in this study, and previous exposure to checkpoint blockade was allowed. Compared to everolimus, cabozantinib did show superiority in terms of PFS (7.4 vs. 3.8 months) and ORR (17% vs. 3%) (Choueiri et al. 2016). Interestingly, the number of patients who progress immediately was lower for cabozantinib than for everolimus (12% vs. 27%) and actually remains one of the lowest among targeted therapies tested, indicating the broad activity of cabozantinib. Cabozantinib also achieved a reduction in mortality (OS 21.4 vs. 16.5 months) as compared to everolimus, with a similar adverse event portfolio in comparison to other established TKIs (mainly: mucocutaneous AEs, hypertension, diarrhea, fatigue) (Choueiri et al. 2016). Dose reductions were necessary in 62% of patients (compared to 25% for everolimus).

Only recently, the phase II CABOSUN trial compared cabozantinib and sunitinib in the first-line setting for patients with intermediate and poor risk. The study showed superior PFS (8.2 vs. 5.4 months; HR 0.69; $p = 0.012$) and ORR (46% vs. 18%), with comparable safety/toxicity profile (Choueiri et al. 2017). The OS showed a trend in favor for cabozantinib (HR 0.80), indicating the potential benefit of cabozantinib in this patient population. More interestingly, the subgroup of patients with bone metastases did extremely well on cabozantinib (PFS: HR 0.51), a schema which also appeared on the METEOR trial, when comparing with everolimus (PFS: HR 0.33).

Lenvatinib

Lenvatinib is the only targeted agent which was approved based on phase II data in mRCC. The HOPE 205 study investigated the role of lenvatinib either with or without everolimus to its single-agent use in a randomized fashion. Patients with exactly one prior TKI were randomized to receive one of the three treatment arms. The primary endpoint was to detect a difference between the combination and single-agent lenvatinib in comparison to everolimus. Surprisingly, the combination outperformed expectations by far and resulted in the best PFS ever seen in TKI-refractory mRCC. PFS for lenvatinib + everolimus, lenvatinib, and everolimus were 14.6, 7.4, and 5.5 months (Motzer et al. 2015a). The corresponding hazard ratios between experimental arms and everolimus were 0.40 ($p = 0.0005$) and 0.61 ($p = 0.048$). Corresponding to this impressive improvement in PFS, the objective response rate was also superior for the combination with 43%, 27%, and 6%, respectively. The number of primary treatment failures was low for lenvatinib arms (4% and 6%, respectively), but 12% and 15% of patients were not assessable in this analysis, which might underestimate the true number of primary treatment failures. More surprisingly, the efficacy benefit was able to translate into OS benefit despite the small number of patients included into the trial. OS was 25.5 and 19.1 months for the experimental arms and 15.4 months for everolimus treatment (Motzer et al. 2015a).

The combination showed acceptable toxicity with a known AE spectrum. However, the incidence of grade $\geq$3 AEs increased with the combination (71%) or lenvatinib single agent (79%) when compared to everolimus (50%). Specifically, gastrointestinal toxicity was profound for the experimental arm with an increase in grade $\geq$3 diarrhea (20% vs. 2% in the everolimus arm) or constipation (37% vs. 0% for everolimus). Other AEs showed also an increase, such as fatigue (18% vs. 2%), hypertension (13% vs. 2%), and renal failure (10% vs. 2%) (Motzer et al. 2015a). Overall, the combination was more toxic and required more frequent dose-reduction for lenvatinib (71%). But also single-agent lenvatinib required dose adjustment in 62%, indicating that dose reductions may not hamper clinical activity.

Immunotherapy

Based on growing evidence on tumor immune escape mechanisms and immune system dysfunction, several key proteins could be identified, which can be selectively blocked via targeted drugs, e.g., CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed cell death protein 1). Both are considered crucial immune checkpoints for initiation and/or blockage of antitumor immune response in cytotoxic T-cells. T-cells expressing PD-1 interact via these immune checkpoints, whereas binding to PD-L1 confers to tolerance against tumor cells. Expression of PD-L1 on tumor cells cannot be detected in all patients, yet clinical evidence suggests that also PD-L1-negative patients show response toward PD-1 blockade resulting in tumor shrinkage (Gandini et al. 2016). So, a much more complete picture of the immune environment may be needed prior to establishment of a predictive marker for immunotherapy. The hunt for the best tumor marker has started and will most likely include more than one marker in order to identify the patient with best chances for benefit from immunotherapy. More likely, future immunotherapies will be tailored based on the tumors' immune environment, involving more than one drug.

Nivolumab

Nivolumab was the first immune checkpoint inhibitor approved by FDA and EMA in 2016 for use in la/mRCC after one or two lines of VEGF-targeting therapy. The pivotal CheckMate 025 phase III trial included patients with up to two lines of previous therapy (mTORi naïve, maximum of two prior TKIs), randomly assigned to receive nivolumab or everolimus, showing an OS benefit of 5.4 months favoring nivolumab (25.0 vs. 19.6 months), which was the primary endpoint of the study (Motzer et al. 2015b) . Of note, the study results did prove not only OS benefit for

treated patients but also five times greater ORR (25% vs. 5%). Also, the quality of life was assessed, showing a consistent improvement for patients in the nivolumab arm. Treatment-related AEs were seen in 79% of patients treated with nivolumab compared to 88% of those treated with everolimus; of note, grade 3–4 AEs were only 19% for nivolumab, mostly fatigue, vs. 37% with everolimus.

The quality of life (QoL) was assessed with a questionnaire, showing an increase in QoL over time under treatment (Motzer et al. 2015b). The role of QoL in mRCC was further explored in an additional analysis of this study. Given the surrogate nature of QoL, QoL may reflect the impact of toxicity or tumor-related symptoms on patients. Patients with an improvement in the QoL score by 2 points (equals the minimally important difference) were grouped as QoL responders, which was more often associated with nivolumab treatment than with everolimus (55% vs. 37%; $p < 0.001$) (Cella et al. 2016). Patients with a QoL response showed also an improvement in OS, indicating the importance of QoL measures in mRCC.

Of note, therapy with checkpoint inhibitors was associated with an unconventional response pattern, which may include increase in size prior to tumor shrinkage (Nishino et al. 2012) . This pattern is mainly seen during the initial phase of treatment. Therefore, a CT scan for evaluation of treatment response should be planned after 12 weeks of therapy. However, immediate tumor staging should be performed in symptomatic patients. In case of progressive disease, a confirmatory scan should be performed in asymptomatic patients with a good performance status and tolerability. Treatment failure is defined by either progression of tumor manifestation (clinical or radiological), tumor-associated symptoms, or intolerable side effects.

mTOR Inhibition

Everolimus, an orally administered mTORi, is approved after failure of VEGF-targeted therapies in mRCC. The pivotal phase III trial (RECORD 1) did compare everolimus with placebo after previous treatment with sunitinib or sorafenib. The PFS benefit was 3 months for everolimus (4.9 vs. 1.9 months) and led to registration (Motzer et al. 2010). Due to the crossover design of RECORD-1, a high number of patients were able to switch to active therapy (76%), which diluted a potential survival benefit for everolimus in this setting. The low PFS on placebo underlines that mRCC patients in later lines have aggressive tumors with rapid progression and are in need of active therapies. Characteristic for the class of agents is the low number of objective responses, which is confirmed by more recent studies and generally is $\leq$5% (Choueiri et al. 2016; Motzer et al. 2010, 2015a, b). However, disease stabilization is the main achievement of mTORi, which may lead to symptom control.

A major advantage of everolimus is its good tolerability. The most common AEs were stomatitis, rash, metabolic effects, and fatigue (Motzer et al. 2010).

Of note, in recent phase III trials comparing cabozantinib and nivolumab with everolimus in the second-line setting, both agents did show clear superiority against the mTORi, degrading it to a mere further-line treatment option or combination partner. However, about 10–15% of patients derive substantial benefit from mTORi treatment and remain on therapy $\geq$1 year. Unfortunately, no test exists to identify these patients. Small series suggest an association with mutation of the AKT-TSC-mTOR axis but are not exclusive (Voss et al. 2014).

The phase II RECORD-3 trial showed inferiority of everolimus as first-line therapy compared to sunitinib and underscores the important role of TKI in the treatment algorithm of mRCC (Motzer et al. 2014b).

Further-Line Treatment

Depending on first- and second-line treatment decisions, third-, fourth-, and further-line therapies are mostly stratified into post-TKI, post-mTOR, or post-nivolumab and are driven by subgroup analyses or small retrospective series (see Table 3).

Recommendations

Due to the diversity of clinical trials and varying results depending on the direct comparison of two or more agents, there still remain a lot of question marks about the sequential therapy in locally advanced and metastatic RCC. And besides clinical data, availability of agents varies substantially among countries and also defines the sequence of agents used. Some general guidelines though have a high grade of recommendation, such as:

- Medical treatment should be applied in sequence
- Current first-line options consist of TKIs (sunitinib or pazopanib), bevacizumab + IFN (favorable and intermediate risk), or temsirolimus (poor risk only)
- Given the survival benefit seen in phase III trials with cabozantinib or nivolumab, these agents are used preferentially as subsequent therapies
- Lenvatinib + everolimus remains an option as second-line therapy and has the merit of a high response rate; however, experience is bound to a single phase II study, which is prone to bias in principle
- Axitinib and everolimus remain treatment options but lack OS benefit in phase III trials and, hence, are not a prime choice in previously treated patients. They should be administered in case if other drugs are not safe, tolerable, or available
- For non-clear cell histology, sunitinib and everolimus are the most explored agents and reassemble the mainstay of therapy

Table 6 summarizes the approved targeted agents in mRCC treatment along with information about the officially approved indication.

Supportive care should always be part of routine clinical treatment of patients with metastatic or locally advanced RCC, comprising osteoprotective measures in osteolytic bone disease, analgesics, surgery and/or stereotactic radiotherapy in locally treatable metastases (e.g., the brain or stenosis of the spinal cord, isolated fractures, or bones with imminent risk of fracture), and last but not least psychological support.

Routine tumor imaging during systemic treatment should be performed every 6–12 weeks, using either CT scan or MRI. Of note, routine follow-up for patients treated with immunotherapy should start at 12 weeks, in order to avoid pseudoprogression, which usually occurs early during the course of treatment with nivolumab. However, symptomatic patients require prompt and adequate measures of diagnosis and treatment.

Summary

Clinical trials and real-world experiences proved the importance of sequential therapy in mRCC. With the continuous exposure of patients to medical treatment, the OS expectation migrated toward 30 months during the past decade, which is where it ceased further development. Novel agents with novel mechanisms of action are needed for further development of the field. Recently, third-generation TKIs and immunotherapies entered the arena and opened a completely

Table 6 Summary of targeted agents and their indication

Agent	Approval	Approved for
Bevacizumab	2004 (FDA), 2005 (EMA)	First line in combination with cytokines
Sorafenib	2005 (FDA), 2006 (EMA)	After cytokine failure
Sunitinib	2006 (FDA, EMA)	Every line of therapy
Temsirolimus	2007 (FDA, EMA)	First line only in poor-prognosis patients
Everolimus	2009 (FDA, EMA)	After VEGF-targeted therapy failure
Pazopanib	2009 (FDA), 2010 (EMA)	First line or after cytokine failure
Axitinib	2012 (FDA, EMA)	Second line after sunitinib or cytokine failure
Cabozantinib	2016 (FDA, EMA)	After anti-angiogenic therapy failure
Lenvatinib	2016 (FDA, EMA)	In combination with everolimus after one prior anti-angiogenic therapy

FDA Food and Drug Administration, *EMA* European Medicines Agency, *VEGF* vascular endothelial growth factor

new avenue of drug development in mRCC. Long-term survivorship is expected with the implementation of these novel measures, and novel strategies incorporate combinations of targeted agents and/or immunotherapies. Today, this is the starting point of a completely new era of mRCC treatment, which offers plenty of opportunities but also risks.

Today, we sequence the currently available agents, but the optimal sequence is not determined. Probably, because too many individual factors do play a role in the choice of therapy, so that the best sequence is an oversimplification of the clinical reality and patient's needs. Performance status, clinician's experiences, as well as histological subtypes, staging and individual risk scoring, patient's expectation on activity, and tolerability are points to consider when making the choice for a specific treatment. Comorbidities may also influence the choice of drug and the risk undertaken during therapy.

Asymptomatic patients or those with low tumor burden and good/intermediate prognosis can pass through a period of watchful waiting until definite progression. Lack of local therapeutic options and/or patient's wish may also determine start of systemic treatment.

Study results underline the fact that tyrosine kinase inhibitors can be used in sequence with proven efficacy or even survival benefit. In summary, after treatment failure (progressive disease) the sequential use of targeted agents should always be conducted.

Treatment should be conducted until definite progression in principle (measured in 6–12 weekly CT scans) or intolerance under adequate supportive care. In case of intolerance, we do prefer watchful waiting until objective or clinical progression over an immediate switch to another line of therapy. However, intermittent therapy is associated with its own risk of progression and should be discussed with the patient frankly.

Combination therapies should only be conducted within clinical trials, except the combinations of lenvatinib and everolimus or bevacizumab and interferon.

Of note, the clinical response to targeted agents remained 6–12 months throughout all studies. It still remains unclear whether the major effect of mTOR and TKI is direct inhibition of the tumor cell or rather of the surrounding endothelial and stromal cells. As in other tumor entities treated with targeted drugs, RCC is thought to adapt to the suppression of the VEGF pathway and/or direct tumoricidal effects of these agents.

Thus, combinations of immunotherapeutics and/or targeted agents might indeed be an innovative way to derive long-term tumor control and suppress tumor growth with the combined force of several mechanisms of action standing up against the various pathways a tumor cell might use to escape antitumor activity.

Despite these major advances during the past decade, the next one offers more aggressive and radical treatment, which hopefully leads to a better survival of mRCC patients or even possible cure.

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Metastatic Surgery in Advanced Renal Cell Carcinoma

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Contents

Abstract

Management of patients with advanced and metastatic renal cell carcinoma is a challenging task, which often demands a multidisciplinary approach. In the cytokine immunotherapy era, cytoreductive nephrectomy in combination with immunotherapy was shown to be superior to immunotherapy alone, thus making cytoreductive nephrectomy a cornerstone of treatment. In the more recent era of targeted molecular therapies, cytoreductive nephrectomy seems to still retain its role in management of these patients despite lack of level 1 evidence so far. However, proper patient

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selection has been shown to be of utmost importance to assure benefit from this surgical endeavor. Prospective trials aiming to inform the field regarding efficacy as well as timing of cytoreductive nephrectomy in the targeted therapy era are underway and eagerly awaited, despite encountering challenges during study enrollment. Additionally, the recent introduction of checkpoint inhibitors once again targeting the immune axis is changing treatment landscape and challenging the benefit of cytoreductive nephrectomy. Metastasectomy on the other hand is currently being utilized for patients with relatively indolent oligometastatic disease. Despite lack of level 1 evidence, available evidence supports long-term remission with metastasectomy for some patients. This chapter aims to summarize the currently available evidence for cytoreductive nephrectomy as well as metastasectomy and give an outlook into the future with regard to new developments in this arena.

Introduction

The worldwide incidence of renal cell carcinoma (RCC) diagnosis varies depending on region, ranging from approximately 1/100,000 in Africa to greater than 15/100,000 in Northern and Eastern Europe and among African-Americans in the United States (Znaor et al. 2015). There are approximately 340,000 new cases of kidney cancers worldwide, with the vast majority (>90%) comprising of RCC (Ferlay et al. 2014). The most common histologies are clear cell (70%), papillary (10–15%), and chromophobe RCC (5%) (Ebele et al. 2004).

Established risk factors for RCC include age, cigarette smoking, obesity, occupational exposure to trichlorethylene, and end-stage renal disease (Guha et al. 2012; Hunt et al. 2005; Renehan et al. 2008; Vajdic et al. 2006; Znaor et al. 2015). Additionally, recent reports indicate a dose–response relationship between risk of RCC and declining renal function, beyond just patients who are dialysis dependent (Lowrance et al. 2014).

While the incidence of RCC diagnosis has been increasing in most countries, particularly in the western world, mortality trends have been relatively stable and even slightly decreasing in Western and Northern Europe (Znaor et al. 2015). Historically, RCC was diagnosed clinically by the triad of flank pain, hematuria, and a palpable mass, findings that indicate advanced stages of disease (Cohen and McGovern 2005). This pattern has changed due to modern cross-sectional imaging, which has resulted in the incidental detection of earlier stage renal masses and downward stage migration of RCC. As of 2004, 57% of RCC was stage I (localized), 14% were stage III (regional lymph node involvement), and approximately 18% were stage IV (distant metastases) at diagnosis (Kane et al. 2008). For the approximately 70% of patients with localized disease, nephrectomy is usually curative; however patients with stage II or III disease have a 30–40% risk of relapse (Janowitz et al. 2013; Zhang 2017). The main recognized drivers for relapse are pathological stage and histologic grade of the tumor; however, the risk of relapse can be individualized using validated prediction models such as the University of California Los Angeles Integrated Staging System (UISS), the "stage, size, grade, and necrosis" (SSIGN) score, or the Karakiewicz nomogram (Karakiewicz et al. 2007; Leibovich et al. 2003; Patard et al. 2004; Zisman et al. 2001).

When RCC is no longer localized, the prognosis is poor with 5-year survival rates at 53% for stage III disease, further decreasing to 8% for stage IV disease (Choueiri and Motzer 2017). Historically systemic treatments for metastatic RCC have been limited due to "chemoresistance" of the tumor, although treatment options have expanded significantly over the past 15 years. Prior to 2005, systemic therapy was limited to immunotherapy in the form of interferon-α (IFN-α) and interleukin-2 (IL-2). These treatments provided minimal chance of improvement in clinical outcomes; high-dose IL-2 is associated with a rare (~5%) complete response rate but chance of long-term durable response (Fyfe et al. 1995). In 2005, the US Food and Drug Administration (FDA) approved sorafenib, followed closely by the approval of sunitinib, based on

improved progression-free survival compared to IFN-α (Escudier et al. 2007; Motzer et al. 2007). This ushered in the era of "targeted therapy," and over the past decade, numerous other anti-angiogenic drugs have been approved including pazopanib, axitinib, bevacizumab, cabozantinib, and lenvatinib (in combination with everolimus). Additionally, another class of systemic therapy – the mammalian target of rapamycin (mTOR) inhibitors – was approved after trials demonstrating improved clinical outcomes with temsirolimus and everolimus (Hudes et al. 2007; Motzer et al. 2008). While these targeted therapies had significantly improved tolerability profiles and response rates compared to traditional immunotherapy, the data supporting their regulatory approvals demonstrated only limited overall survival benefit, and all patients would eventually become refractory to these medications and succumb to their disease. A resurgence of interest in immunotherapy for cancer led to the development of novel immune checkpoint inhibitors – of particular interest are those targeting the programmed cell death 1 (PD-1) receptor or its ligand (PD-L1). Nivolumab, a PD-1 inhibitor, was compared to everolimus in the second-line setting in RCC and demonstrated an improved tolerability profile as well as a survival benefit. Most strikingly, the response rates could be long-lasting, a finding that gives great hope to patients otherwise faced with a dismal prognosis (Motzer et al. 2015). Just like in the proliferation of targeted therapy, we will undoubtedly see the proliferation of more immune checkpoint inhibitors, both for the PD-1/PD-L1 axis and novel targets in development that will further complicate matters for urologists and oncologists, but bring much needed hope to patients.

Thus, in the third era of systemic therapy for RCC, a persistent question has been the role of local therapy in the nonlocalized setting. Spurred by the lack of effective systemic therapies and apocryphal cases of spontaneous regression of metastatic disease after the removal of the primary renal tumor, urologists have been evaluating the role of surgery for metastatic RCC for decades. Many attempts have been made to definitively answer this question, including two randomized trials during the initial immunotherapy era, two ongoing trials in the targeted therapy era, and numerous retrospective analyses. But as systemic treatment options have evolved, so too must our analysis of the role of surgery in this scenario. In this chapter, we aim to bring historical context and clinical evidence and offer opinions on the rational use of cytoreductive nephrectomy (CN) and metastasectomy in metastatic RCC (mRCC).

Cytoreductive Nephrectomy

The cornerstone of treatment in kidney cancer has always been surgical. For decades, it has been known that conventional chemotherapy is not effective for RCC, while radiotherapy is not effective when applied to the primary tumor (Yagoda et al. 1993). For this reason, the primary treatment of localized kidney cancer is extirpative surgery, including partial nephrectomy whenever possible, with ablative techniques and active surveillance being further options for small renal masses. Perioperative therapies are not routinely used, and recent studies have not shown any survival benefit of adjuvant targeted therapy, despite one study showing a slight improvement in progression-free survival (Haas et al. 2015; Ravaud et al. 2016). On the contrary, management of mRCC is quite challenging with the need for a multidisciplinary approach. As these patients are mostly non-curable, historically, CN (referring to the surgical removal of the renal primary) had a place in the management of mRCC for prevention or treatment of local complications. In addition, the primary tumor has the potential to be a source of further metastatic spread. However, there are a multitude of conceptual advantages and disadvantages to consider with performance of CN, which might influence decision-making (Table 1).

Evidence of Cytoreductive Nephrectomy in the Pre-targeted Molecular Therapy (TMT) Era

The perceived benefit of CN for mRCC aside from treatment or prevention of local complications is

Table 1 Conceptual advantages and disadvantages of cytoreductive nephrectomy

Advantages	Disadvantages
Reduction of large and potentially immunosuppressive tumor burden	Risk of perioperative mortality and morbidity
Prevention or palliation of local symptoms such as discomfort, hematuria	Delay of systemic treatment
Improvement of tolerance of systemic therapy by improved performance status and cachexia	Negative effect on quality of life, time spent recovering from surgery in patients with limited life expectancy
Reduction of paraneoplastic syndromes such as anemia, anorexia, weight loss, fever, hypertension, and hypercalcemia	

due to the rare phenomenon of spontaneous regression of mRCC metastases (mostly lung), which occurs in 1–5% of the patients. Despite evidence being scarce and the literature being generally informed by case reports without histologic confirmation of the metastatic sites, these observations gave birth to the concept of immunogenicity of mRCC with the tumor playing an immune-suppressive role (Lokich 1997; Walther et al. 1993). It should be mentioned that spontaneous regression is not a phenomenon reported in mRCC exclusively but is encountered in other cancer types such as embryonal carcinomas, breast cancer, neuroblastoma, as well as melanoma (Kucerova and Cervinkova 2016). Furthermore, it is not solely observed after surgical removal of the primary tumor but can be seen under surveillance as well. In a study of 73 patients with measurable metastatic disease, three and two patients had complete and partial spontaneous regressions without any therapy, and four further patients had prolonged stable disease for more than 12 months (Oliver et al. 1989). Accordingly, spontaneous regression of mRCC is generally attributed to the immunogenic properties of the tumor and overall is uncommon to observe; however, if present, the regression is often durable. These observations and thoughts of immunogenic potential, as well as lack of efficacy of conventional therapies, lead to immunotherapies being investigated for mRCC, especially IFN-α, IL-2, as well as combinations. IFN-α was one of the first drugs available for systemic treatment of mRCC, after demonstrating some efficacy in retrospective studies in combination with CN. In addition, two subsequent randomized controlled trials published in 2001 revealed a better survival in patients undergoing CN before the initiation of IFN-α compared to receipt of IFN-α alone, making CN a standard of care in mRCC management.

CN and IFN-α

The first study (SWOG-8949) randomized 246 patients to immediate CN followed by therapy with IFN-α or immediate IFN-α therapy without surgery, and the primary endpoint of overall survival (OS) was met (11.1 months for CN plus IFN-α vs. 8.1 months for IFN-α alone ($p = 0.05$)) (Flanigan et al. 2001). It is worth mentioning that the survival advantage with CN was independent of performance status, location of metastatic site, and the presence or absence of a measurable metastatic lesion. Similarly, the second study (EORTC 30947, $n = 78$) found an increased time to progression (5 months vs. 3 months, HR 0.60, 95% CI 0.36–0.97) and better OS (17 months vs. 7 months, HR 0.54, 95% CI 0.31–0.94) in patients with combined treatment as well (Mickisch et al. 2001). As the study protocols and inclusion criteria were identical (biopsy-proven mRCC without brain metastases, ECOG 0–1 as well deemed fit for surgery), a combined analysis was performed for increased statistical power. This combined analysis, including a total of 324 patients evaluable for analysis, revealed a median survival of 13.6 months for CN plus IFN-α vs. 7.8 months for IFN-α alone, which accounts for a 31% decrease in the risk of death ($p = 0.002$). One-year survival was 51.9% for the CN arm vs. 37.1% for the IFN-α-only arm, whereas objective response rate was 6.9% for the combination vs. 5.7% ($p = 0.60$) for IFN-α alone (Flanigan et al. 2004).

In addition to the survival advantage, these studies also clarified other issues. First of all, they demonstrated low morbidity of CN in the metastatic setting within their selection of good surgical candidates by only including patients with ECOG 0–1. In both studies, surgery was performed in a standardized fashion using a transabdominal, flank, or thoracoabdominal approach with early ligation of renal vein and artery. Despite including patients with venous involvement, SWOG-8949 reported only 1% perioperative deaths and severe complications in 4.9% patients. Meanwhile, EORTC-30397 reported no postoperative deaths but 14.2% high-grade perioperative complications. Still, only few patients (5.6%) were not able to receive IFN-α after CN due to decline in performance status. Furthermore, despite including large tumors (median diameter 11.5 cm), side effects of IFN-α such as myelotoxicity, nausea, anorexia, and neurological and psychological disorders were equally distributed between the treatment groups. However, dose reduction was necessary in 44% of patients after CN, while only in 22% of those receiving IFN-α alone.

Secondly, SWOG-8949 reported on predictors of survival in addition to performance status revealing that low disease burden and site of metastases are independently important for survival (presence of lung metastases only HR 0.73, $p = 0.028$), indicating that risk stratification influences survival estimates. Furthermore, it was shown that patients who progressed rapidly (within 3 months of CN) did not benefit of surgery and had the same overall survival as the patients without CN, highlighting again the importance of appropriate patient selection. Lastly, both studies showed that progression of metastases was delayed approximately 2 months in the CN arm, supporting the theory of the importance of CN for better immunological balance by removing an immune-suppressing primary, especially as the effect of immunotherapy on the primary tumor is modest (Lara et al. 2009).

CN and IL-2

The available evidence for CN before IL-2 therapy is less extensive than for IFN-α therapy because of two reasons. First and foremost, significant toxicity of high-dose (HD) IL-2 limits its application to highly selected patients, which poses problems for recruitment goals into a randomized controlled trial. Walther et al. calculated the number of patients needed to determine the efficacy of CN before IL-2 with 80% power of detecting a difference is 480 (10% IL-2 response rate)–1420 (20% IL-2 response rate) at a $p = 0.05$ level (Walther et al. 1997). Secondly, since IFN-α and IL-2 use the same immunobiological mechanisms to fight tumor cells, the gain of insight from a controlled randomized trial seems limited. Therefore, only a few studies addressed the use of CN prior to systemic IL-2 treatment, however demonstrating higher objective response rates with increasing doses of IL-2 than with IFN-α (5.6–23.2% vs. 5.7% in the combined IFN-α trial) (Alva et al. 2016; Fyfe et al. 1995; McDermott et al. 2005; Negrier et al. 1998, 2007; Walther et al. 1997; Yang et al. 2003). In one of these, Pantuck et al. identified 89 patients treated with IL-2-based regimens after undergoing CN who met the eligibility criteria for the SWOG-8949 (Pantuck et al. 2001). A total of 120 patients from the SWOG-8949 were included, and the median OS of the patients treated with CN and IL-2 was 16.2 months, which was found to be twice as long as the IFN-α-only group and 5 months longer than the combination group of SWOG-8949 ($p < 0.05$) (Flanigan et al. 2004; Pantuck et al. 2001). Furthermore, Wagner et al. reported 6% (3/51 patients) achieving complete or partial response after IL-2 without CN, whereas Walther et al. found complete or partial response in 18% (19/107 patients) for IL-2 with CN, indicating the additive benefit of CN to immunotherapy (Wagner et al. 1999; Walther et al. 1997). Therefore, in highly selected mRCC patients who choose to be treated with IL-2, CN should be considered as part of the multidisciplinary approach. However, it is worth mentioning that higher doses of IL-2 therapy did not significantly prolong median overall survival time while placing the patient to a risk of grade 3 or 4 adverse event in up to 62.1% and mortality in up to 4%, which led to the conclusion that lower-dose IL-2 was adequate for treatment (Fyfe et al. 1995; Hanzly et al. 2014; Negrier et al. 2007; Yang et al. 2003).

Evidence of Cytoreductive Nephrectomy in the Targeted Molecular Therapy Era

Systemic therapy of kidney cancer has changed profoundly after introduction of the first tyrosine-kinase (TKI) inhibitors. As a result, conventional immunotherapies were less frequently used for the treatment of metastatic disease because of their inferior response rates as well as their unfavorable side effect profile when compared to targeted molecular therapies (TMT). It is known that TMT such as sunitinib (which was tested against IFN-α) offers higher treatment response rates (47% vs. 12%), longer progression-free survival (11 months vs. 5 months), and better OS (26.4 months vs. 21.8 months) (Motzer et al. 2007). A SEER registry investigation underscored this finding in an unselected population and showed that the median survival of patients with CN increased in the TMT era to 19 months, whereas it was 13 months in the immunotherapy era (Conti et al. 2014).

Still, the rapid developments and approval of multiple agents with improved efficacy as opposed to previous immunotherapy had important impact on utilization of CN in the TMT era. Tsao et al. reported that the use of CN remained stable between 2001 and 2005 at 50% per year, while it decreased to 38% in 2008 (Tsao et al. 2013). Meanwhile, Psutka et al. identified patients from a private insurance company database who underwent CN between the years of 2004 and 2010 and found that CN use decreased even further from 31.3% in 2005 to only 14.8% in 2010 (Psutka et al. 2015). These trends possibly reflect the belief that CN is not necessary in the TMT era and more diverse systemic treatment options as well as improved patient selection due to better risk stratification tools. Patients undergoing CN in the TMT era were more likely to be younger, male, and married and had larger tumors, highlighting the development with regard to patient selection (Conti et al. 2014). However, racial disparities were also noted with African-Americans and Hispanics being 18% and 14% less likely to undergo CN than Caucasians (Tsao et al. 2013).

Benefit of CN with TMT

To date, there are no RCTs informing about the benefit and timing of CN in the TMT era. In order to overcome this deficiency, the "Clinical Trial to Assess the Importance of Nephrectomy" (CARMENA: NCT0093033) and the "Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer" (SURTIME: NCT01099423) are currently ongoing (Hirano et al. 2012; Williams et al. 2013). In CARMENA, patients are randomized to CN followed by sunitinib vs. sunitinib alone until disease progression to inform about the benefit of CN in this patient population, whereas SURTIME was designed to address the question of timing of CN by randomizing patients to sunitinib followed by CN vs. CN followed by sunitinib.

Notwithstanding, both studies faced significant accrual problems, and SURTIME study closed early in 2016 now probably underpowered to inform about the predefined endpoints (PFS and OS) (Stewart et al. 2016). Meanwhile CARMENA is likely to complete recruitment in late 2017 (almost 6 years later than originally planned), however probably only able to draw conclusions with regard to "equivalence" but not "significant difference" as more patients would have had to be included for the latter conclusion (Stewart et al. 2016).

Surgical RCTs in general pose special problems for recruitment including but not limited to patients not wanting to be randomized; lack of clinical equipoise from patients, physicians, as well as physicians across specialties; and, last but not least, unwillingness to randomize patients due to surgeon/oncologist bias (Stewart et al. 2016). Future trial designs for surgical RCTs might be enhanced by conducting initial pilot of feasibility studies, considering other clinical personnel to provide information in a less biased manner than involved providers, and insurance of a clear reward process (Stewart et al. 2016).

In lack of prospective data, multiple retrospective analyses as well as meta-analyses have been conducted to assess the benefit of CN in the TMT era, generally showing benefit for CN; however one has to keep in mind the inherent selection bias

of such approaches. Available evidence is summarized in Table 2. A recent meta-analysis by Petrelli et al. included 11 retrospective publications with available data regarding OS and reported a reduced risk of death of CN with TMT compared with those treated with TMT alone (HR 0.46; 95% CI 0.32–0.64, $p < 0.01$; $I^2 = 95\%$, median follow-up 39 months); however there was significant heterogeneity between the studies (Petrelli et al. 2016). In one of the largest series published so far, Hanna et al. reported the outcomes of 15,390 patients out of the National Cancer Database (NCDB), who received TMT for mRCC between 2006 and 2013, out of which 5374 initially underwent CN (Hanna et al. 2016). The authors found that median OS of patients with and without CN was 17.1 months (95% CI 16.3–18.0 months) vs. 7.7 months (95% CI 7.4–7.9 months; $p < 0.01$), respectively. The 1-, 2-, and 3-year OS rates were 62.7, 39.1, and 27.1% vs. 34.7, 17.1, and 9.8% for patients with and without CN. In this study, statistically significant patient predispositions in favor of receipt of CN were younger age, private insurance, treatment at academic centers, and lower T stage as well as clinical lymph node-negative disease, highlighting the inherent selection bias of the retrospective approach to this question as patients receiving CN are more likely to harbor favorable patient as well as tumor characteristics. As an example, in the study by Heng et al., comparing 982 patients with CN and TMT vs. 676 patients with TMT alone, patients with poor-risk disease comprised only 28% of those treated with CN vs. 54% of the group without CN, clearly attributing to different outcomes of both groups

Table 2 Retrospective studies comparing patients with and without CN and treated with TMT (Adapted from Bex and colleagues (2016))

Study Setting Study period	Total no. of patients	Patients with CN	Patients without CN	Median follow-up (months)	Median OS with CN (months)	Median OS without CN (months)	Statistically significant factors favoring receipt of CN
Choueiri et al. (2011) Multi-institutional 2004–2008	314	201	113	NR	19.8	9.4	Younger age Better KPS One metastatic site Less calcium
Conti et al. (2014) SEER 1993–2010	20,104	6915	13,189	NR	19	4	Younger age Male White Single
Heng et al. (2014) IMDC 2005–2013	1658	982	676	39.1	20.6	9.6	Better IMDC risk Less non-clear RCC Fewer bone metastasis Fewer liver metastasis
Bamias et al. (2014) Multi-institutional 2006–2011	186	150	36	34	23.9	9.0	Younger age Better PS Less neutrophilia Lower LDH Previous cytokines
Abern et al. (2014) SEER 2005–2009	2382[a]	1521	861	13	20[b]	6[b]	Younger age Male White Single

(*continued*)

Table 2 (continued)

Study Setting Study period	Total no. of patients	Patients with CN	Patients without CN	Median follow-up (months)	Median OS with CN (months)	Median OS without CN (months)	Statistically significant factors favoring receipt of CN
Aizer et al. (2014) SEER, non-clear cell 2000–2009	591	377	214	NR	14	6	Younger age Male White Single Westcoast location
Mathieu et al. (2015) Multi-institutional 1999–2009	351	298	53	NR	38.1	16.4	Better MSKCC risk Better ECOG score
de Groot et al. (2016) Population-based registry[c], propensity score matching 2008–2010	227	74	151	NR	17.9	8.8	T stage <T3/T4 One metastatic site Fewer bone metastasis
Hanna et al. (2016) National Cancer Database 2006–2013	15,390	5374	10,016	NR	17.1	7.7	Younger age Privately insured Academic center Lower T stage cN0

CN cytoreductive nephrectomy, *ECOG* Eastern Cooperative Oncology Group, *IMDC* International metastatic Renal Cell Carcinoma Database Consortium, *KPS* Karnofsky performance status, *LDH* lactate dehydrogenase, *MSKCC* Memorial Sloan Kettering Cancer Center, *NR* not reported, *OS* overall survival, *PS* performance status, *RCC* renal cell carcinoma, *SEER* Surveillance, Epidemiology, and End Results Registry

[a]T3 subset of a total of 7143 patients

[b]Estimated from Kaplan–Meier analyses

[c]Only patients receiving sunitinib in the first-line treatment

(Heng et al. 2014). Furthermore, a known shortcoming of the NCBD data is that there is no information about further lines of treatment, such that it is unknown if the survival effect is merely attributable to CN alone, the selection bias toward CN, or also the number and duration of subsequent lines of therapy. Overall, median-reported OS derived from retrospective series ranges between 14 and 38 months in patients with CN; whereas median OS is between 4 and 16 months in patients without CN (Table 1). However, CN seems to also affect time to treatment failure (TTF) and overall response rate (ORR) to TMT, advocating for a benefit beyond tumor mass reduction. ORR and TFF of patients with CN and TMT was 26.3% and 8.1 months vs. 11.5% and 5.5 months for those who did not undergo CN (Choueiri et al. 2011).

Active Surveillance After CN

Generally, TMT is given soon after convalescence from CN. However, in patients with low-volume disease, which is still deemed unresectable, surveillance after CN might also be an option. Recently, Rini et al. used initial active surveillance (AS) in 48 evaluable mRCC patients to identify which patients might benefit from AS in this setting (98% of patients had undergone prior nephrectomy) (Rini et al. 2016). The authors reported median time on surveillance as 14.9 months and identified high IMDC risk group as well as higher number of metastatic sites as significant factors associated with progression and therefore shorter surveillance period. Meanwhile, the authors defined a favorable group for AS as 0–1 IMDC risk factors and ≤ 2 organs involved by metastatic disease. Estimated

median survival time was 22.2 months (95% CI 13.8–33.3 months) for patients in the favorable for AS group, while it was 8.4 months (3.2–14.1 months; $p = 0.0056$) in the remainder of patients (unfavorable group). Similarly in 28 patients with initially metastatic disease undergoing CN followed by AS, the median time to targeted therapy and OS was 14 months (3–43 months) and 21.5 months (4–75 months), respectively (Bex et al. 2016). Despite active surveillance in metastatic disease seems to be an option, studies with extended number of patients are needed to clarify these preliminary outcomes, especially since the OS estimates in the CN and AS population seem to be rather short in light of current advances in the field.

Surgical Considerations for CN

There is current evidence, suggesting that performance of lymphadenectomy (LND) at the time of CN is not associated with superior oncologic outcomes, despite possible removal of further tumor volume. In a study by Gershman et al. including 305 patients, out of whom 62% underwent LND with 24% of those patients showing pathologically positive nodes, the survival after a median follow-up of 8.5 years was not significantly impacted by performance of LND (Gershman et al. 2017). However, there might still be some value of LND in some select patients. For example, in patients who have oligometastatic disease, possibly amenable for downstream metastasectomy and therefore an unlikely but possible chance on cure of disease, performing a LND during CN might be beneficial to avoid local progression and necessity for further surgical interventions; however there are no data with regard to this specific situation.

With regard to surgical approach, there is data that CN can be safely performed with a minimally invasive (laparoscopic/robotic-assisted) approach in select patients, without excess surgical complications or sacrifice of oncological principles (Nunez Bragayrac et al. 2016). During surgical planning and decision-making toward the surgical approach to CN, specific factors should be weighed carefully, including tumor size, presence of parasitizing vessels or tumor thrombus, lymphadenopathy, as well as presence of tissue planes between the kidney and surrounding organs as well as possible tumor invasion of the latter. During the surgery, one should be prepared to convert to open surgery quickly, as it is necessary in a certain number of cases even in expert hands (around 5%), due to intraoperative bleeding or unforeseeable technical difficulties (Nunez Bragayrac et al. 2016).

CN might be beneficial for prevention or palliation of local as well as systemic symptoms like hematuria, pain, anemia, as well as tumor-associated cachexia. Further, paraneoplastic syndromes are identified in less than 5% of patients with RCC including hypercalcemia, polycythemia, hepatic dysfunction, amyloidosis, fever, and weight loss, which are generally associated with adverse pathologic features and more advanced disease (Motzer et al. 1996). For localized disease, paraneoplastic syndromes are generally resolved after radical nephrectomy. This situation is rather complicated in patients with metastatic disease, where improvement of paraneoplastic symptoms is not necessarily driven by the primary tumor alone (Walther et al. 1997).

Decision-Making Toward or Against CN

Decision-making toward or against CN is complex and includes issues such as disease burden, patient factors, as well as prognostic factors to estimate the natural course of disease in order to make beneficial decisions and avoid harm. Tumor volume doubling time is estimated to be slow in patients with small renal masses or organ-confined RCC (around 70 weeks); however, rapidly growing RCCs are known as well (Lee et al. 2008). Growth kinetics are very heterogeneous, even in patients with mRCC, where some show stable lesions for months without any treatment, whereas others show fast progression despite systemic treatment efforts. The SWOG-8949 and EORTC-30947 trials demonstrated that it is not beneficial but possibly harmful, as it may cause further deterioration of performance status precluding patients from receiving systemic treatment without the benefits of tumor volume

reduction. Therefore an attempt of inductive TMT in patients deemed to be at high risk of progression and death of mRCC might serve as a litmus test to further determine if CN might be beneficial in the long run. However, the challenge remains to risk-stratify patients accordingly and select the patients most likely to benefit from CN vs. the patients most likely to not benefit from CN.

Evidence from the pre-TMT era revealed that patients with metastatic disease to only one organ system had significantly better survival than patients with multiple organ systems involved. Han et al. reported that the median OS was 31 months vs. 13 months for mRCC patients who underwent CN followed by immunotherapy with metastatic sites in the lung or bone only vs. multiple organ systems (Han et al. 2003). Meanwhile, the response rates to immunotherapy after CN differed with 44%, 20%, and 14% in the lung, bone, and multiple organ sites, respectively. This leads further into the concept of "percentage of tumor volume removable by CN." In the immunotherapy era, Fallick et al. found a threshold of >75% "fractional percentage of tumor volume removed" (FPTV) to be beneficial toward outcomes, while more recent reports support a threshold of >90% to consider CN potentially beneficial (Barbastefano et al. 2010; Fallick et al. 1997; Pierorazio et al. 2007). This is in line with the finding that each additional centimeter of tumor burden removed is associated with improved survival (Iacovelli et al. 2012).

Patient Factors Influencing Benefit from CN

Besides tumor- and disease-specific factors, patient-specific factors like age and comorbidities are very important to consider during decision-making for CN. Reports indicate that likelihood for receipt of CN declines by 30% for every 10-year increase in age (Conti et al. 2014). In a multivariable logistic regression model for prediction of receipt of CN, Tsao et al. reported that patients 60–69, 70–79, and 80 years and older were significantly less likely (OR = 0.68, 0.45, 0.18) to undergo CN than their younger counterparts (Tsao et al. 2013). This study also revealed that patients with a Charlson comorbidity index (CCI) ≥2 were also less likely (OR = 0.74; $p < 0.01$) to undergo CN. This is due to the higher likelihood of complications and perioperative morbidity in the elderly with up to 20% vs. 1.1% mortality rate of mRCC patients over 75 years vs. less than 75 years old, when matched for performance status and tumor characteristics (Kader et al. 2007).

The Eastern Cooperative Oncology Group Performance Status (ECOG PS) is an established tool to assess overall functional status of patients and was, unsurprisingly, found to be an independent predictor of OS for patients with mRCC in many studies using multivariable analyses models (Flanigan et al. 2001). It is often used as an inclusion criterion as well as stratification tool in clinical trials, most often biasing the investigated cohorts toward better outcomes than a real-world population as more favorable patients are selected by default (ECOG 0–1). Despite this, performance status (PS), measured with various tools, is one of the main criteria used to determine possible benefit of CN for mRCC patients. Data indicate that patients with good PS (Karnofsky PS 80% or greater) had a median overall survival of 23.9 months with CN and TMT, while it was only 14.5 months for those who did not receive CN ($p < 0.01$) (Choueiri et al. 2011). However, patients with lower PS of less than 80% only experienced a marginal survival benefit (10.1 months vs. 6 months, $p = 0.08$), highlighting once again the importance of patient selection for CN before TMT. On the other hand, Shuch et al. reported that patients who had an ECOG PS 2/3 with non-debilitating bone metastasis demonstrated a similar survival to that of patients with an ECOG PS of 1 (17.7 months vs. 13.8 months, $p = 0.46$) (Shuch et al. 2008). The authors therefore proposed grouping patients in ECOG PS 2/3a (visceral disease) and b (bone involvement) and suggested to use palliative measures for ECOG PS 2/3a disease while considering CN for patients with ECOG PS 2/3b, pointing out the need for specific markers and risk stratification tools to determine usefulness of CN in patients with mRCC. Meanwhile, the survival of patients with debilitating (non-weight bearing) bone metastasis is as low as 2.1 months such that these patients should be treated with palliative measures only.

Histological Factors Influencing Benefit from CN

As it is known that patients with non-clear histology such as papillary RCC (pRCC) or sarcomatoid differentiation do not respond as well to the available medications, they receive TMT less often than their clear cell RCC (ccRCC) counterparts (Smaldone et al. 2015). Therefore, the question of benefit of CN in this subgroup of patients is valid, as it might influence decision for surgical debulking. Aizer et al. by using SEER database reported that patients with non-ccRCC histology who underwent CN had significantly lower 2-year disease-specific survival estimates than patients with ccRCC (59.2% (95% CI 53.1–64.8%) vs. 74.2% (95% CI 66.4–80.4%)), highlighting the difference in efficacy of TMT (Aizer et al. 2014). Meanwhile, patients who underwent CN for non-RCC histology had still higher estimates of OS compared to patients who did not (14 months vs. 6 months, $p < 0.001$); however the inherent biases of these analyses have to be recognized. In detail, in all histologies except medullary/collecting duct carcinoma, the use of CN was associated with lower estimates of RCC-specific mortality, even though possibly less pronounced than for ccRCC in certain subgroups (papRCC) and more in others (chromophobe RCC (chrRCC)) indicating a more aggressive vs. benign natural history of disease in comparison to ccRCC (Smaldone et al. 2015). Of note, sarcomatoid histology was excluded from some of these studies and is known as one of the most important adverse histological features (Sanli et al. 2010). You et al. reported that patients with sarcomatoid histology yielded a 2.9-fold risk of disease progression and 2.7-fold increased overall risk of death than those without sarcomatoid differentiation in a group of patients treated with or without CN (You et al. 2011). Similarly, Shuch et al. reported that median OS of patients with sarcomatoid differentiation was 4.9 months vs. 17.7 months for patients without sarcomatoid features (Shuch et al. 2008). Overall, addition of CN may have value in patients with non-ccRCC histology, and histology alone should not preclude a patient form undergoing CN.

Risk Stratification Tools

It is logical that comprehensive risk stratification tools should be of greater utility in outcome prediction, compared to individual factors. Historically, the MSKCC risk classification model and its modified version, including a total of five clinical (Karnofsky PS <80%), time from initial diagnosis to treatment (replaced absence of prior nephrectomy from the initial model), and laboratory variables (lactate dehydrogenase >1.5 than the upper limit of normal (ULN), hemoglobin <lower limit of normal (LLN), and corrected serum calcium >10 mg/dl), were used to risk-stratify patients into three risk groups, which correlated well with survival estimates (Motzer et al. 1999, 2002).

However, these risk classification systems were created from data in the immunotherapy era, and therefore the extrapolation of these tools for TMT therapy was questionable. In a multi-institutional and multinational effort (IDMC group), Heng et al. retrospectively identified independent prognostic factors including 645 patients from three US and four Canadian centers treated with TMT (Heng et al. 2009). The authors identified four of five variables of the MSKCC risk classification model (hemoglobin <LLN, corrected calcium >ULN, Karnofsky PS <80%, and time from diagnosis to treatment less than 1 year) as being independent predictors of outcomes for this patient population as well. Further, they identified neutrophils >ULN and platelets >ULN to complete the IMDC risk model. The authors reported that the estimated 2-year OS for the favorable-risk group (no risk factors), intermediate-risk group (one to two risk factors), and poor-risk group (three to six risk factors) was 75%, 53%, and 7%, respectively. Further external validation of these criteria with 849 patients revealed good discrimination of risk groups with these variables and revealed OS estimates of 43.2, 22.5, and 7.5 months in these three risk categories with a concordance index of 0.71 (95% CI 069–0.73) (Heng et al. 2013). Today, the IMDC model is widely used to stratify patients in clinical trials, and regarding the short survival time in the poor-risk patients, poor-risk status might be an indication for a limited benefit of CN (Li et al. 2015). However, these criteria were established in a largely nephrectomized population, which might

limit its applicability to estimate benefit of CN, and further, some of the risk factors might even be modifiable by CN therefore possibly changing the individual patient risk group stratification.

In an attempt to possibly address the shortcomings of the development cohort of the IDMC criteria, Culp et al. set out to develop a sum score including seven preoperative clinical variables to identify patients who will not benefit from CN utilizing a retrospective cohort with 566 mRCC patients (Culp et al. 2010). The number of preoperative risk factors was correlated with the overall risk of death and was inversely proportional to the median OS of patients who underwent CN (Table 3). The authors concluded that patients who had ≥4 risk factors did not appear to benefit from CN.

Further, prognostic nomograms are other valuable tools for individualized patient management and are currently being used in many areas of urooncology. Recently, Margulis et al. developed a preoperative and postoperative nomogram for prognostication of cancer-specific survival at 6 and 12 months after CN using a cohort of 601 patients (Margulis et al. 2013). The preoperative nomogram included the parameters albumin and LDH, whereas the parameters included in the postoperative nomogram in addition to albumin and LDH were pathological tumor stage ≥pT3, pathological nodal stage, as well as receipt of a blood transfusion. Both nomograms demonstrated an acceptable discriminative accuracy of 0.76 and 0.74, therefore suggesting possible utility in selection of patients who might not benefit from CN.

Table 3 Variables as predictors of survival defined by Culp et al. (2010)

Serum albumin <LLN
Serum lactate dehydrogenase (LDH) level >UNL
Clinical tumor classification T3 or T4
Symptoms at presentation caused by a metastatic site (e.g., bone pain, neurologic symptoms, etc.)
Presence of liver metastasis
Radiographic evidence (≥1 cm) of retroperitoneal adenopathy
Radiographic evidence (≥1 cm) of supradiaphragmatic adenopathy

Timing of CN

Despite the gain of information with the previously mentioned stratification tools, the ability to predict the kinetics of disease progression is challenging. While some patients might have a more benign natural course of disease, it is not possible to predict this at first encounter. Therefore, some investigators have suggested utilization of systemic therapy initially as a litmus test to identify patients who will progress fast and therefore not benefit from CN. Bex et al. used the clinical response to immunotherapy in a small cohort of mRCC patients for making a better selection for CN (Bex et al. 2002). The authors suggested that patients who progressed under systemic treatment within 3 months should be spared from CN, whereas patients with stable disease or partial response should undergo CN, as the survival estimates for the latter patients exceed the estimates for the former by far (median OS 11.5 months vs. 3 months). Another study including 75 patients used primary tumor response (defined as ≥10% decrease within 60 days of treatment initiation) to TMT as a surrogate for estimating oncologic outcomes (Abel et al. 2011). Median OS for patients without minor primary tumor (PT) response, with minor PT response after 60 days, and with early PT response were found to be 10.3 months, 16.5 months, and 30.2 months, respectively. Additionally, there is recent evidence suggesting that presurgical TMT may be advantageous. In the study by Hanna et al., where 88.4 and 11.6% of patients received CN before and after the initiation of TMT, it was reported that the 1- and 3-year OS rates for patients undergoing CN before and after TMT were 61.2 and 26.6% vs. 73.3 and 35.3% ($p < 0.01$), respectively (Hanna et al. 2016).

Further, not only may TMT be used as a litmus test to estimate benefit from CN; it might also lead to some downstaging of the primary tumor to facilitate surgery; however that effect seems to be modest. In a recent systematic review, the percentage of median tumor diameter reduction as a response to presurgical TMT was between 9.6 and 28.3%; however the median absolute change in tumor diameter was only between 0.8 and 3.1 cm (Borregales et al. 2016). When evaluated by RESIST criteria, 0–46% of patients showed a

partial remission, while no patients showed complete remission (Borregales et al. 2016). There is no consensus about which agent is the most effective in this setting; however, the only prospective study to address this question utilized axitinib prior to nephron sparing surgery (Borregales et al. 2016).

Finally, the effect of TMT on tumor-associated thrombus seems to be modest. While around 45% of tumor thrombi show a decrease in height, 28% each show stability or some increase in height (Cost et al. 2011). Overall, only 12% had a clinically relevant change in tumor thrombus level, which only minimal impact on surgical management (Cost et al. 2011).

Advantages and Disadvantages of Presurgical TMT Versus Upfront CN

A possible downside of presurgical TMT is the concern for wound healing complications associated with manipulation of the VEGF axis. While there are not necessarily differences with regard to complications within the first 30 days after CN, an increased incidence of prolonged wound healing complications may be expected after presurgical TMT in up to 20% of patients, which can lead to a delay of further systemic therapy (Jonasch et al. 2009; Margulis et al. 2008). Preoperative withdrawal of these drugs should be balanced with regard to prevention of postoperative complications versus possible progression in the treatment-free interval. Currently, experts suggest to withhold TMT two to three half-lives before surgery, which is around 1–3 days for oral TKIs versus up to 4 weeks for bevacizumab (Margulis et al. 2008).

One advantage of TMT prior to surgery is immediate impact of systemic therapy on metastatic sites. Kutikov et al. reported that, of 141 patients who underwent CN, up to 30.5% did not receive systemic therapy due to rapid progression of disease (30% of non-receivers of TMT), patient refusal, and perioperative death or the decision toward initial postsurgical surveillance (Kutikov et al. 2010). Further data indicate that among patients for whom TMT is indicated after CN, 61% did not receive TMT within 60 days due to disease-related, surgery-related, and neither surgery- nor disease-related factors in 27.5%, 11% (5% Clavien grade $\geq$III), and 22%, respectively (Gershman et al. 2016). Predictors for delay in treatment were the presence of liver metastasis, pathological nodal involvement, and necessity of intraoperative blood transfusion.

Despite some convincing benefits to presurgical TMT in the setting of mRCC, one has to keep in mind that this strategy can lead to delay of CN due to deterioration of performance status due to adverse events or even disease progression precluding further CN altogether. Therefore, RCTs are needed to clarify the actual benefit of presurgical TMT, even with the recent advances in immunotherapy and possible alteration of treatment landscape associated with it as well as the recruitment issues with the awaited trials as discussed above. Also, the questions on the choice of drug and duration of drug to be used for tumor size reduction before CN remain to be answered.

Overall, the performance of CN previous to or after an initial round of TMT should be carefully debated with regard to the concepts discussed above as well as individual patient factors to include possible advantages and disadvantages in the decision-making. The European Association of Urology (EAU) guidelines recommend CN to patients with good performance status, large primary tumors, and relatively low metastatic volume (Bex et al. 2016). Meanwhile, CN is generally not recommended in patients with poor performance status or poor-risk disease according to IMDC or MSKCC risk score, with relatively small primary tumors and high metastatic volume, and/or with sarcomatoid tumors.

Future Prospects for CN in the "New" Immunotherapy Era

With the recent introduction of "new" immunotherapeutic drugs into practice for various malignancies, including mRCC in later line therapy, the concept of performance and timing of CN might be challenged further. However, to date, there are no reliable data available yet. The phase III trial leading to the FDA approval for nivolumab (first and to this day only approved checkpoint inhibitor for RCC) for second-line treatment of mRCC has, as the trials of the TMT

era, included almost 90% of patients with prior nephrectomy (Motzer et al. 2015). Therefore subgroup analysis with regard to efficacy in patients with their kidney in place has very limited power and was not published so far. With regard to the mechanism of action, the new immunotherapeutic agents might be most beneficial with the primary tumor still in place, as there will be more tumor antigen to be recognized by the (re)activated T cells, possibly affecting the magnitude of the immune response. However, as these patients are metastatic, and therefore will have leftover tumor after CN, this might not be of such importance and even lead to higher response rates in case that tumor burden plays a role in overcoming tumor-induced immunosuppression via checkpoint inhibitors. Large-scale studies will be needed to prove this, and until then the urological and oncological communities should make a combined effort to learn as much as possible from our patients. Currently, MD Anderson Cancer Center at Houston has an open protocol (NCT02210117, ClinicalTrials.gov 2017a) for pre-CN treatment of patients with previously untreated mRCC with various regimens (nivolumab alone, nivolumab plus bevacizumab, as well as nivolumab plus ipilimumab) followed by CN to investigate the efficacy of these drugs and combinations in the presurgical space as well as the immunological changes in the tumor tissue and peripheral blood (ClinicalTrials.gov 2017b). This study will provide important insight into the effect of checkpoint inhibitors on the primary tumor in mRCC.

Metastasectomy

In 1939, Barney and Churchill reported the first case in the literature of a patient who underwent simultaneous nephrectomy and excision of a solitary lung metastasis. This patient survived for 23 years, only to die later of coronary artery disease (Barney and Churchill 1939). The central aim of metastasectomy is to achieve a complete clinical response in the absence of effective systemic therapy (1), while secondary aims are palliation (2) and the potential to defer systemic therapy (3). Yet the promising results of this initial report cannot be generalized, and the vast majority of patients who present with or develop mRCC will die within a short period of time, regardless of attempts at aggressive surgical management of distant disease. Yet it is also true that complete surgical resection is one of the few reliable ways of rendering a patient cured of disease (up to 20% long-term remissions, even if only temporarily in many cases) and there is a wide body of retrospective literature associating metastasectomy with favorable long-term oncologic outcomes.

As in CN, the question of a survival benefit to metastasectomy can only be answered with a prospective, randomized clinical trial as the selection biases of retrospective reports on this subject are simply too strong to be able to quantify the benefit, if any, for treatment of metastatic RCC lesions. Yet there are no randomized trials concerning any of the many questions regarding the role of metastasectomy in mRCC and none are currently ongoing. Such a clinical trial would be exceedingly difficult to complete; mRCC is a very heterogeneous disease, and it would require an extraordinarily large number of patients to stratify all the various permutations of patient and disease characteristics. Similar to CN, the growing number of systemic treatment options further complicates the issue as evidence of the role of metastasectomy in the initial immunotherapy era may no longer be applicable in the TMT era and now immune checkpoint inhibitor era. Further questions arise with regard to sequence of surgery in patients presenting with metastatic disease, as metastasectomy can be performed in combination with nephrectomy prior to systemic therapy, after systemic therapy, or in a separate setting. Additionally, there is no consensus on how to proceed in the management of patients who have already undergone a previous metastasectomy and now have recurrent disease. In lieu of level 1 evidence, we are left with attempts at interpreting existing retrospective literature.

Supporting Clinical Evidence for Metastasectomy

Numerous studies report on single or multicenter retrospective outcomes of metastasectomy for mRCC. Van der Poel et al. reported on 152 resections of RCC metastases in 101 patients, of which 41 patients underwent repeated resections (van der

Poel et al. 1999). However, only 7% of patients were reported to have long-term OS >5 years. Kierney et al. reported on 41 patients with solitary metastases (excluding bone, nodal, and spinal cord metastases), who underwent curative intended resection and reported a 31% 5-year OS rate (Kierney et al. 1994). The only factor that was found to correlate with improved OS was a lower histologic grade in the metastatic site compared to the primary. Kavolius et al. compared the outcomes of resection of solitary metastases in 141 patients who underwent curative metastasectomy with 70 patients who underwent non-curative resection and 67 patients who underwent nonsurgical management and reported 5-year OS rates of 44%, 14%, and 11%, respectively (Kavolius et al. 1998). Multivariate analysis of factors associated with improved OS included disease-free interval >12 months, a solitary first recurrence (vs. multiple), curative/complete metastasectomy (vs. incomplete or nonsurgical management), and male gender. Studies from Korea reported that metastasectomy was an independent predictor of overall survival, both before systemic therapy and in patients who could not or were not willing to receive systemic therapy (Kwak et al. 2007; Lee et al. 2006). Eggener et al. combined the MSKCC risk grouping (originally developed for predicting survival of patients with mRCC treated with IFN-α) with the presence or absence of metastasectomy and found that on multivariate analysis, surgical intervention on metastases was still independently associated with improved survival (Eggener et al. 2008). Alt et al. reported on a large series of 887 patients with multiple RCC metastases, 125 (14%) of which underwent complete resection of all lesions (Alt et al. 2011). Complete resection was associated with improved survival in multiple clinical scenarios including lung-only metastases, non-lung-only metastases, 3+ metastatic lesions, and both synchronous and asynchronous metastases. On multivariate analysis, good performance status, lung-only metastases, asynchronous metastases, and complete resection were all variables associated with improved CSS and OS. Researchers from the University Hospitals Leuven and the University of Udine analyzed the records of 132 patients who underwent metastasectomy at different anatomic sites for mRCC (Tosco et al. 2013). Based on multivariate analysis of factors associated with outcomes, the authors created four "Leuven–Udine" (LU) prognostic groups that accurately predicted survival with an area under the curve (AUC) of 0.87 and 0.88 at 2 years and 5 years, respectively.

Although none of the heterogeneous studies related to metastasectomy in mRCC had complete concordance of factors associated with improved patient survival, several patterns emerge. Lung-only metastases, longer disease-free intervals between initial diagnosis and development of metastases, and ability to achieve complete surgical resection appeared to be relatively consistently associated with improved outcomes following metastasectomy (Table 4).

Table 4 Retrospective studies reporting on metastasectomy

Authors Setting Years	No. of patients	Clinical scenario	Factors associated with improved outcomes
Van der Poel et al. (1999) Multicenter 1985–995	Total ($n = 101$) Solitary ($n = 40$) Repeated resections ($n = 41$)	Solitary or multiple metachronous mRCC	Lung metastases Complete resection DFI >2 years
Kierney et al. (1994) Mayo Clinic 1970–1990	Total ($n = 41$) Complete resection ($n = 41$)	Solitary metachronous mRCC	Lower histologic grade of metastatic lesion relative to original RCC
Kavoulius et al. (1998) MSKCC 1980–1993	Total ($n = 278$) Complete resection ($n = 141$) Incomplete resection ($n = 70$) No resection ($n = 67$)	Solitary metachronous mRCC	DFI >12 months Solitary recurrence Complete resection Male gender

(*continued*)

Table 4 (continued)

Authors Setting Years	No. of patients	Clinical scenario	Factors associated with improved outcomes
Lee et al. (2006) Seoul, Korea 1999–2003	Total ($n = 57$) Metastasectomy ($n = 20$) Non-metastasectomy ($n = 37$)	mRCC who were treated with immunochemotherapy	Solitary metastasis Complete metastasectomy Lung metastasis
Russo et al. (2007) MSKCC 1989–2003	Total ($n = 91$) Complete resection ($n = 61$) No resection ($n = 30$)	Synchronous mRCC	Metastasectomy
Kwak et al. (2007) Seoul, Korea 1990–2004	Total ($n = 62$) Metastasectomy ($n = 21$) No resection ($n = 41$)	mRCC who did not receive systemic therapy	Metastasectomy
Eggener et al. (2008) MSKCC 1989–2007	Total ($n = 129$) Complete resection ($n = 44$) No resection ($n = 85$)	Metachronous mRCC following nephrectomy	Metastasectomy Lower MSKCC risk criteria
Alt et al. (2011) Mayo Clinic 1976–2006	Total ($n = 887$) Complete resection ($n = 125$)	mRCC with multiple metastases	Complete resection Lung metastases Good performance status Asynchronous metastases
Tosco et al. (2013) Udine, Italy Leuven, Belgium 1988–2011	Total ($n = 109$) Complete resection ($n = 82$) Incomplete resection ($n = 27$)	mRCC with synchronous or metachronous, solitary, or multiple metastases	pT stage <3 Fuhrman grades 1–2 Lung metastases Solitary metastases Complete resection

DFI disease-free interval, *mRCC* metastatic renal cell carcinoma, *MSKCC* Memorial Sloan Kettering Cancer Center

Location of Metastases

The most common site of metastatic disease in mRCC is the lung (45–69%), followed by lymph nodes (20–40%), bone (30%), liver (20%), and less commonly adrenal (9%), brain (8%), and other organs (Bianchi et al. 2012; McKay et al. 2014). The impact of tumor location on patient survival has been described earlier in this chapter, and these considerations are as relevant to the potential benefits of metastasectomy as they are for CN. Additionally, specific locations of metastatic lesions may have an impact on quality of life or could directly contribute to mortality, and these factors should be considered in the evaluation of a patient for aggressive local treatment of metastases.

Lung Metastases

As the lungs are the most common site of RCC metastases, there are many reports on the utility of pulmonary metastasectomy in mRCC (Assouad et al. 2007; Hofmann et al. 2005; Kanzaki et al. 2011; Kawashima et al. 2011; Meimarakis et al. 2011; Murthy et al. 2005; Pfannschmidt et al. 2002; Piltz et al. 2002). Five-year survival rates in patients with pulmonary metastases range from 21 to 60% following complete metastasectomy (Meimarakis et al. 2011). Many of these studies report similar factors associated with improved outcomes following pulmonary metastasectomy including disease-free interval, number of metastatic sites, and the degree of resectability. Hofmann et al. defined risk factors as a disease-free interval <36 months and more than one pulmonary metastasis (Hofmann et al. 2005). Patients were stratified into group 1 (resectable, no risk factor), group 2 (resectable, one risk factor), group 3 (resectable, two risk factors), and group 4 (unresectable). The 5-year survival rates were 53%, 48%, 22%, and 0%, for each group, respectively. Meimarakis et al. report on a prognostic tool (Munich score) to determine the utility of pulmonary metastasectomy;

based on their multivariate analysis of 175 cases, complete metastasectomy (R0), metastasis size >3 cm, positive nodal status of the primary tumor, synchronous metastases, pleural infiltration, and tumor-infiltrated hilar or mediastinal lymph nodes were reported as independent prognostic factors for survival (Meimarakis et al. 2011). Risk groupings were defined as low-risk patients (complete resection, no risk factors), intermediate-risk patients (complete resection, one or more risk factors), and high-risk patients (grossly incomplete resection or positive surgical margins) and reported 5-year survival data at 63%, 29%, and 0%, respectively.

Bony Metastases

Bony metastases as the second most common site of distant disease in mRCC are associated with significantly lower OS compared to lung metastases. As metastatic lesions to the bone are associated with disabling pain and can result in pathologic fracture, surgical intervention on bony lesions should not solely be based on questions of oncologic benefit but also palliation based on expected patient life expectancy, disease burden, and recovery time after intervention (Evenski et al. 2012; Kollender et al. 2000; Smith et al. 1992). Orthopedic procedures have long been used to palliate patients with mRCC, but there may also be a survival benefit to local therapy. Fuchs et al. compared outcomes for 60 patients with solitary bony metastasis from RCC and found that 5-year cancer-specific survival was significantly higher (38% vs. 8%) for those who underwent curettage and intramedullary bone stabilization compared with no surgical treatment (Fuchs et al. 2005). Similarly, Kitamura et al. reported on a multivariate analysis of 149 patients with RCC bony metastases in Japan from 2003 to 2012 and indicated that bone surgery, but not bone-modifying agents or radiotherapy, was associated with improved OS (Kitamura et al. 2016).

Brain Metastases

RCC lags only behind lung cancer and melanoma for its predisposition to metastasize to the brain (Barnholtz-Sloan et al. 2004). RCC metastases to the brain are typically diagnosed by symptoms, and until recently the prognosis has been considered dismal, with most patients surviving approximately 4–7 months (Culine et al. 1998; Wronski et al. 1997). Poor prognosis in these cases is related to both local effects of brain lesions and the association of brain metastases with more widespread disease (Samlowski et al. 2008). Due to inferior survival outcomes, patients with brain metastases are typically excluded from clinical trials of systemic therapies, and there are no validated treatment guidelines (Heng et al. 2014). Additionally, there was concern that the blood-brain barrier/blood-tumor barrier may inhibit drug penetration into malignant cells and targeted therapy might result in devastating intracranial hemorrhage; however, both of these suppositions have been debunked (Carden et al. 2008). Despite this, patients with brain metastases are still being excluded from newer immune checkpoint inhibitor studies, despite a recent case report of a patient treated with pembrolizumab (anti-PD-1 antibody) demonstrating regression of brain metastasis (Motzer et al. 2015; Rothermundt et al. 2016). Historically, neurosurgery, often combined with radiotherapy, provided the only chance of longer survival in a select set of patients, in particular those with limited superficial cerebral lesions, those who were asymptomatic at presentation, and those without extracranial disease (Culine et al. 1998; Harada et al. 1999). Very often, lesions were deemed to be unresectable at presentation, and whole brain radiotherapy (WBRT) was the only available option (Culine et al. 1998, Wronski et al. 1997). Inherent "radioresistance" of RCC was deemed to be the culprit of poor local control rates, but as we will describe below, high-dose radiation in the form of stereotactic radiosurgery (SRS) has challenged this dogma (Amendola et al. 2000; Andrews et al. 2004; Samlowski et al. 2008; Schoggl et al. 1998). Since the advent of SRS, craniotomy has largely been reserved for cases of cerebral lesions larger than 3 cm in size or those which are rapidly symptomatic resulting in midline shift (Dabestani et al. 2014).

Adrenal Metastases

Robson et al. reported a survival benefit in patients who underwent radical nephrectomy including an ipsilateral adrenalectomy; however improvements in presurgical imaging have

rendered this strategy a probable overtreatment in the vast majority of cases of localized RCC (Kletscher et al. 1996; Robson et al. 1968). Nonetheless, RCC does have a predisposition toward adrenal metastases, and autopsy series demonstrate involvement in up to 29% of cases (Siemer et al. 2004). In the case of synchronous adrenal metastases, adrenalectomy can be readily performed at the time of CN. Similar to other sites of metastases, when the adrenal gland is the only site of metachronous metastases and when the disease-free interval is long, adrenalectomy is a potentially curative option with reports of long-term cancer-specific survival (Alt et al. 2011; Kuczyk et al. 2005; Tsui et al. 2000).

Pancreatic Metastases

Although isolated pancreatic metastases are rare, RCC metastases seem to have a predisposition toward the pancreas. Typically, metastases from RCC to the pancreas present late and are commonly the only site of disease (Ghavamian et al. 2000). In a review of 243 patients from 17 institutions who underwent pancreatic metastasectomy, 61.7% of cases were due to metastatic RCC (Reddy and Wolfgang 2009). Of the tumors that were metastatic to the pancreas, RCC was associated with, by far, the best outcomes as 66% of patients were alive at 5 years.

Atypical Metastases

With the exception of case reports, the majority of published reports on metastasectomy concern the most common sites of metastases; however RCC, like other malignancies, can spread to any organ. The largest series exploring the role of metastasectomy in atypical sites was published by Antonelli et al. who performed a retrospective review of metastasectomy in 37 cases in an atypical site with 57 cases of pulmonary metastasectomy (Antonelli et al. 2012). Atypical sites included the skin, muscle, thyroid, testicle, nasopharynx, vagina, omentum, spleen, stomach, breast, and pancreas. Compared to lung metastases, the authors identified no difference in cancer-specific survival and concluded that the role of surgery in the atypical setting is probably no different than in the case of lung metastases.

Complications of Metastasectomy

Given the lack of level 1 evidence supporting metastasectomy, the limited life expectancy of most patients who develop metastatic disease, and the comorbidities and poor performance status associated with mRCC, the safety of the metastasectomy must be heavily weighed against the perceived benefits. Tosco et al. reported on surgical complications of 124 patients who underwent metastasectomy at different metastatic sites (Tosco et al. 2013). The mean hospitalization length was 9 days, and 13% experienced a Clavien–Dindo grade 3 or higher complication. Due to the heterogeneity of patient factors, tumor size, number, and location, it is difficult to provide meaningful estimates of metastasectomy complication rates. Nonetheless, careful consideration of these factors, as well as patient preferences and quality of life considerations, should be of upmost importance prior to embarking on metastasectomy. A good example is that of pancreatic metastases. Although these lesions are associated with relatively favorable OS when resected, pancreatic resection remains a significant surgery with a perioperative mortality rate of 2% and morbidity rate of 38% in primary pancreaticoduodenectomy (Winter et al. 2006).

Radiotherapy: An Alternative to Surgery

Although complete surgical resection of metastatic lesions has been the mainstay of localized treatment for RCC metastases, patient preference, health status, and tumor factors (accessibility, resectability) may make this approach unfeasible, and radiotherapy may provide a noninvasive alternative to surgery. Although it was previously believed that RCC is "radioresistant," a growing body of literature is refuting this dogma (Dengina et al. 2016). While conventionally fractionated radiation typically involves daily fractions of 1.8–3.0 Gy and does not appear to be effective in RCC, high-dose radiotherapy in the form of stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) results in destruction of

tumor vasculature and is effective in tumors highly dependent on angiogenesis, including RCC (De Meerleer et al. 2014; Mehta et al. 2005).

The majority of published reports of radiotherapy in metastatic RCC are in the case of brain or bony metastases. The efficacy of radiotherapy compared to surgery for bony metastases has been questioned; however this should be considered in light of lower doses of radiation in these previous reports (Hunter et al. 2012; Kitamura et al. 2016). Zelefsky et al. reported on 105 patients with RCC metastases to the bone treated with single-dose image-guided intensity-modulated radiotherapy (SD-IGRT) of 18–24 Gy and hypofractionation regimens (three to five fractions, 20–30 Gy) (Zelefsky et al. 2012). At 3 years, the local progression-free survival (LPFS) after high single dose (24 Gy) was 88%, significantly higher than the 21% and 17% LPFS of low single-dose (<24 Gy) and hypofractionation regimens, respectively. These favorable results have been confirmed by other reports, yet the durability of response remains to be seen (Amini et al. 2015).

With regard to brain lesions, numerous contemporary studies have demonstrated favorable local control rates with SRS and durable long-term survival in patients with limited metastatic disease (Amendola et al. 2000; Fokas et al. 2010; Ikushima et al. 2000; Majewski et al. 2016). Due to the concern for neurological deterioration following WBRT, there is debate about the benefit of adding WBRT to SRS, in particular in the case of solitary or limited cerebral lesions. A randomized trial of SRS + WBRT vs. SBRT alone in the treatment of brain metastases did not show any improvement in survival with the addition of WBRT, although local control rates were improved in the SRS + WBRT arm (Aoyama et al. 2006).

While the majority of SBRT data in mRCC is in bony lesions, this radiation modality has also been increasingly studied in soft tissue lesions, with similarly favorable results. In a report of 36 lesions treated with SBRT (most common fractionation was 50 Gy in five fractions), with thoracic, abdominal, and skin/soft tissue sites of RCC metastases, the median radiographic control rate at 36 months was 93.4% (Altoos et al. 2015). Due to advances in radiation delivery, toxicities, even at such high doses, were low, and there were no grade 4 or 5 adverse events reported. Other institutions have demonstrated similar results with consistently high local control rates (Ranck et al. 2013; Wersall et al. 2005).

Abscopal Effect

The "abscopal effect" is a phenomenon wherein local radiotherapy of metastatic cancer is associated with tumor regression at a non-irradiated distant site (Mole 1953). It is believed to be mediated by immune system activation and has been reported in numerous malignancies, including mRCC (Robin et al. 1981; Wersall et al. 2006). While the true impact of the abscopal effect is still being debated, the advent of effective immune checkpoint inhibitors has resulted in the interest of augmenting the immune system with radiotherapy (Park et al. 2015). It is theoretically possible that improved oncologic outcomes come from ablative SBRT of metastatic lesions rather than extirpative resection. To this point, our institution has recently started a phase II trial (SAbR) of nivolumab and SBRT for metastatic clear cell RCC (ClinicalTrials.gov 2016).

Local Recurrence

Isolated local recurrence following radical nephrectomy is rare, reported in only 1–2% of cases (Bruno et al. 2006; Esrig et al. 1992; Itano et al. 2000; Margulis et al. 2009; Tanguay et al. 1996). Historically, even isolated local recurrences were believed to be associated with a poor prognosis (Dekernion et al. 1978). However, multiple contemporary reports have demonstrated the feasibility and successful management of locally recurrent RCC. When associated with widely metastatic disease, local recurrence appears to be associated with poor outcomes regardless of attempts at surgical resection (Bruno et al. 2006). However in patients with isolated recurrences, Margulis et al. demonstrated that aggressive resection can be associated with durable local control and survival (Margulis et al. 2009). In the largest series published on the subject, the authors identified

54 patients with isolated local recurrence in the renal fossa, ipsilateral adrenal gland, or retroperitoneal lymph nodes, who were managed with surgical resection. Median recurrence-free survival and cancer-specific survival were reported at 11 months and 61 months, respectively. Risk factors associated with worse outcomes included positive surgical margin, tumor size (≥5 cm), sarcomatoid features, elevated serum alkaline phosphatase, and elevated lactate dehydrogenase. Patients with zero risk factors had a cancer-specific survival of 111 months, compared to 8 months for those with two or more risk factors. In this series, 4% of patients suffered perioperative mortality and 15% experienced major complications, highlighting the importance of patient selection for resection of locally recurrent RCC, where the high morbidity associated with reoperative retroperitoneal surgery must be weighed against the potential survival benefit (Margulis et al. 2009).

Metastasectomy to Defer Systemic Therapy

The optimal time to initiate systemic therapy in patients with metastatic RCC is not known. It is apparent that some patients will experience an indolent growth pattern of metastatic disease, and a recent prospective phase II trial demonstrated the safety of observation before starting systemic therapy (Rini et al. 2016). Metastasectomy of solitary or oligometastatic disease could be used to augment the delay before initiation of systemic therapy, although published reports of this method are limited. Mitchell et al. reported on 60 patients with metastatic RCC who were managed initially without initial systemic therapy. The most common (60%) initial strategy was metastasectomy alone, while another 12% received multiple local treatment modalities (Mitchell et al. 2015). Patients treated with metastasectomy generally fared quite well, and a follow-up period of 4.7 years after surgery, just 31% went on to receive systemic therapy, and the mean time to systemic therapy was 36.5 months. There is currently an ongoing clinical phase III trial led by the Eastern Cooperative Oncology Group (NCT01575548) assessing the role of pazopanib vs. placebo in patients who have no evidence of disease following metastasectomy and the RESORT phase II trial assessing the role of sorafenib following metastasectomy (ClinicalTrials.gov 2017b; Procopio et al. 2014). While none of these trials directly assess the benefits of metastasectomy vs. immediate systemic therapy, the results will be the first prospective data in this topic.

Conclusions

Decision-making for or against CN for mRCC is a complex venture. There is level 1 evidence to support the use of CN in combination with IFN-α; however this "older" immune therapy is rarely used after the introduction of TMT a little over a decade ago. As we lack level 1 evidence supporting the use of CN in the TMT era, we have to rely on retrospective reports, which suffer from inherent biases, despite commendable efforts to adjust for confounding factors. Nonetheless, the best available evidence does suggest a benefit to CN in correctly selected patients. There has been considerable effort in defining patient selection criteria for CN. Leading drivers of outcomes include tumor factors including "fraction of removable tumor volume," patient factors, and laboratory parameters, which are bundled in multiple risk stratification tools. The EAU guidelines recommend CN for patients with good performance status, large primary tumors, and relatively low metastatic volume, whereas patients with poor performance status, poor-risk features, high metastatic volume, and relatively small primary tumors might not benefit from CN. Level 1 evidence through the SURTIME and CARMENA trials is eagerly awaited, although difficulty with patient accrual may limit conclusions. The role of CN will need to be reevaluated following the recent introduction of newer immunotherapeutics (i.e., checkpoint inhibitors), which are poised to reshape the current treatment landscape for mRCC.

Limited conclusions can be drawn from the available retrospective data purporting a survival advantage to metastasectomy. Significant selection bias inherent in choosing a patient to undergo

metastasectomy, including performance bias (participants and personnel are unmasked), detection bias (outcome is unmasked), and attribution bias (incomplete outcome data), and selective reporting of the retrospective studies performed on oncologic role of metastasectomy should preclude any conclusion beyond the finding that some patients – often those with a complete resection of solitary, lung-only metastases with a longer disease-free interval between diagnosis and development of metastases – can experience long periods of recurrence-free survival after metastasectomy. It is unknown whether the intervention has any effect on the natural history of the disease or whether a more indolent tumor biology underlies the favorable outcomes in such cases. The most problematic factor is the assessment of "resectability" – an arbitrary parameter that is difficult to capture on multivariate analysis. Despite these concerns, the best literature available seems to suggest a survival advantage. As such, it is prudent to offer highly selected patients the option for metastasectomy, in particular if complete resection is feasible and safe. Advances in radiotherapy, in particular SRS and SBRT, have demonstrated significant efficacy with favorable intermediate-term local control rates and reduced morbidity. Multidisciplinary approaches combining surgery and radiotherapy are likely to play an increasing role in the management of RCC metastases.

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Advisable Follow-Up for Kidney Tumors

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Abstract

Currently, no consensus has been reached regarding follow-up strategies after treatment of nonmetastatic renal cell carcinoma (RCC). Apart from functional control and a psychosocial need to follow patients after the diagnosis and treatment of cancer with curative intent, evidence is lacking whether follow-up changes the natural history of RCC after local treatment. Nevertheless, most guidelines recommend follow-up, and retrospective data suggest that risk of recurrence, type of treatment, and competing risks such as comorbidity and age can be used to individualize follow-up in patients with RCC.

Introduction

The method and timing of follow-up regimen have been the subject of many publications. There is no consensus on follow-up after treatment for RCC, and in fact, there is no evidence that early versus later diagnosis of recurrences improves survival (Table 1).

Strategies for follow-up will therefore include a mix of both, depending on individual functional and oncological risks. Apart from functional control and a psychosocial need to follow patients after the diagnosis and treatment of cancer with curative intent, the key question is whether follow-up after complete resection or treatment of a malignancy changes the course of the disease. This question has not been studied, let alone answered, for renal cell carcinoma (RCC). Unfortunately, no comparative study – prospective nor retrospective – has ever addressed if follow-up after treatment of RCC improves survival.

Table 1 The aim of surveillance is directed to follow-up on functional and oncological outcomes

Aspects of follow-up for renal tumors	
Functional	Monitoring of renal function, management postoperative complications
Oncological	Detection of local intrarenal recurrence after partial nephrectomy or other nephron-sparing strategies; locoregional recurrence including lymph node metastases and adrenal or venous tumor thrombi; recurrence in the contralateral kidney; distant solitary or multiple metastasis

Rationale

The rationale for follow-up is based on early detection of recurrent or metastatic disease followed by either local or systemic therapy which subsequently changes the natural history of the disease and translates into a survival benefit or even cure. Yet, this rationale contains a number of uncertainties irrespective of the multitude of recommended follow-up strategies. In RCC, published data suggest that probably only local recurrences or resectable solitary and oligometastasis are accessible for local treatment with curative intent such as metastasectomy, stereotactic radiotherapy, and ablation (Dabestani et al. 2014). Although a systematic review of local treatment of metastases from RCC consistently found a survival benefit of complete metastasectomy versus no or incomplete metastasectomy, the exclusively retrospective studies are prone to a very high risk of bias and confounding (Dabestani et al. 2014). The major flaw of all retrospective metastasectomy studies is an indication bias, in that a group of patients with low-volume disease who had surgery was compared to a subset of patients with multiple metastatic sites and rapid disease progression which never were candidates for metastasectomy. In addition, there is little evidence regarding the pattern of relapse in terms of potentially resectable local recurrences or metastases. Local treatment of these lesions may lead to cure, whereas multiple metastases require non-curative systemic therapy at some point in time. While randomized phase III placebo-controlled crossover studies in metastatic RCC suggest that a delay in effective targeted therapy does not negatively influence survival (Sternberg et al. 2010), no data are available that confirm that a delay in detection of local recurrences or oligometastases is unfavorable with regard to cure. While isolated local recurrence is rare, the frequency of potentially resectable

metastases must be higher but is unknown. Although validated risk scores for patients with nonmetastatic RCC predict the metastasis rate after surgery with curative intent, the rate of patients with metachronous recurrence who are candidates for local therapy and the true resection rate as well as the course of disease after metastasectomy are uncertain because these data were not evaluated in the context of subsequent local or systemic treatment strategies. For example, a population-based database of >11,000 patients with metastatic RCC suggests a > 50% rate of single-site metastasis across all age groups, but that rate does not imply that these patients were all candidates for local treatment of metastases (Bianchi et al. 2012). On the contrary, a whole-nation study from Iceland showed that of 55 patients with primary pulmonary metastases as only metastatic site, only 11 were deemed resectable on retrospective evaluation, while it was actually performed in only a single patient (Oddsson et al. 2012). Without knowing the decisions made for or against local treatment of potentially curable oligometastatic disease and the factors involved, it will be difficult to establish recommendations for follow-up.

Two recent publications analyzed the recurrence patterns after surgically managed nonmetastatic RCC (Kuijpers et al. 2016; Dabestani et al. 2016). In a Dutch study on 234 patients with a median follow-up of 61.9 months after curative surgery for RCC, 68 patients (29.1%) developed metastases of which 28 (41.2%) were considered potentially curable. However, only 13 of potentially curable lesions (19% of all recurrences) received local therapy. Ultimately, only 4 (1.7% of all patients followed) remained free of disease at the cost of multiple consultations and more than 3000 imaging procedures over the years (Kuijpers et al. 2016). In a Swedish population-based study of 3107 patients with localized disease at presentation, 623 (20%) patients had a recurrence during follow-up (Dabestani et al. 2016). Of the patients with recurrence, 50% received systemic treatment, while metastasectomy was performed in only 17% of the recurrences, out of which 68% were with a curative intent. Based on GLOBOCAN data, annual incidence and mortality rates for RCC are 338,000 and 143,500, respectively (Li et al. 2015). Calculating with numbers of these epidemiological studies (Dabestani et al. 2016; Thorstenson et al. 2014), globally 159,000 RCC patients (37,000 of whom with non-clear cell subtype) will develop metastatic disease annually. The recent data suggest therefore that 17–19% may be candidates for metastasectomy or other forms of local therapy worldwide, amounting to 17,000–19,000 patients annually who may benefit from follow-up.

Surveillance for Functional Outcomes

Regarding functional surveillance, postoperative complications and renal function can be readily assessed by the patient's history, physical examination, and measurement of serum creatinine and estimated glomerular filtration rate (eGFR). This assessment is usually limited to the first 3–6 months postoperatively. Repeated long-term monitoring of eGFR seems only indicated if there is impaired renal function before surgery or postoperative deterioration. Postoperative complications should be graded by Clavien-Dindo (Dindo et al. 2004).

Surveillance for Oncological Outcomes

To understand the necessity for oncological follow-up, it is important to realize that metastatic disease is not curable by current systemic therapy. Follow-up should therefore be directed to detect local recurrences, locoregional recurrences, and distant solitary lesions because surgical resection or focal therapy of these lesions can potentially cure these patients. For all others, especially in multiple metastatic disease, diagnosis of progression is only insofar important as it will be used in the decision to start systemic therapy. Since placebo-controlled crossover studies with TKI or mTOR inhibitors have not shown a poorer outcome when active therapy was delayed in the placebo-controlled arms (Sternberg et al. 2010), the type and interval of imaging techniques used for follow-up may be less important in patients with a very high risk to develop systemic disease rather than local recurrences. However, only very few data exist suggesting that the risk of developing multiple metastases exceeds the risk of potentially resectable disease

in high-risk patients. A study that analyzed the pattern of recurrence in patients with low, intermediate, and high risk according to Leibovich and UICC/AJCC found that within the high-risk patient groups, early recurrence mainly consisted of multiple metastatic disease (Kuijpers et al. 2016). For patients under systemic therapy, follow-up at regular intervals follows a different aim. In those cases, progression will identify those patients who no longer benefit from a toxic treatment.

The likelihood to develop local recurrences and distant metastasis depends on well-described risk factors that are incorporated into scoring systems for clinical use. However, type, frequency, and pattern of recurrence are additionally linked to aspects of management and nephron-sparing techniques.

Local Recurrence in the Kidney After (Laparoscopic) Partial Nephrectomy

Recurrences after partial nephrectomy in the ipsilateral kidney are observed in 2–2.5%. In a recent retrospective database analysis from a large center in the United States (Kreshover et al. 2013), of 360 patients with pT1a and pT1b tumors, only 8 recurrences (2.2%) were observed after a mean follow-up of 34 +/− 17 months. Taking a relatively short surveillance of 3 years into account, it was concluded that most of the recurrences occurred within 1–2 years. Of those eight recurrences, only four were within the ipsilateral kidney, two were locoregional, and two were distant metastatic. Only tumors >3 cm with clear cell pathology and a Fuhrman grade > 1 recurred. This suggests that tumors <3 cm and Fuhrman grade 1 or non-clear cell subtype have little chance to develop local recurrences and the overall risk seems low.

Conversely, this seems to suggest that patients with pT1a/pT1b tumors and:

- Tumors >3 cm
- Clear cell subtype
- Fuhrman grade > 1

should be followed more intensively within the first 2 years for local recurrence, while the risk to develop distant metastasis should follow the general suggestions for risk-adapted follow-up. Other factors associated with possibly even higher risk of intrarenal and locoregional recurrence are:

- Hilar or central tumors of >4 cm
- Lymphovascular or vascular invasion in surrounding healthy renal tissue (Akatsu et al. 2007; Shindo et al. 2013)
- Fuhrman grade 3–4 (Borghesi et al. 2013)
- Positive margin (Borghesi et al. 2013; Marszalek et al. 2012)
- Tumor spill (ruptured malignant cyst or tumor capsule)

In these situations, three monthly CT may be advised in the first year to detect potentially curable local or locoregional recurrences.

Local Recurrence in the Kidney After Ablation

Ablative techniques have a higher rate of local and locoregional recurrences. In some series, up to 12% have been observed. In a recent publication from a larger series in the UK on 200 RFA-treated tumors of T1a/T1b stage with a mean size of 2.9 cm (range 1–5.6 cm) and a mean follow-up of 46.1 months (Wah et al. 2014), the recurrence rate in the kidney was 2.5% with a 5-year local recurrence-free survival (which included lymph nodes and venous thrombi) of 87.7%. The Kaplan-Mayer curves indicated that these locoregional recurrences including the local recurrences all occurred after >4 years with a mean detection at 58.3 months. This is of concern as the recurrences were observed at a time standard surveillance protocols would advise cross-sectional imaging once a year at best.

This seems to suggest that patients after ablation, certainly after RFA for T1a/T1b tumors, need long-term follow-up beyond 5 years with regular cross-sectional imaging owing to a high locoregional recurrence rate. Obviously, this needs to be adapted to life expectancy, comorbidity, and renal function which are more of concern in this often elderly patient group (Stewart-Merrill et al. 2015). Again, patients were more likely to develop recurrences with Fuhrman grade > 1 and tumors >3 cm.

Locoregional Recurrence in the Kidney Rest and Retroperitoneum

Data in the literature are conflicting since many retrospective series included adrenal metastases in locoregional recurrence definition. However, isolated kidney rest recurrence is rare (1.3–2.9%) (Psutka et al. 2016). Early diagnosis may be of benefit for the patient, since the most effective treatment is surgical resection (Bruno et al. 2006; Sandhu et al. 2005). Another series demonstrated a poor outcome with a median time to recurrence of 1.5 years after nephrectomy among 33 patients with isolated local recurrence (Psutka et al. 2016). Overall, median CSS was only 2.5 years after diagnosis of an isolated recurrence. Nevertheless, in this series, locally directed therapies were associated with a significantly decreased risk of death from RCC (HR 0.26, $P < 0.001$). Recurrence in the contralateral kidney is also rare (1.2%) and is related to positive margins, multifocality, and grade (Bani-Hani et al. 2005). Though a rare event in general, patients can potentially be cured if detected early and resected or treated focally. The risk to develop an isolated local recurrence is higher in high-risk patients. One series reported that at multivariable analysis, advanced pathological stage and coagulative necrosis were independently associated with increased risk of isolated local recurrence (Psutka et al. 2016). Both pathological stage and necrosis are part of several risk models. Follow-up should follow risk-adapted imaging strategies.

Distant Metastasis

Removal of all metastatic lesions, when technically feasible and clinically appropriate, provides the only potentially curative treatment. Since decades, retrospective data of patients with solitary or oligometastatic disease consistently suggest that complete resection is a favorable prognostic factor, independent of race or geographical location. Controversy exists as to whether this is due to a relatively benign tumor biology, metastasectomy, or both. Due to a fundamental flaw of preselection, no reliable data exist on the proportion of patients with mRCC who will be eligible for local therapy of their metastases. Depending on age at diagnosis, 57–65% of patients with metastatic RCC have single sites (Bianchi et al. 2012). However, this does not mean that these single sites contain oligometastases or solitary lesions accessible for resection. In addition, patient factors may play a role in estimating operability. Estimates have been made suggesting that 17–25% of patients with metachronous metastasis may be candidates for local therapy (Alt et al. 2011; Kuijpers et al. 2016; Dabestani et al. 2016). Regarding synchronous metastatic disease, this proportion may be much lower. A Scandinavian whole-nation study on prevalence and potential resectability identified 154 patients (16.9%) with synchronous lung metastases in whom the proportion of metastasectomy was evaluated (Oddsson et al. 2012). Only 11 patients with solitary lesions were considered for surgical resection which eventually was performed in only 1 patient.

With few exceptions, follow-up directed in high-risk groups to detect early metastatic disease will most often lead to initiation of systemic therapy rather than surgical resection. However, data suggest that a delay in diagnosis of systemic disease does not influence the response to targeted therapy (Sternberg et al. 2010). Therefore, the imaging modality to detect metastatic disease could be adapted for the different course of disease expected and the comorbidity and life expectancy of the patient. In patients who are very likely to progress systemically and rapidly at multiple sites or who may not be surgical candidates or have comorbidity, a chest X-ray may be sufficient; however, in those in whom early detection of solitary lesions may lead to cure if resected, cross-sectional imaging and CT of the chest are warranted.

Prognostic Models and Nomograms to Assess Risk of Recurrence, Metastasis, and Death

Several cooperative groups have designed scoring systems and nomograms to quantify the likelihood of patients developing tumor recurrences, metastases, and subsequent death. These systems have been compared and validated. Despite their adequate prognostic ability, none of these models

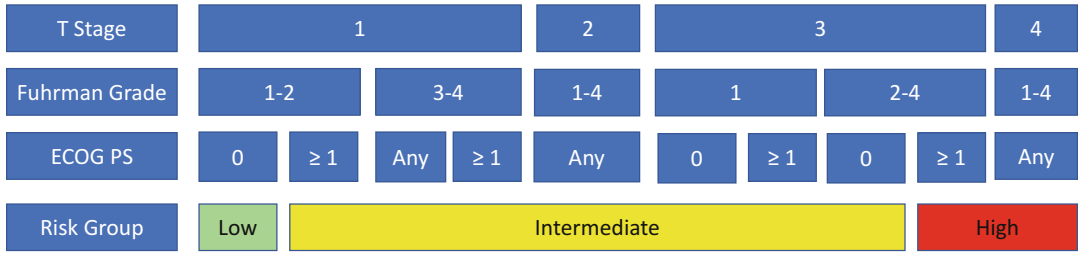

Fig. 1 The UCLA-UISS risk model for non-metastatic clear-cell renal cell carcinoma

or nomograms is 100% accurate with c-indices ranging from 74% to 82.2% for assessment of recurrence and 68% to 89% for assessment of cancer-specific mortality. The risk models have been summarized in complete and thorough overviews (Sun et al. 2011; Capogrosso et al. 2015). A commonly used model is the UCLA integrated staging system (UISS) using TNM stage, ECOG performance status, and Fuhrman grade (Zisman et al. 2001; Patard et al. 2004) (Fig. 1). The Leibovich score adds necrosis and tumor size (Leibovich et al. 2003) (Table 2), but both UCLA and Leibovich model are limited to clear cell RCC. Overall, because of a lack of 100% accuracy, historical differences in the use of TNM staging systems, differences in assessments (survival, mortality, recurrence-free survival, etc.), and subtypes (clear cell only vs. all subtypes), it may not be of importance in clinical practice which of the models or nomograms are used as long as a risk stratification can be achieved. It has to be accepted that a plateau has been reached and that all include a certain error rate. However, the risk groups established for low, intermediate, and high risk allow for tailoring follow-up protocols, and the choice should be made for a system that is easy to use during the clinic.

Given all the differences in methodology and patient groups, the metastasis-free survival or "failure" with either the Leibovich score or the UISS for low, intermediate, and high risk is surprisingly similar (see Tables 3 and 4). The Leibovich score provides information over a longer period of follow-up which is essential (Leibovich et al. 2003). For ease of use, recently developed nomograms are easier in daily practice, although the risk groups are easier to define by point scoring systems than by nomograms using a gliding scale of probabilities. In 2005, Kattan provided a postoperative nomogram for clear cell RCC which uses straightforward clinical factors and indicates the 5-year probability of freedom from recurrence (Sorbellini et al. 2005). Klatte et al. developed a similar nomogram for papillary RCC, but this has not been validated (Klatte et al. 2010). Though not scientifically accurate, both nomograms can readily be adapted and scaled to low-, intermediate-, and high-risk data of the Leibovich and UISS scores for ease of use. Both nomograms would cover the most common types of RCC although some subtypes are excluded.

Table 2 Leibovich risk score

Risk factor	Points	List individual points
pT1a	0	
pT1b	2	
pT2	3	
pT3a	4	
pT3b	4	
pT3c	4	
pT4	4	
pNx/pN0	0	
pN1–2	2	
Tumor size >10 cm	0	
Tumor size </=10 cm	1	
Fuhrman grade I–II	0	
Fuhrman grade III	1	
Fuhrman grade IV	3	
Necrosis no	0	
Necrosis yes	1	
		Sum:

Table 3 Metastasis-free survival (MFS) per Leibovich score

Leibovich score	MFS 1 year (%)	MFS 3 years (%)	MFS 5 years (%)	MFS 7 years (%)	MFS 10 years (%)
Low risk (0–2)	99.5	97.9	97.1	95.4	92.5
Intermediate risk (3–5)	90.4	79.8	73.8	69.1	64.3
High risk >/=6	57.5	37.1	31.2	27.3	23.6

Table 4 Any failure rate (local and systemic) per UISS risk score

UISS score	Failure 1 year (%)	Failure 2 year (%)	Failure 3 year (%)	Failure 4 year (%)	Failure 5 year (%)
Low risk	97	96	94	91.4	91.4
Intermediate risk	88.5	80.1	76.7	70.6	64
High risk	74.3	57.5	46.9	40.7	37.3

Established Guideline Recommendations for Follow-Up

Several guidelines have developed recommendations for follow-up, but a major problem remains the low quality of the evidence. The European Association of Urology (EAU) guideline has a very simple recommendation based on expert opinion (Ljungberg et al. 2015). The EAU guideline took multiple publications into account demonstrating that the sensitivity of CT chest is higher in detecting pulmonary or mediastinal metastases rendering conventional chest X-rays rather useless for follow-up. However, there may be certain situations in patients with competing risk or a very high likelihood to develop multiple metastatic disease sites in which conventional chest X-rays may help to limit the frequency of CT chest. In addition, there are multiple radiological publications and nomograms indicating the likelihood over time to develop metastases of several tumor types when a given CT was negative. The intervals were up to 1 year in some instances which may be considered in view of the aggressiveness of the disease and adapted to risk (Ljungberg et al. 2015). Currently, the National Comprehensive Cancer Network (NCCN) and the American Urological Association (AUA) guidelines provide the most recognized follow-up protocols for surgically resected RCC (Williamson et al. 2016). However, an analysis of both guideline recommendations in 3651 patients who underwent surgery for M0 RCC between 1970 and 2008 revealed that if rigidly followed, both the 2014 NCCN and AUA guidelines would miss up to one third of RCC recurrences, most of them in the abdomen and among pT1Nx-0 patients (Stewart et al. 2014).

Length of Follow-Up

There is no consensus on the optimal duration of follow-up. Some authors argue that follow-up with imaging is not cost-effective after 5 years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumors that develop in the contralateral kidney can be treated with nephron-sparing surgery if the tumors are detected when small. To estimate the risk over time, data on conditional survival are paramount and have been published recently (Abdollah et al. 2014). The post-operative recurrence – or progression-free survival period – has implications for the subsequent clinical progression risk and differs per risk group and therefore implications for designing follow-up. Patients who have survived a certain time following curative treatment do not carry the same risk throughout the subsequent years. Two recent publications addressed this issue for patients with RCC.

Abdollah et al. analyzed the conditional progression-free survival in 1454 patients for

anatomical stages I, II, and III–IV for 1, 5, and 10 years (Abdollah et al. 2014) (see Table 5). In conclusion, anatomical stage I carries a very low risk over the period of 10 years. Interestingly, for stages III–IV, which were analyzed together because of the relatively low number of patients, the risk was highest in the first year, declining after 5 years with the same risk as in stage I for the period of 5–10 years. This suggests that stages III–IV are aggressive diseases and if no recurrence has occurred soon, it is very unlikely that it will occur later. It also suggests that the frequency of imaging and surveillance for stages III–IV can be reduced to the level for stage I after 5 years. Only for stage II, the risk remained similar over the period of 10 years suggesting that recurrences occur steadily over time. A very similar observation was made in a Dutch study and another analysis on more than 40,000 patients from the SEER database (Bianchi et al. 2013; Kuijpers et al. 2016). Improved 5-year cancer-specific survival probabilities were highest for patients with stage III and IV disease, provided that they survived 1 and 2 years after nephrectomy.

A retrospective study of AUA and NCCN guideline recommendations in 3,651 patients who underwent surgery for M0 RCC demonstrated that to capture 95% of recurrences, surveillance was required for 15 years for low-risk tumors after partial nephrectomy, 21 years for low-risk tumors after radical nephrectomy, and 14 years for intermediate- to high-risk tumors (Stewart et al. 2014). According to the authors of this study, the most prominent reason for missed recurrences among current guidelines appears to be the duration of recommended follow-up limited to 5 years (Stewart-Merrill et al. 2015).

Table 5 Conditional PFS per anatomical stage

Anatomical stage	PFS at 1 year (%)	PFS at 5 year (%)s	PFS at 10 years (%)
Stage I	98	97	98
Stage II	92	87	94
Stages III–IV	69	88	96

Stage I, T1 N0 M0; stage II, T2 N0 M0; stage III, T3 N0 M0 or any T, N1 M0; stage IV, T4 N0 M0 or any T, any N, M1

The Impact of Competing Risk

Follow-up is associated with high costs, while it has been recognized that follow-up can be individualized based on risk of recurrence, comorbidities, and age. Several studies from the United States and Europe have demonstrated that the cost-effectiveness ratio of follow-up in terms of potential cure achieved after focal treatment of a recurrence versus costs involved is poor (Stewart-Merrill et al. 2015; Kuijpers et al. 2016). In 2511 patients who underwent surgery for M0 RCC between 1990 and 2008, Stewart-Merrill et al. compared the risk of recurrence to the risk of noncancer-related death. In addition, they also analyzed the location of the recurrence.

Patients aged 80 years and older with pT1Nx-0 disease and a Charlson comorbidity index of ≤ 1 had a risk of non-RCC death which was higher than the risk of abdominal recurrence at 6 months. However, in patients younger than 50 years, the risk to develop abdominal recurrence remained greater for more than 20 years. Interestingly, for patients with pT1Nx-0 disease but a comorbidity index of ≥ 2, the risk of non-RCC death was higher than the risk of abdominal recurrence already as early as 30 days after surgery, regardless of patient age. These data clearly demonstrate that competing risk is of influence in estimating necessity and length of follow-up for the individual patient.

Evidence-Based Suggestions for Follow-Up

Low-Risk RCC After Nephrectomy (Any Subtype)

Evidence summary and rationale: Data suggest that there is a very low but steady recurrence/metastasis rate of approximately 2–3% per 5-year period of follow-up. Course of disease is nonaggressive, and any recurrence is more likely to be solitary or oligometastatic. This increases chance of cure in case of local treatment. Follow-up should therefore be a compromise between long-term control and radiation exposure. Validated risk scores should be used to estimate individual risk.

Table 6 Suggested follow-up schedule for patients after ablation <3 cm

	Year 1					Year 2		Year 3		Year 4		Year 5	
Imaging	2–4 wk	3 mnd	6 mnd	9 mnd	12 mnd	18 mnd	24 mnd	30 mnd	36 mnd	42 mnd	48 mnd	54 mnd	60 mnd
Lab	×	×	×	×	×								×
CT abdomen	×	×	×	×	×								×
CT thorax		×											
Ultrasound							×		×		×		

Intermediate-Risk RCC After Nephrectomy (Any Subtype)

Evidence summary and rationale: Conditional survival data suggest a slightly higher risk of recurrence/metastasis for these patients in the first 5 years which then levels off to the risk for low-risk RCC. This seems to justify a closer follow-up in the first 5 years with CT of chest and abdomen every 6 months in the first 2 years, followed by alternating CTs and US/CXR per 6 months until 5 years. Then the regimen follows low risk for the interval 5–10 years. Validated risk scores should be used to calculate the risk.

High-Risk RCC After Nephrectomy (Any Subtype)

Evidence summary and rationale: Conditional survival data suggest that if patients survive the first 2 years without metastases, their risk to develop recurrence parallels that of low to intermediate risk. Without curative systemic treatment, intensive follow-up during the first 24 months in this patient group is debatable because contrary to low-risk disease, it is more likely that those patients develop early onset and more extensive systemic disease which will be in 40% at more than 1 site or, if single sites will be involved, frequently containing more than 1 lesion. This is likely to preclude local therapy of metastases with curative intent in most cases. In addition, a Dutch study has shown that once multiple metastases were detected during follow-up, the decision to start systemic therapy was delayed in 50% due to low-volume multiple metastases (Kuijpers et al. 2016). A low-dose CT thorax may therefore be sufficient.

Low-Risk RCC After Partial Nephrectomy

Evidence summary and rationale: Low risk after partial nephrectomy requires a different definition focusing on locoregional recurrence rather than metastases. If any of the following three conditions apply data suggest almost complete absence of recurrence or metastases:

- Margin-negative resected tumor <3 cm, clear cell RCC with Fuhrman grade 1
- Margin-negative resected tumor <3 cm, non-clear cell subtype

These could be defined as "low risk" after partial nephrectomy. Follow-up should therefore be directed at documenting postoperative anatomy by CT, renal function, and ultrasound at yearly intervals to detect unlikely gross changes. Metastases may occur but are very unlikely. Low-dose CT thorax is sufficient.

High-Risk After Partial Nephrectomy

Evidence summary and rationale: Conversely, high risk of locoregional recurrence may apply whenever one or more of the following situations exist:

Situation
Hilar or central tumors of >4 cm
Peritumoral vascular invasion
Fuhrman grade 3–4
Positive margin
Tumor spill

Table 7 Suggested follow-up schedule after ablation of tumours > 3 cm

	Year 1					Year 2		Year 3		Year 4		Year 5		Year 6	Year7	Year8	Year 9	Year10
Imaging	2–4 wk	3 mnd	6 mnd	9 mnd	12 mnd	18 mnd	24 mnd	30 mnd	36 mnd	42 mnd	48 mnd	54 mnd	60 mnd	72 mnd	84 mnd	96 mnd	108 mnd	120 mnd
Lab	×	×	×	×	×	×	×		×		×		×					×
CT abdomen	×	×	×	×	×	×	×		×		×		×					
CT thorax		×			×		×		×		×		×					
Ultrasound														×	×	×	×	×
Individualized approach to follow-up based on renal function and body mass index																		
If calculated MDRD GFR < 45 MRI instead of CT																		
If calculated MDRD <30 MRI without contrast medium If patient obesity makes them unsuitable for ultrasound (as indicated by radiologist) CT instead of ultrasound																		

Cross-sectional imaging is better at detecting early recurrence than ultrasound and a protocol with CT of the abdomen every 6 months in the first 2 years, followed by alternating CTs and US per 6 months until 5 years should be followed to detect early locoregional recurrence. Since most of these patients will have an intermediate risk to develop distant metastases, imaging includes detection of distant metastatic disease.

Intermediate Risk After Partial Nephrectomy

Evidence summary and rationale: Those with the situations not matching low or high risk may be best followed at less rigorous intervals. Imaging to detect distant metastases should be equivalent to low-risk Leibovich score, and cross-sectional imaging should be applied for detection of locoregional metastases only.

Follow-Up for Patients After Ablation <3 cm

Evidence summary and rationale: Data suggest that tumors <3 cm carry a low risk to recur as has been shown for partial nephrectomy. Likewise, a surveillance protocol as shown in Table 6 may be sufficient for these patients. Often, patients who were treated with ablation have higher competing risk, which should be taken into account when designing the individual follow-up. This includes concerns about renal function in this population. Cross-sectional imaging may therefore need to be adapted to certain situations.

Follow-Up After Ablation for Tumors >3 cm

Evidence summary and rationale: In view of the higher recurrence rate seen after ablation and the late onset of recurrences, the following protocol may be considered (Table 7).

Outlook

Currently, there is no high-level evidence supporting a specific follow-up protocol, let alone evidence for an improvement in survival. The absence of evidence requires the comparison of pattern and time of recurrence per risk group with different imaging frequencies and strategies and subsequent documentation of outcome parameters in relation to local and systemic treatment modalities applied. Large retrospective databases and data from adjuvant treatment trials can be used to identify comparators, which could be investigated in prospective randomized protocols with survival, saved resources, and radiation exposure as potential end points. Without this effort, the key rationale for follow-up in RCC – changing the natural history of the disease – will remain without scientific support.

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Part V

Testicular Cancer

Epidemiology, Risk Factors, and Histopathology in Testicular Cancer

42

Tim Nestler and Hans Schmelz

Contents

Abstract

Though germ cell tumor of the testis (GCT) is rare in general, it is the most common cancer of man aged 20–45 years. It is more common in Europe and the United States with an increase in northern parts. Since the introduction of platinum-based chemotherapy, cure rates are excellent, also in metastasized patients.

The most important and validated risk factors for GCT are history of a contralateral

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tumor, cryptorchidism, genetic predisposition, infertility, or height.

Accurate pathological diagnostic is mandatory for a correct staging and therapy recommendation according to the current WHO and TNM classification. Metastasized patients should be risk stratified by the IGCCCG classification which influences the therapy. Therefore, this chapter will provide information concerning the basic pathologic work-up and information about different types of GCT.

Introduction

Germ cell tumor of the testis (GCT) is rare in general but the most common cancer in young man. However, it has excellent cure rates due to their chemosensitivity, especially to cisplatin-based chemotherapy (Hoffmann et al. 2014). Since introduction of cisplatin-based chemotherapy in the 1980s, the cure rate of localized and even disseminated GCT has increased significantly (Einhorn and Donohue 1977). Thus, GCT has become one of the best curable cancers (RKI 2017).

To be aware which patients should be scheduled with focus, it is important to know about the age distribution and risk factors. For a correct treatment, it is mandatory to diagnose and classify GCT, both clinically and pathologically, strictly according to the current TNM classification.

Epidemiology

Incidence

GCT is the fourth most common urological tumor and accounts for about 1–2% of male cancers in western countries (RKI 2017). The incidence in western societies varies from 3% to 10% (RKI 2017; Rosen et al. 2011). The worldwide incidence was estimated with 52,322 newly diagnosed cases in 2008 (Table 1) (Znaor et al. 2014). Looking at Germany, the incidence was 10.3 per 100,000 males per year, and there were about 4100 newly diagnosed GCT in 2014 (RKI 2017). The prevalence is reported with almost 40,000 men who had a GCT in Germany during the last 10 years (RKI 2017). Within the last decade, the incidence of GCT has increased on average 1% per year (Znaor

Table 1 Worldwide distribution of incidence and death rates of GCT are shown, basing on the GLOBOCAN report from 2008 (Znaor et al. 2014)

	Incidence		Death	
Region	Cases (n)	ASR	Cases (n)	ASR
World	52,322	1.5	9874	0.3
Europe	18,326	4.8	1627	0.4
Northern Europe	3365	6.7	130	0.2
Southern Europe	3363	4.2	260	0.3
Western Europe	7399	7.8	295	0.2
Central and Eastern Europe	4199	2.6	942	0.6
America	16,845	3.5	1836	0.4
North America	9017	5.1	413	0.2
Central America	2910	3.7	523	0.7
South America	4764	2.4	848	0.4
Asia	14,775	0.7	5525	0.3
Eastern Asia	4182	0.5	817	0.1
Southeast Asia	2166	0.8	945	0.3
South-Central Asia	6661	0.8	3032	0.4
Western Asia	1766	1.5	731	0.6
Australia/New Zealand	868	6.7	27	0.2
Africa	1481	0.4	849	0.3

ASR age-standardized rate

et al. 2014; Nigam et al. 2015; Le Cornet et al. 2014; Ghazarian et al. 2015). However, rates have recently stabilized in some countries. Reasons for this development are currently unknown.

Although GCT is a rare cancer, it is the most common cancer in the group of men aged 20–45 (RKI 2017). Since decades, the peak age is shifting to higher ages (Ruf et al. 2014). The GCT subgroups seminoma and non-seminoma differ in their peak incidence. For non-seminoma, the peak incidence is the third decade of life and for pure seminoma the fourth decade. Furthermore, there is a geographic difference as GCT mainly affects western countries (Table 1). Within these countries, there is additionally a gradient from north to south with highest incidences in Scandinavia (Rosen et al. 2011).

Synchronous tumors are diagnosed in about 1% of cases. Metachronous contralateral GCT occur between 2.5% and 5% of patients with initial unilateral GCT (Harland et al. 1993). Screening programs are not recommended by any international guideline because of a low incidence and a good prognosis (Albers et al. 2018; Force USPST 2011). Also the use of serum tumor markers is not recommended in routine diagnostics (Gilligan et al. 2010). Besides the potential benefits of a screening, it has to be taken into account that a screening for a seldom disease will result in several false-positive findings, leading in worst cases to unnecessary ablations of testis. However, self-examination as a very simple means of early diagnosis should be shown to each young patient visiting a general practitioner or an urologist (Rovito et al. 2015; Saab et al. 2016).

Mortality

The disease-specific mortality has been declining since the 1970s. About 9000 GCT-related deaths were estimated worldwide in 2008 (Ferlay et al. 2010). In the European Union, a decline of about 26% was reported from the 1990s to the 2000s from 0.47 to 0.35 per 100.000 (−26%) (La Vecchia et al. 2010). In Germany, there were 145 disease-specific deaths in 2015 (RKI 2017). Mortality rates can be very different within one country. While the mortality rate was 5.5 per million person-years in East Germany, it was only 2.6 in the western part (Stang et al. 2015).

Higher mortality rates were reported in regions with lower incidences of GCT like Central and South America or Central Asia and vice versa (Rosen et al. 2011).

Survival

The probability of survival is excellent in GCT. Compared with the general population, the 5- and 10-year survival rates are 96% in Germany (RKI 2017). In early stages, a survival rate of even 99% can be reached. Thus, GCT is one of the malignancies (similar to Hodgkin's lymphoma or retinoblastoma) with the highest survival probability (RKI 2017). The individual prognosis is mainly based on the histology and tumor stage according to the IGCCCG risk classification for metastatic GCT (Mead and Stenning 1997). Therapy-related toxicities have an impact on survival, too. Early therapy-related side effects, which might cause mortality, are, for example, thromboembolic events. Second malignancies due to chemo- or radiotherapy are late side effects (Kvammen et al. 2016).

Risk Factors

Etiology of GCT has not been fully understood yet. Research is mainly based on clinical investigations and epidemiologic evaluations. By these approaches, different clinical risk factors have been identified. The following chapter mainly describes such risk factors, which are significantly associated with GCT; finally, a rough summary of risk factors which are under debate is provided. Neither testicular trauma nor mumps orchitis elevate the risk for developing a GCT.

History of a Contralateral Tumor

History of GCT is the most important risk factor for developing a second GCT of the contralateral testis. The risk for a metachronous cancer is

estimated between 2.5% and 5% in patients who had a unilateral GCT (Harland et al. 1993).

Cryptorchidism

Cryptorchidism is the best known risk factor for the development of GCT. A current meta-analysis provides a relative risk (RR) of 2.90 (95% CI 2.21–3.82) or and odds ratio (OR) of 4.30 (95% CI 3.62–5.11) (Lip et al. 2013; Cook et al. 2010). The contralateral normal descended testis might be at a higher risk, too (Giwercman et al. 1987; Moller et al. 1996). Intra-abdominal cryptorchidism is supposed to have a higher risk for malignancy compared to inguinal testis (Batata et al. 1982; Abratt et al. 1992). It is recommended to treat cryptorchidism within the first year of life. This reduces the probability of GCT significantly compared to a therapy in later years (Chan et al. 2014; Pettersson et al. 2007; Banks et al. 2012).

Genetic Predisposition

Familial clustering is more common in GCT compared to most other cancers (Mai et al. 2010). A Scandinavian study showed a RR of 2.0 (95% CI 1.7–2.4) if the father had a GCT, a RR of 4.1 (95% CI 3.6–4.6) if the brother had a GCT, a RR of 17 (95% CI 10–26) if more than one relative had a GCT, and a RR of 20 (95% CI 13–31) for twins (Kharazmi et al. 2015). Genome-wide association studies identified 19 gene loci (single nucleotide polymorphisms), which are associated with GCT (Litchfield et al. 2015). Currently a polygenic pathogenesis model is assumed where GCT is triggered by several low penetrating genes (Greene et al. 2015).

Infertility

Infertile men have a higher incidence of GCT with a probability of 1:200 (Raman et al. 2005; Olesen et al. 2017). GCT develop from germ cell neoplasia in situ (GCNIS), which affects the spermatogenesis negatively with a consecutive impaired semen quality. Especially severe forms of infertility are significantly associated with risk for GCT (Latif et al. 2017).

Height

A correlation between body size and risk for GCT was shown by different studies (Lerro et al. 2010). Men with a height $>$ 195 cm seem to be at a particularly high risk (OR 3.35) (Dieckmann et al. 2008).

Microlithiasis

Microlithiasis has been associated with GCT but is more and more questioned as an independent risk factor. Current meta-analysis showed a RR between 8.5 (95% CI 4.5–16.1) and 12.7 (95% CI 8.18–19.71) (Tan et al. 2010; Wang et al. 2015). Main limitations of these reviews were that co-occurring of GCT, and microlithiasis was analyzed but not the risk of a group of patients with microlithiasis to develop GCT over time. However, a large follow-up study comprising 442 patients with microlithiasis showed that only 0.5% developed a GCT (Patel et al. 2016). Also, a review, which included 5.899 patients, questioned the impact of microlithiasis as an independent risk factor. Only 4% of patients with microlithiasis developed GCT compared to 1% without microlithiasis (van Casteren et al. 2009). Thus, microlithiasis should not be used as an independent risk factor anymore but in combination with other validated risk factors (Richenberg et al. 2015).

Testicular Dysgenesis Syndrome

Testicular dysgenesis syndrome (TDS) is a male reproduction-related condition characterized by the presence of symptoms and disorders like

hypospadias, cryptorchidism, poor semen quality, or histopathological changes which can lead to GCT (Skakkebaek 2004). However, this concept has to be validated.

Risk Factors Under Debate

There are different potential risk factors for GCT, but the data are not sufficient enough yet. *Cannabis* consumption was described in two studies as a risk factor, as well as trisomy 21 or estrogen excess during the prenatal phase (Gurney et al. 2015; Callaghan et al. 2017; Hasle et al. 2016; Strohsnitter et al. 2001).

Histopathology

There is a variety of benign and malignant tumors of the testis according to the WHO classification (Table 2). The term testicular cancer usually summarizes germ cell cancers of the testis, which account for the vast majority of up to 98% of testicular malignancies (Trabert et al. 2015). It is believed that most GCT of the testis are germ cell neoplasia in situ (GCNIS)-derived like seminoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, or the postpubertal type of teratoma. The much smaller group comprises non-GCNIS-derived GCT like spermatocytic tumor, prepubertal type of yolk sac tumor, or prepubertal type of teratoma (Moch et al. 2016a). The remainder comprises sarcoma, carcinoma, and sex cord-stromal tumors like Leydig or Sertoli cell tumors.

Mandatory pathological information being provided by the collaborating pathologist are the following macroscopic features: side, testis size, maximum tumor size, and macroscopic features of the epididymis, spermatic cord, and tunica vaginalis. Sampling should be performed as follows: a 1 cm^2 section for each centimeter of maximum tumor diameter, including normal macroscopic parenchyma (if present), albuginea, and epididymis. Furthermore, at least one proximal and one distal section of the spermatic cord

Table 2 Shows the World Health Organization classification of germ cell tumors of the testis, which should be used for classifying GCT (Moch et al. 2016b)

WHO classification 2016	ICD-O
Germ cell tumors derived from germ cell neoplasia in situ	9064/2
Noninvasive germ cell neoplasia	
Germ cell neoplasia in situ	
Specific forms of intratubular germ cell neoplasia	
Tumors of a single histological type (pure forms)	
Seminoma	9061/3
Seminoma with syncytiotrophoblast cells	
Non-seminomatous germ cell tumors	
Embryonal carcinoma	9070/3
Yolk sac tumor, postpubertal-type	9071/3
Trophoblastic tumors	
Choriocarcinoma	9100/3
Non-choriocarcinomatous trophoblastic tumors	
Placental site trophoblastic tumor	9104/1
Epithelioid tumor	9105/3
Cystic trophoblastic tumor	
Teratoma, postpubertal-type	9080/3
Teratoma with somatic-type malignancy	9084/3
Non-seminomatous germ cell tumors of more than one histological type	
Mixed germ cell tumors	9085/3
Germ cell tumors of unknown type	
Regressed germ cell tumors	9080/1
Germ cell tumors unrelated to germ cell neoplasia in situ	9063/3
Spermatocytic tumor	
Teratoma, prepubertal-type	9084/0
Dermoid cyst	
Epidermoid cyst	
Well-differentiated neuroendocrine tumor (monodermal teratoma)	8240/3
Mixed teratoma and yolk sac tumor, prepubertal-type	9085/3
Yolk sac tumor, prepubertal-type	9071/3
Sex cord-stromal tumors	8650/1
Pure tumors	
Leydig cell tumor	
Malignant Leydig cell tumor	8650/3
Sertoli cell tumor	8640/1
Malignant Sertoli cell tumor	8640/3
Large cell calcifying Sertoli cell tumor	8642/1
Intratubular large cell hyalinizing Sertoli cel neoplasial	8643/1

(*continued*)

Table 2 (continued)

WHO classification 2016	ICD-O
Granulosa cell tumor	
Adult granulosa cell tumor	8620/1
Juvenile granulosa cell tumor	8622/1
Tumors in the fibroma-thecoma group	8600/0
Mixed and unclassified sex cord-stromal tumors	
Mixed sex cord-stromal tumor	8592/1
Unclassified sex cord-stromal tumor	8591/1
Tumor containing both germ cell and sex cord-stromal elements	9073/1
Gonadoblastoma	

plus any suspected area should be included. Microscopic diagnostics should provide information concerning histological type (individual components and relative quantification) according to the current WHO classification of 2016 (Table 2) (Albers et al. 2018; Moch et al. 2016b). The presence or absence of peritumoral venous and lymphatic invasion; invasion of tunica albuginea, tunica vaginalis, rete testis, epididymis, or spermatic cord; and information concerning the presence or absence of GCNIS in non-tumor parenchyma should be provided. The pT category should be according to the current TNM classification of 2016 (Table 3) (Brierley et al. 2016). For immunohistochemically diagnostics, antibodies should be used as appropriate (Table 4) (Moch et al. 2016a).

GCNIS

The precursor lesion of malignant GCT is germ cell neoplasia in situ (GCNIS). These cells appear seminoma-like and are aligned along the basement membrane of seminiferous tubules. GCNIS cells are uniformly positive for OCT3/4 like seminoma or embryonal carcinoma (Table 4) (Moch et al. 2016a). Although GCNIS cells are usually positive for KIT, it has to be taken into account that normal spermatogonia may be positive, too. Until the WHO classification of 2016, GCNIS was termed intratubular germ cell neoplasia in situ (IGCNU), testicular intraepithelial neoplasia (TIN), or initially carcinoma in situ (CIS). These names should not be used any longer.

Seminoma

Seminoma cells "are considered the malignant counterparts of the primordial germ cells/gonocytes present during early embryonic development" (Moch et al. 2016a). About 60% of GCT are pure seminomas, whose relative proportion of all GCT has been increasing since years (Ruf et al. 2014). The median age of patients with pure seminoma is about 41 years. Up to 20% of seminomas excrete human chorionic gonadotropin (hCG) to the serum. Per definition, there is no seminoma excreting alpha-fetoprotein (AFP). Macroscopically, seminoma looks like white fish meat, occasionally with necrosis or intratumoral bleeding. Sometimes it is challenging to differentiate seminoma from similar appearing tumors like sex cord-stromal tumors or carcinoma metastasis to the testis. Seminoma-specific markers are OCT3/4, KIT, and/or SALL4 (Table 4), if needed in combination with markers for potential differential diagnosis (Ulbright et al. 2014). Markers to diagnose an early transformation from seminoma to another tumor type (e.g., CD30 for an embryonal carcinoma phenotype) are still under debate, because the correlation remains imperfect (Williamson et al. 2017).

NSGCT

All GCT, which are not consisting of pure seminoma, are classified as non- seminomatous germ cell tumors (NSGCT). They can contain a single histological type or are mixed (Table 2). The median onset of NSGCT is in the thirties. The most common NSGCT is a combination of embryonal carcinoma and teratoma, while the most common single histological tumor type is the embryonal carcinoma.

Embryonal carcinoma (EC) is defined as a tumor "composed of tumor cells resembling embryonic stem cells with ovoid to columnar

Table 3 Shows the TNM classification for testicular cancer according to the 8th edition of UICC (Brierley et al. 2016)

pT	**Primary tumor**			
	pTX	Primary tumor cannot be assessed (see note 1)		
	pT0	No evidence of primary tumor (e.g., histological scar in testis)		
	pTis	Intratubular germ cell neoplasia (carcinoma in situ)		
	pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis		
	pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion or tumor extending through tunica albuginea with involvement of tunica vaginalis		
	pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion		
	pT4	Tumor invades scrotum with or without vascular/lymphatic invasion		
N	**Regional lymph nodes – clinical**			
	NX	Regional lymph nodes cannot be assessed		
	N0	No regional lymph node metastasis		
	N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension		
	N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension or more than five nodes positive, none more than 5 cm or evidence of extra nodal extension of tumor		
	N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Pn	**Regional lymph nodes – pathological**			
	pNX	Regional lymph nodes cannot be assessed		
	pN0	No regional lymph node metastasis		
	pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
	pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or more than 5 nodes positive, none more than 5 cm, or evidence or extra nodal extension of tumor		
	pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M	**Distant metastasis**			
	MX	Distant metastasis cannot be assessed		
	M0	No distant metastasis		
	M1	Distant metastasis		
		M1a non-regional lymph node(s) or lung metastasis		
		M1b distant metastasis other than non-regional lymph nodes and lung		
S	**Serum tumor markers**			
	SX	Serum marker studies not available or not performed		
	S0	Serum marker study levels within normal limits		
		LDH (U/l)	**hCG (mIU/ml)**	**AFP (ng/ml)**
	S1	<1.5 × upper limit of normal LDH and	<5000 and	<1000
	S2	1.5–10 × upper limit of normal LDH or	5000–50,000 or	1000–10,000
	S3	>10 × upper limit of normal LDH or	>50,000 or	>10,000

LDH lactate dehydrogenase, *hCG* human chorionic gonadotrophin, *AFP* alpha fetoprotein

profiles, clear to granular or amphophilic cytoplasm, and markedly pleomorphic nuclei that are arranged in diverse morphological patterns" (Moch et al. 2016a). It accounts for up to 10% of NSGCT and in mix forms up to 80%. The peak incidence is around the 30th year of age. Immunohistochemically EC is usually positive for OCT3/4, CD30, and SOX2 but negative for KIT and Glypican-3 (Table 4).

Yolk sac tumor (postpubertal-type) "differentiates to resemble extraembryonic structures, including the yolk sac, allantois and extraembryonic mesenchyme." (Moch et al. 2016a) It is the most common testicular cancer in children

Table 4 Shows expressed proteins in different GCT subtypes which are used for diagnostic purposes

	AFP	CD30	Glypican-3	KIT (CD 117, cKIT)	NANOG	OCT3/4	PLAP	SALL4	SOX2	SOX 17	ßhC G
GCNIS	–	–	–	+	+(100%)	+(100%)	+	+	–	+	–
Seminoma	–	–	–	+(100%)	+(100%)	+(100%)	+(90–100%)	+(100%)	–(<1%)	+(95%)	–
Embryonal carcinoma	±(8–36%)	+(84–93%)	–(5%)	–	+(100%)	+(100%)	+(79–86%)	+(100%)	+(96%)	–	–
Teratoma	±	–	±(17%)	–	–	–	–	±(52%)	±	±	–
Yolk sac tumor	+(74–100%)	–	+(100%)	±(59%)	–	–	±(1–85%)	+(100%)	–	±(50%)	–
Choriocarcinoma	–	–	+(80%)	–	–	–	+	±(69%)	–	–	+(100%)

It is adapted by the WHO manual of 2016 (Moch et al. 2016a)
GCNIS germ cell neoplasia in situ

(prepubertal-type) but also occurs in adults. Most adult patients are between 15 and 40 years of age. Usually it is part of up to 40% of mixed NSGCT while a sole appearance is rare. Yolk sac tumor is always positive for Glypican-3 and mostly for AFP, while OCT3/4 and CD30 are negative. There is also a strong correlation between the presence of yolk sac tumor and elevated serum AFP (Table 4) (Moch et al. 2016a).

Choriocarcinoma "differentiates to resemble the trophoblastic cells of the extraembryonic chorion, including cytotrophoblastic, and intermediate, and syncytiotrophoblastic cells" (Moch et al. 2016a). It is relatively seldom and occurs pure only in <1% of GCT and in about 8% of mixed NSGCT. Typical age of onset is the third and fourth decade. Serum hCG is always elevated, often significantly increased (>50,000 mIU/ml). It is immunohistochemically positive for hCG but not for OCT3/4, KIT, or CD30 (Table 4). Pure and predominant choriocarcinoma have a poor prognosis.

Pure *teratoma* is "composed of several types of tissue representing one or more of the germinal layers (endoderm, mesoderm, and ectoderm). It may be composed exclusively of well-differentiated, mature tissues or have immature, embryonic-type tissues" (Moch et al. 2016a). It accounts for about 3–7% of NSGCT and for about 50% of mixed GCT. It is important to distinguish between prepubertal and postpubertal teratoma. Postpubertal teratoma is GCNIS derived and regarded as malignant GCT and metastasizes in 22–37% (Moch et al. 2016a). There is no specific single marker for teratoma, but the different elements forming teratoma might express a corresponding immunoprofile. Differentiating between mature and immature teratoma is not recommended, due to the lack of a prognostic value (Williamson et al. 2017). It is clinically important that metastasized tumors do not respond to chemotherapy, and the treatment of choice is the complete surgical resection.

In addition, *teratoma with somatic-type malignancy* has to be distinguished from postpubertal teratomas. It is defined as "teratoma that develops a distinct secondary component that resembles a somatic-type malignant neoplasm, as seen in other organs and tissues (e.g., sarcomas and carcinomas)" (Moch et al. 2016a). Usually it develops in metastasis, often after a cisplatin-based treatment. In some cases, it develops and varies between initial diagnosis and an interval of more than 30 years. Immunohistochemically it shows features similar to its counterparts in other organs. Usually, it is negative for OCT3/4 and AFP (Moch et al. 2016a).

Prepubertal teratoma is not associated with GCNIS, usually shows normal spermatogenesis, and has no metastatic spread (Moch et al. 2016a). Although it is called prepubertal, nonetheless, it can be found in adult patients, too. This group also includes benign forms such as dermoid or epidermoid cysts.

Non-germ Cell Tumors

Non-germ cell tumors are seldom (2–5% of testicular tumors in adults) and develop mostly from testicular stromal parts like the group of sex cord-stromal tumors comprising Leydig, Sertoli, or granulosa cells. Most of non-germ cell tumors occur in older patients and are mostly benign (Banerji et al. 2016).

Leydig cell tumors account for about 1–3% of testicular tumors in adults and are the most common non-germ cell tumors and most likely in older men (third to sixth decade). They occur more frequently in patients with Klinefelter syndrome. Since they are emerging from testosterone producing Leydig cells, hormonal disorders (low testosterone, high estrogen) might appear in up to 80%. About 10% of Leydig cell tumors are malignant. Malignant features are DNA aneuploidy, increased MIB-1 proliferation, large size (>5 cm), vascular invasion, or increased mitotic activity. Usually Leydig cell tumors express vimentin, inhibin, protein S-100, and focally cytokeratin (Albers et al. 2018).

Sertoli cell tumors account for <1% of testicular tumors with a peak age of 45 years and emerge from Sertoli cells of the testis. Up to 20% of Sertoli cell tumors are malignant, often showing a size >5 cm, vascular invasion, pleomorphic nuclei, and an increased mitotic activity. They are often positive for vimentin and cytokeratin staining (Albers et al. 2018).

Granulosa cell tumors are very rare (reported <100 cases). A juvenile type can be distinguished from an adult type (peak age 45 years). While the juvenile type is benign, size >4 cm or lymphovascular invasion (Albers et al. 2018).

Cross-References

- Clinical Aspects and Investigations in Genitourinary Cancer
- Clinical Trials and Their Principles in urologic Oncology
- Epidemiology, Risk Factors, and Histopathology in Testicular Cancer
- Follow-Up for Testicular Cancer
- Management of Clinical Stage I (CSI) Disease in Testicular Cancer
- Management of Germ Cell Neoplasia In Situ (GCNIS)
- Management of Residual Tumor in Testicular Cancer
- Molecular Basics on Genitourinary Malignancies
- Symptoms, Diagnosis, and Staging in Testicular Cancer
- Treatment of Clinical Stage II (CS II) Disease in Testicular Cancer
- Treatment of Local Disease in Testicular Cancer

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Symptoms, Diagnosis, and Staging in Testicular Cancer

43

Mark Schrader

Contents

Abstract

Typical symptoms of testicular cancer are painless enlargement and hardening of the testicle; in rarer cases, they are noticed due to their metastases. Eighty-five of primary tumors can be recognized through palpation alone. The primary diagnostic work-up should include physical examination including the palpation of the supraclavicular lymph nodes as well as high-resolution ultrasound of both testicles. The ultrasound examination of the unaffected testicle is important for recognizing testicular microlithiasis. Clinically established tumor markers are α-fetoprotein, β-hCG, and LDH. The definitive diagnosis is achieved by exposing the testicle in surgery through an inguinal access. A biopsy of the contralateral testicle can be discussed if risk factors for a GCNIS are present. Tumor staging includes CT of the thorax and abdomen, MRI of the abdomen is an alternative, and an FDG-PET-CT is only recommended in the follow-up of patients with a seminoma postchemotherapy and a residual mass larger than 3 cm and should not be performed before 8 weeks after chemotherapy. Histogenetically, testicular tumors are divided into malignant germ cell tumors, stromal tumors, mixed germ cell stromal tumors, and other tumors. Seminoma is the most common tumor among malignant germ cell tumors (60%), and 40% are non-seminoma (mixed forms from various histological types are classified as non-seminoma even if seminoma is present). Clinically relevant stromal tumors are Sertoli cell and Leydig cell tumors. Malignant

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testicular tumors are classified according to the TNM classification (UICC) and in metastatic tumor stages according to the prognostic-based staging system for metastatic germ cell cancer (IGCCCG).

Symptoms

Testicular cancer usually presents as a painless enlargement of the affected testicle. Smaller tumors can also present as a palpable hardening within the testicle or on its surface (Germa-Lluch et al. 2002). Occasionally (10–20% of cases), the affected patients report unspecific pain in the affected testicle which can make the differential diagnosis of epididymitis difficult. Rarely, testicular tumors are noticed through symptoms occurring as a result of metastasis. Large retroperitoneal lymph node metastases can lead to back and abdominal pain and mediastinal lymph node metastases to swallowing problems. Lung metastases can cause hemoptyses or dyspnea and brain metastases corresponding to neurological symptoms. In a metastasized state, many patients also report unspecific symptoms such as fatigue and loss of weight (Germa-Lluch et al. 2002).

Clinical Examination

Around 85% of primary tumors are diagnosed through testicular palpation alone (Albers et al. 2015). Both testicles should always be examined using a bimanual technique so that the size, surface, and consistency of the testicle can be assessed. Palpable changes of the epididymis and spermatic cord can indicate infiltration by the tumor. For around 30% of patients, there is an accompanying hydrocele which can make the assessment by palpation of the testicle impossible. In slim patients, large retroperitoneal lymph node metastases can be diagnosed through deep palpation of the abdominal wall. The physical examination should also include the palpation of the supraclavicular lymph nodes to identify lymph node metastases in the opening of the ductus thoracicus in the angulus venosus, which occur in approx. 5% of cases (Albers et al. 2015). Inspection of the mammary glands can lead to the identification of a unilateral or bilateral gynecomastia which occurs in 2–5% of cases (more common in non-seminomatous tumors) as the result of hormonal dysregulation caused by the testicular tumor.

Patients with a familiar history of testis cancer, as well as their family members, should be advised to perform regular testicular self-examinations.

Imaging of the Testis: Ultrasound and MRI

A high-resolution ultrasound (5–10 MHz) is used as diagnostic method for suspected tumor findings. US sensitivity is almost 100%, and US has an important role in determining whether a mass is intra- or.

extratesticular (Richie et al. 1982). US should be performed even in the presence of clinically. MRI of the scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis (Sohaib et al. 2011).

For unclear findings, the use of ultrasound allows a differentiation between extra- and intratesticular lesions as well as between solid and cystic findings. Most testicular tumors are noticed in ultrasound through an outlined disturbance of the testicular parenchyma which shows a homogenous reflex pattern. In contrast to normal testicular parenchyma, tumor areas show a mostly hypo-echogenic, often also inhomogeneous, reflex pattern. Uncertainties can arise if the whole testicle is affected by the tumor and shows a relatively homogenous ultrasound image. Here, a comparative ultrasound of the contralateral testicle is helpful to identify a differentially distinct echogenicity of the testicle. In rare cases of a "burned-out tumor," only discrete changes in the affected testicle are visible in the form of small outlined microcalcifications. The ultrasound of the contralateral testicle should be included in all patients as in around 1% of cases, synchronous bilateral tumors are present.

Serum Tumor Markers at Diagnosis

Around two thirds of malignant testicular tumors produce serum tumor markers. Tumor markers are α-fetoprotein (AFP), which is produced by yolk sac cells, and the β-subunit of the human chorionic gonadotropin, which is produced by trophoblast cells (Albers et al. 2015). While AFP is only produced by non-seminoma, an increased β-hCG value can be present in seminoma as well as non-seminoma. Aside from a few exceptions where a false-positive marker increase can occur, β-hCG and AFP are specific for the presence of a malignant testicular tumor (Salem and Gilligan 2011). The half-life for AFP is 5–7 days and for β-hCG is 24–36 h. It is recommended to perform serum determination of tumor markers, both before and 5–7 days after orchiectomy for staging and prognostic reasons (Aparicio et al. 2011).

Of note, negative marker levels do not exclude the diagnosis of a germ cell tumor (Table 1).

A further relevant tumor marker in diagnosing malignant testicular tumors is lactate dehydrogenase (LDH). LDH may be increased in numerous diseases and therefore is relatively unspecific, yet it has significance for monitoring treatment and prognostic classification. The determination of the placental alkaline phosphatase or the neuron-specific enolase no longer places a role in clinical practice due to its low diagnostic value (Tandstad TKlepp 2003; Decoene et al. 2015).

Table 1 Causes of a false-positive AFP or β-hCG increase

AFP	β-hCG
Hepatocellular carcinoma	Pituitary tumor
Status posthepatitis	Hypergonadotropic hypogonadism
Cirrhosis of the liver	Terminal renal failure
Drug-induced liver cell damage	Serum or living cell treatment
Other carcinoma (pancreas, gastrointestinal tract, lungs)	
Tumor lysis	
Serum or living cell treatment with a buildup of heterophilic antibodies against foreign proteins	

Inguinal Exploration and Orchiectomy

The definitive diagnosis of a malignant testicular tumor is done by an inguinal surgical exploration with exteriorization of the testis within its tunics. In cases of life-threatening metastasis, chemotherapy should be given up front (Albers et al. 2015; Germa-Lluch et al. 2002).

During the operative exposure, the testis is mobilized and explored via an inguinal approach. For uncertain findings, a representative sample is taken for cryosection analysis. After confirmation of a malignant tumor, the spermatic cord is resected next to the internal inguinal ring. If there is a single testicle, an organ-saving tumor enucleation can be attempted with all the necessary precautions (less than 30% of the testis is affected, normal testosterone level, adjuvant radiation therapy with 20 Gy). A hemiscrotectomy is only necessary in rare cases of an infiltration of the testicular tumor into or via the parietal sheet of the tunica vaginalis testis.

A biopsy of the contralateral testicle is performed to rule out a germ cell neoplasia in situ (GCNIS) which occurs in up to 9% of testicular tumor patients (Dieckmann and oy 1996; Hoei-Hansen et al. 2003). A double biopsy increases sensitivity and in several European country's standard. If a GCNIS is present, there is a 50% risk that a malignant testicular tumor will develop within 5 years (von der Maase et al. 1986). On the other hand, a negative double biopsy has a high negative predictive value and makes follow-up easier, since the risk for a contralateral secondary tumor is negligibly low. The routine biopsy of the contralateral testis is discussed controversially due to the fact that metachronous secondary tumors mostly have clinical stage I. However, in the end, a contralateral biopsy should be considered carefully at least on patients with a high GCNIS risk (testicular volume < 12 ml, cryptorchidism or hypofertility, aged <30 years, microlithiasis of the testis). The listed considerations also apply for primary extragonadal mediastinal or retroperitoneal germ cell tumors, whereby the biopsy must occur bilaterally here. For patients with retroperitoneal germ cell tumors, a GCNIS can be detected in approximately

28–34% of cases which is associated with the risk of a metachronous testicular tumor – even after chemotherapy.

Staging Diagnostics

The retroperitoneal and mediastinal lymph nodes as well as the organs relevant for metastasis should be assessed using a contrast-enhanced computer tomography (CT) of the abdomen/pelvis (CT or MRI) and thorax (CT). This examination is recommended for all patients with newly diagnosed malignant testicular tumors. The supraclavicular nodes are best assessed by physical examination.

The sensitivity of the abdomen/pelvis CT is 70–80%. Magnetic resonance imaging (MRI) has an identical accuracy but higher costs and less availability. Contrast-enhanced CT thorax has a high sensitivity in the primary diagnostics of the lung and mediastinum and should be preferred in primary diagnostics to the conventional x-ray examination of the thorax.

In staging diagnostics and during follow-up of testicular tumor patients, CT is increasingly replaced by MRI to reduce radiation exposure. The MRI assessment of the retroperitoneum is challenging and requires the radiologist to have sufficient expertise. Depending on the primary stage, the thorax CT can be replaced by a conventional x-ray diagnosis, whereby the follow-up care recommendations differ in principle between localized and metastasized stages.

The fluorodeoxyglucose positron emission tomography (FDG-PET)-CT has only a limited value for the diagnostic work-up of testicular tumors (Yacoub et al. 2016). FDG-PET-CT is only recommended in the follow-up of patients with a seminoma postchemotherapy and a residual mass larger than 3 cm and should not be performed before 8 weeks after chemotherapy (de Wit et al. 2008). The sensitivity is about 72% and the specificity is about 93%. It should be pointed out that the FDG-PET-CT plays no role in staging diagnostics and in non-seminoma during follow-up.

Further imaging examinations such as a targeted ultrasound of the liver, a bone scan, or an MRI of the skull should be carried out if there is a clinical suspicion of the presence of metastases in these regions of the body. A CT or MRI of the skull is advisable in patients with non-seminoma and poor prognosis IGCCCG risk group. For these patients, the routine staging should be supplemented with a tomography of the skull, preferably an MRI (Yacoub et al. 2016; Sohaib et al. 2011).

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Treatment of Local Disease in Testicular Cancer

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Julia Heinzelbecker

Contents

Abstract

The primary treatment of local disease in testicular cancer has hardly changed during the last 100 years. High inguinal orchiectomy still represents the standard of care. The histological results of the operation together with the staging analysis and tumor markers form the basis for the further adjuvant treatment of testicular cancer. The implementation of a biopsy of the contralateral testis at the time of inguinal orchiectomy for the diagnosis or exclusion of germ cell neoplasia in situ (GCNIS) still remains controversial. In specific conditions such as synchronous and metachronous testicular cancer or a solitary testis, testis-sparing surgery followed by radiation therapy has gained wide acceptance. At the time of inguinal orchiectomy, the implantation of a testicular prosthesis can be offered safely to the patient.

Introduction

The primary treatment of local disease in testicular cancer has hardly changed during the last 100 years with high inguinal orchiectomy still presenting the standard operation technique. Nevertheless, with the introduction of testis-sparing surgery and the availability of testicular prosthesis, new aspects in the primary treatment of testicular cancer evolved.

Inguinal Orchiectomy

The primary treatment of testicular cancer is the inguinal orchiectomy of the tumor-bearing testis with the resection of the testis and the spermatic

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cord up to the level of the internal inguinal ring. An inguinal incision is performed and the spermatic cord is isolated. The dogma of using a tourniquet with the idea of preventing tumor seeding has to be questioned as current concepts of tumor biology rather favor specific molecular tumor characteristics for the development of metastasis than mechanical stress. The testis is then exteriorized and the gubernaculum ligated. In case of uncertainty for the malignant etiology of the tumor, an intraoperative frozen section can be performed. If malignancy of the testicle lesion is confirmed, the spermatic cord is dissected up to the internal inguinal ring. To guarantee high vessel control, the spermatic vessels are isolated from the spermatic cord and ligated separately. Afterward the aponeurosis is approximated and the specific wound layers are closed.

Scrotal violation should carefully be avoided as it is associated with a higher local relapse rate (2,9% versus 0,4%, respectively). Nevertheless in case of accidentally performed scrotal violation, no different adjuvant treatment compared to the inguinal access is necessary (Capelouto et al. 1995).

From the time point of diagnosis, the primary therapy should be performed in a timely manner as testicular cancer is one of the malignant diseases that is associated with a worse outcome in case of delayed diagnosis and treatment (Neal et al. 2015).

The results of the operation deliver the precise histology and together with the tumor markers and staging procedures provide the basis for the further adjuvant strategy in the treatment of testicular cancer. (See ▶ Chap. 43, "Symptoms, Diagnosis, and Staging in Testicular Cancer," this handbook.)

Biopsy of the Contralateral Testis

Performing biopsies of the contralateral testis at the time of inguinal orchiectomy has long since been under debate (Dieckmann et al. 2011; Heidenreich 2009). This is mainly due to the low incidence of GCNIS and metachronous testicular cancer and the debatable pathological value of GCNIS. Nevertheless there is consensus that testicular biopsy of the contralateral testis should be discussed with patients at higher risk for GCNIS preoperatively. Testicular cancer patients with testicular atrophy of the remaining testis (volume <12 ccm), age less than 40 years, a history of retained testis, or limited spermatogenesis bear a higher risk for GCNIS (Albers et al. 2015).

When conducting a biopsy, a double biopsy should be performed. The biopsies should be taken from the cranio-lateral part of the testis to avoid vessel injury. They should comprise a 3–4 mm part of testicular parenchyma (Dieckmann et al. 2011). The biopsies should be conserved in Bouin or Stieve's solution.

For the treatment of GCNIS, refer to the ▶ Chap. 45, "Management of Germ Cell Neoplasia In Situ (GCNIS)" from this handbook.

Testis-Sparing Surgery

In specific situations testis-sparing surgery might be an alternative to orchiectomy. In case of metachronous contralateral or synchronous bilateral testicular cancer or in tumors of a solitary testis, a partial orchiectomy may be performed. Thus endocrinological function and fertility can be retained and potential psychological stress avoided (Heidenreich et al. 2001). Nevertheless, this only seems rationale in case of small tumors given that a normal testosterone synthesis of the remaining testis can be preserved. Furthermore androgen insufficiency should be rolled out preoperatively.

Access to the testis is gained via standard inguinal incision. The spermatic cord is isolated. Occlusion of the spermatic vessels can be achieved with a tourniquet although some centers have abandoned ischemia. The testis is then exteriorized and the gubernaculum testis sectioned. For the exact localization of the tumor ultrasound, or small-caliber needles may be used. After complete resection of the tumor, biopsies of the tumor bed sent to frozen section can exclude tumor infiltration. Whether cold or warm ischemia should be used remains controversial (Giannarini et al. 2010).

Because of the appearance of GCNIS in the accompanying parenchyma in virtually all testicular cancers, radiation therapy should be performed. Its optimal dose still remains

controversial. Nevertheless, as studies applying less than 20 Gy failed to prove the eradication of TIN, the application of 20 Gy applied in ten fractions within 2 weeks is recommended (Giannarini et al. 2010; Heidenreich et al. 2001; Woo and Ross 2016). A certain amount of testicular cancer patients treated with testis-sparing surgery and radiation therapy becomes androgen insufficient. Furthermore the application of radiation therapy obligatory results in infertility. Thus in patients wanting to achieve paternity, the benefits of immediate or deferred local irradiation therapy must be weighted carefully against infertility. (See the ▶ Chap. 45, "Management of Germ Cell Neoplasia In Situ (GCNIS)," this handbook.)

Testicular Prosthesis

With testicular cancer becoming a highly curable disease, also quality of life aspects of long-term survivors have gained more and more importance. Thus aspects of long-term psychosexual aspects and body image issues have to be taken into account nowadays. In the 1940s the first testicular prosthesis was implanted. In the 1970s silicone devices became available and are nowadays the most commonly used devices. There is consensus that issues of implanting a testicular prosthesis should be discussed with testicular cancer patients before inguinal orchiectomy. According to the literature, 30–50% of testicular cancer patients favor the implantation of a prosthesis. A recent study concluded that an implantation of a testicular prosthesis can safely be administered at the time of inguinal orchiectomy without deferring adjuvant treatment (Bodiwala et al. 2007; Dieckmann et al. 2015; Robinson et al. 2016).

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Management of Germ Cell Neoplasia In Situ (GCNIS)

45

Pia Paffenholz

Contents

Abstract

Germ cell neoplasia in situ (GCNIS, also called testicular intraepithelial neoplasia (TIN) or carcinoma in situ (CIS) of the testis) is the precursor of testicular germ cell tumors (TGCT) and can be found in 5% of contralateral testes in TGCT patients. Although GCNIS can be diagnosed with a high accuracy using a two-site biopsy, the clinical relevance of contralateral testis biopsy remains to be discussed. According to the EAU guideline recommendations, a biopsy of the contralateral testis should only be performed in patients at high risk for GCNIS (testicular volume < 12 ml, history of cryptorchidism, poor spermatogenesis, > 40 years). In case of a contralateral GCNIS in the presence of unilateral TGCT, local radiotherapy (16–20 Gy) is the treatment of choice. However, radiotherapy will lead to infertility due to radiation-induced destruction of germ cells as well as the need of androgen substitution due to radiation-induced Leydig cell insufficiency in 20% of all patients. Consequently, fertile patients who wish to have children should perform sperm banking or may delay radiation therapy.

Introduction

Germ cell neoplasia in situ (GCNIS, also called testicular intraepithelial neoplasia (TIN) or carcinoma in situ (CIS) of the testis) is the precursor of testicular germ cell tumors (TGCT). GCNIS is found in approximately 5% of contralateral testes in TGCT patients (Dieckmann et al. 2007; Albers et al. 2015) and will progress to invasive cancer in

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50% of cases within 5 years if treatment is not performed (Hoei-Hansen et al. 2005). Treatment options encompass orchiectomy, local radiotherapy of the testis, or surveillance according to EAU guideline recommendations (Albers et al. 2015).

Pathohistological Features and Development of GCNIS

Microscopically, GCNIS cells are large with distinct nucleoli. They are in a typical pattern located in a single row at the usually thickened basement membrane of seminiferous tubules, which have decreased diameters (Hoei-Hansen et al. 2005). In general, there is no active spermatogenesis in the GCNIS-bearing tubules.

Detection of GCNIS is accomplished by standardized immunohistochemical staining methods (Berney et al. 2016). The most commonly used marker in clinical practice to identify GCNIS is placental-like alkaline phosphatase (PLAP), a tissue-specific alkaline phosphatase (Manivel et al. 1987). According to recent recommendations from experienced centers, immunohistochemistry for PLAP is mandatory for the adequate diagnosis of GCNIS (van Casteren et al. 2009).

The initiation of malignant transformation from a precursor cell to the GCNIS cell most likely takes place in utero during the early development of the germline stem cells. The target cell is probably a gonocyte, based on morphological resemblance between GCNIS cells and gonocytes with subsequent studies demonstrating overlapping expression patterns between fetal gonocytes and GCNIS cells of several proteins, for example, KIT, OCT3/4, and AP-2γ, which are not detectable in the adult testis and which can be used as markers in immunohistochemical staining methods (Hoei-Hansen et al. 2005; Hoei-Hansen et al. 2004; Rajpert-De Meyts et al. 2015; Jørgensen et al. 1995). Furthermore, all TGCTs are believed to originate from GCNIS, their common precursor, and have the differentiation potential to give rise to either the germ cell determined lineage (seminoma) or the pluripotent embryonal carcinoma, teratomas and even extraembryonic elements, such as yolk sac tumor and choriocarcinoma (Fig. 1).

Contralateral Biopsy

Currently, a testicular biopsy is the most common and reliable method to diagnose GCNIS having an accuracy of 99% and a sensitivity of 95% (Albers et al. 2015; Heidenreich 2009; Dieckmann and Loy 1996). However, it is still a controversial issue on whether the existence of contralateral GCNIS must be identified in all cases, and thus contralateral testis biopsy should be performed in all patients with unilateral testicular germ cell tumors. The following reasons underline this

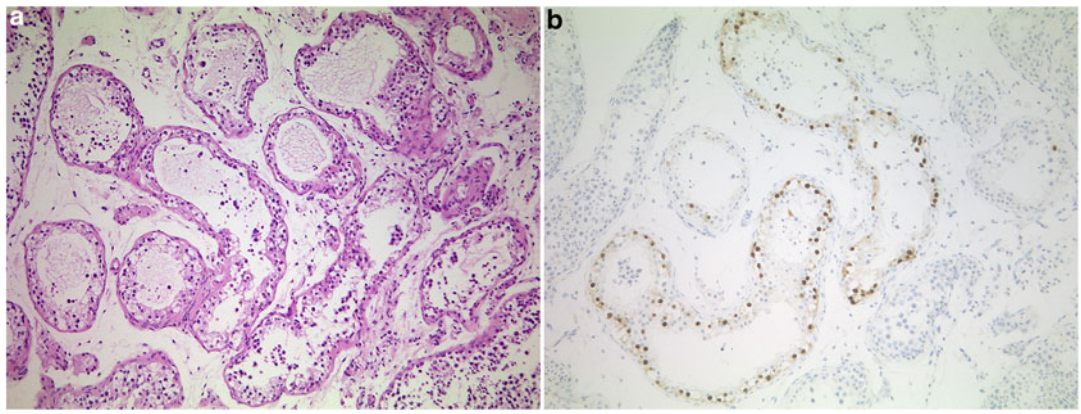

Fig. 1 (**a**) Germ cell neoplasia in situ shown by hematoxylin and eosin (H&E) (**a**) and highlighted by (**b**) octamer binding transcription factor 3/4 (OCT3/4) immunohistochemistry

discussion: the low incidence of GCNIS (approximately 9%) and contralateral metachronous testicular tumors (approximately 2.5%), a false-negative biopsy rate of 0.5–1.0%, and the fact that most of metachronous tumors are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy in all patients as well as the morbidity of GCNIS treatment, namely, infertility due to eradication of spermatogenesis and impairment of endocrine Leydig cell function following radiation therapy (Heidenreich 2009; Harland et al. 1998; Andreassen et al. 2011; Albers et al. 1999).

However, biopsy of the contralateral testis should be performed in patients at high risk for contralateral GCNIS, which have been defined as testicular volume < 12 ml, a history of cryptorchidism, or poor spermatogenesis (Johnson Score 1–3) (see Table 1) (Albers et al. 2015). Furthermore, a contralateral biopsy should not be offered to patients older than 40 years without risk factors (Albers et al. 2015; Heidenreich 2009; Heidenreich and Moul 2002).

Due to the multifocal spread of GCNIS throughout the testicle, a random biopsy of 3 mm will be sufficient to detect GCNIS if ≥10% of the testicular volume consists of tubules with GCNIS (Berthelsen and Skakkebæk 1981). However, a prior prospective study of 2318 patients with TGCT showed that a systematic two-site biopsy is significantly more sensitive for detecting GCNIS compared to a single testis biopsy (Dieckmann et al. 2007; Kliesch et al. 2003). The study furthermore showed that 31% of biopsies were discordant and that discordancy was significantly more frequent in patients with a normal testicular volume and unimpaired spermatogenesis (Heidenreich 2009). Taken together, a two-site surgical testis biopsy should be favored over a single testis biopsy for an accurate diagnosis of GCNIS. However, patients should be informed that a TGCT may arise in spite of a negative biopsy (Souchon et al. 2006).

Table 1 Risk factors for contralateral GCNIS in patients with unilateral TGCT (Heidenreich 2009)

Risk factor	Relative risk (95% CI)
Testicular atrophy (<12 ml)	4.3 (2.83–6.44)
History of cryptorchidism	2.1 (1.21–3.63)
Age < 30 years	1.7 (1.17–2.6)
Family history of testis cancer	2.2 (1.25–12.3)
Infertility	1.6 (1.10–10)

Treatment of GCNIS

The most common clinical situation is the case of contralateral GCNIS in the presence of unilateral testicular cancer. Local radiotherapy (16–20 Gy in fractions of 2 Gy) is the treatment of choice in these patients (Albers et al. 2015). It is an effective therapeutic measure eradicating all GCNIS cells, thus preventing the development of secondary testicular cancer. Furthermore, it preserves the external shape of the scrotum for the preservation of the masculine body image. However, testicular radiotherapy will result in infertility due to radiation-induced destruction of germ cells, resulting in a "Sertoli cell-only" syndrome, and increased long-term risk of Leydig cell insufficiency in 20% of all patients leading to lifelong androgen substitution (Albers et al. 2015; Heidenreich 2009; Heidenreich and Angerer-Shpilenya 2012; Petersen et al. 2002). Therefore, testosterone levels should be evaluated every 6 months during follow-up (Albers et al. 2015). Consequently, fertile patients who wish to have children may delay radiation therapy and be followed by regular testicular ultrasound instead (Dieckmann et al. 2007; Albers et al. 2015). In case of a solitary testis after orchiectomy of the contralateral testis, chemotherapy is significantly less effective and the cure rates are dose-dependent (Albers et al. 2015; Dieckmann et al. 2013).

If metastatic disease of the primary tumor requires chemotherapy, the treatment of GCNIS should be deferred, as 30% of all GCNIS cases will persist and 42% will recur after chemotherapy (Albers et al. 2015). A repeat biopsy of the remaining testicle should be done 1 year after completion of chemotherapy (Albers et al. 2015). In cases with persistent GCNIS, additional radiotherapy should be given (Albers et al. 2015).

If only GCNIS is diagnosed and the contralateral testis is healthy (in case of infertility screening or primary extragonadal TGCT), treatment

options are orchiectomy or close observation, with patients having 50% risk of developing TGCT within 5 years (Albers et al. 2015; Hoei-Hansen et al. 2005). Radiotherapy is not feasible in these cases because of shielding problems with the healthy testis (Albers et al. 2015). Patients with bilateral CIS should be offered radiation therapy (Albers et al. 2015).

GCNIS and Fertility

Generally spoken, the treatment of GCNIS should be adapted to the particular situation of each patient as patients with GCNIS have only small residual potential of fertility and the eradication of GCNIS implies the loss of fertility (Dieckmann et al. 2007). Consequently, fertility aspects have to be considered before any kind of treatment.

As stated before, local testicular radiotherapy will have influence on the exocrine and endocrine testicular function.

First, it will result in the disappearance of all germ cells, thus leading to an irreversible infertility, which can be shown by a Sertoli cell-only syndrome on histopathological analysis of a biopsy after radiotherapy (Heidenreich 2009). Nevertheless, proponents of testicular radiation propose that the semen quality is low anyway as GCNIS is significantly associated with poor spermatogenesis and with testicular atrophy, so that radiotherapy will not significantly contribute to the development of infertility (Dieckmann et al. 2007; Petersen et al. 1999). However, poor sperm quality at the time of orchiectomy can improve during follow-up time, thus resulting in conception, which have been shown in various cases (Heidenreich 2009; Dieckmann and Loy 1993; Heidenreich et al. 1997; Kliesch et al. 1997). Consequently, semen analysis can be performed at time of diagnosis, and local radiation can be delayed for the purpose of paternity (Heidenreich 2009). Furthermore, sperm banking or cryopreservation of testicular tissue for future sperm extraction (TESE) and assisted fertilization should be offered to highly oligospermic patients with a strong desire for fatherhood.

Second, endocrine testicular function will be impaired after radiotherapy. Prior studies described an impairment of Leydig cell function in 20–30% of all patients as well as androgen substitution in 25% of all cases after radiation with 20 Gy due to GCNIS in a solitary testis (Giwercman et al. 1991). However, these patients might already have a compensated Leydig cell insufficiency before treatment, being more susceptible to an additional gonadotoxic treatment (Heidenreich 2009).

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Management of Clinical Stage I (CSI) Disease in Testicular Cancer

46

Susanne Krege

Contents

Abstract

Though imaging does not give any hint to metastases, clinical stage I testis cancer patients might harbor micrometastases within the retroperitoneal lymph nodes. For this reason it was standard to offer adjuvant treatment at least to patients with a high risk for occult metastases. In seminoma a tumor size >4 cm and a rete testis infiltration were identified as risk factors; in nonseminoma it was vascular invasion. High-risk seminoma patients received adjuvant radiation of the paraaortal/paracaval region. Later, one course of carboplatinum became the favored option as application was short and with few side effects. Radiotherapy also became unattractive after reports about an increase of secondary malignancies in the long term. Recent data showed a decrease of recurrences (15–20% in case of high risk and 2–3% in case of low risk) even without adjuvant treatment, while recent publications about carboplatinum report about a 9–10% relapse rate in the long term. Therefore actually it is discussed to recommend surveillance for all clinical stage I seminoma patients.

Risk-adapted treatment in clinical stage I nonseminoma offered one course of PEB chemotherapy to high-risk patients with 30–50% occult metastases and recommended surveillance for low-risk patients with 10–15% micrometastases. As large series from Canada and the northern European countries reported excellent survival data also for high-risk patients under surveillance, the latter is discussed as general recommendation for all clinical stage I nonseminoma patients. Another argument for such a recommendation is long-term toxicity of polychemotherapy, especially cardiovascular events.

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Introduction

Testicular cancer is a rare disease with about 4500 cases per year in Germany. About 60% present as clinical stage I, which means tumor markers are normal and imaging does not show metastases. But, especially imaging of the retroperitoneal lymph nodes might be false negative. Micrometastases can't be detected. Therefore adjuvant therapy should be considered, especially in those patients, who are at high risk for micrometastases. The risk depends on risk factors of the primary tumor, which are a tumor size >4 cm and a rete testis infiltration for seminomas and vascular invasion for nonseminomas (Warde et al. 1997; Albers et al. 2003). Over the time the importance of these factors changed, especially for those concerning seminoma. But recently at least tumor size was confirmed to be a strong predictor for recurrence by several publications (Tandstad et al. 2016). There is also discussion about the kind of adjuvant therapy. For several decades adjuvant radiotherapy was the standard treatment for seminomas. Then a randomized study showed comparable results for one course of carboplatinum (Oliver et al. 2005). And after reports about an increased risk for secondary malignancies after adjuvant radiotherapy, carboplatinum became the new standard (Horwich et al. 2014). In case of nonseminoma first two courses of polychemotherapy with cisplatin, etoposide, and bleomycin (PEB) were given. After a study showed comparable results for 1xPEB and prospective data confirmed this, adjuvant treatment was reduced to 1xPEB (Tandstad et al. 2014). Recently surveillance, which is offered in case of a low-risk situation, is discussed for all clinical stage I seminomas and nonseminomas (Cohn-Cedermark et al. 2015; Kollmannsberger et al. 2015).

CSI Seminoma

Clinical stage I (CSI) seminoma is the most common tumor stage among testicular cancer. In 1997 Warde et al. presented a retrospective analysis of 638 patients and could show that a tumor size >4 cm and a rete testis infiltration correlated with a higher rate of micrometastases within the retroperitoneal lymph nodes and therefore with a higher rate of recurrences, exactly 12% in case of no risk factors, 15.9% with one, and 31.5% with two risk factors (Warde et al. 1997). Because of these differences, adjuvant treatment was recommended for patients with one or two risk factors. For decades radiotherapy of the retroperitoneum (paraaortal/paracaval and ipsilateral iliacal with 30 Gy) was favored (Warde et al. 1995). Over the time studies were performed to reduce the field as well as the dosage (Fossa et al. 1999; Jones et al. 2005). Finally this resulted in the recommendation to perform radiation of the paraaortal and paracaval lymph nodes with 20 Gy. In parallel the option of carboplatinum monotherapy was established. At first several working groups gave two courses of carboplatinum, 400 mg/qm, and then one course according to AUC7 was favored. Oliver et al. performed a randomized trial comparing adjuvant radiation as mentioned above and one course of carboplatinum. The study showed a comparable oncological outcome with 3.3% recurrences in the radiation arm and 2.3% recurrences in the carboplatinum arm at 2 years of follow-up, though subjective parameters were in favor of carboplatinum. Patients after chemotherapy reported less fatigue and could start work again much earlier than patients after radiotherapy (Oliver et al. 2005). Especially the comfortable way of application in the outpatient clinic, once over about 2 h, established carboplatinum as the new standard. This was confirmed when reports about an increased rate of secondary malignancies after adjuvant radiotherapy were published (Lewinshtein et al. 2012). Horwich reported about 2543 patients with a median follow-up of 21,8 years. The standardized incidence ratio for secondary malignancies was 1,53, especially concerning cancer of the bladder, pancreas, and stomach (Horwich et al. 2014). Though it must be said that only a minority of patients were treated according to the modern concept of reduced field and dose.

Comparing recurrence rates in CSI seminoma without adjuvant therapy reported by Warde (12%, 16%, and 31% for no, one, or two risk factors) and the recurrence rate after 1 x carboplatinum with 5.3% within the long-term analysis of Oliver et al., it seemed worthwhile to

recommend adjuvant carboplatinum (Warde et al. 1997; Oliver et al. 2011). This was confirmed by data from the Spanish Germ Cell Cancer Group. Two hundred twenty-seven patients were reviewed. Those with no or only one risk factor underwent surveillance, and those with two risk factors received carboplatinum, but two courses. Recurrence rates were 4.8% in case of no risk factor, 13.6% for tumors >4 cm, 20% for rete testis infiltration, and 1.4% in case of both risk factors and adjuvant carboplatinum (Aparicio et al. 2011). Recent data from the SWENOTECA revealed a diminished recurrence rate of only 2.9% in patients without risk factors and 21.7% in case of one or two risk factors, which might result from better diagnostics (Tandstad et al. 2011). Logically for low-risk patients, carboplatinum is of no profit.

An even newer analysis of the SWENOTECA with 897 prospectively treated patients and 221 patients from the former study, done for validation of the risk factors, confirmed their significance, especially concerning tumor size. This even was a continuous variable to predict relapse. In the group of prospectively treated patients, 53% received carboplatinum, though only 12% had two risk factors, the only group for which adjuvant treatment was recommended in the study, similar as in the former mentioned Spanish publication (Tandstad et al. 2016). This reflects the popularity this kind of therapy has reached in the meantime. The recurrence rates are shown in Table 1.

But the study also revealed a much higher recurrence rate for 1x carboplatinum AUC7 in the long term. After a median follow-up of 5,6 years, it was 10.6% for patients with both risk factors. This means every 10th patient will develop a recurrence after adjuvant carboplatinum.

Table 1 Results from the SWENOTECA VII trial (Tandstad et al. 2016)

Recurrence rate (%)	Surveillance	1 x carboplatinum
Overall	7.5	6.2
No risk factor	4.0	2.2
p-value	<0.001	0.001
1–2 risk factors	15.5	9.3
According to recommendation	7.7	10.6
(1xCarbo in case of 2 risk factors)		

Another recent publication by Dieckmann et al. reported about treatment of CSI seminoma in Germany. Among 1050 patients, collected between 2008 and 2013, 725 patients had a sufficient follow-up (med. 40 months) for analysis. Two hundred fifty-six men underwent surveillance, 41 received radiotherapy, 362 received one course of carboplatinum AUC7, and 66 patients got 2xcarboplatinum, 400 mg/qm. The recurrence rates were 8.2%; 2.4%; 5.0%, and 1.5% (Dieckmann et al. 2016).

All these recent data create doubts about the effectiveness of carboplatinum, especially one course, in the adjuvant setting. Therefore the present recommendation prefers surveillance independent of risk factors. Then the question about the best follow-up scheme arises. The SWENOTECA study and the publication by Dieckmann et al. report about the majority of recurrences within the first 2 years of follow-up. And most relapses occurred within the retroperitoneum. Two publications about late relapses after active surveillance mention a recurrence rate of 4–5% after 5 years (Mortensen et al. 2016; Hosni et al. 2016). With a median follow-up of 15 years among 2000 patients, the conditional relative risk of recurrence after 5 years was 5% and after 10 years 1% in the publication by Mortensen et al. (2016). Hosni et al. reported a late recurrence rate of 4% among 766 patients under surveillance and 1% among 294 patients after adjuvant radiotherapy. Patients were treated without considering risk factors (Hosni et al. 2016). Again under surveillance nearly all recurrences occurred within the retroperitoneum and after radiotherapy in the pelvis or mediastinum.

Conclusions for the Treatment of CSI Seminoma

In the low-risk situation, no kind of adjuvant therapy can lower the recurrence rate of only 3–4%.

In the high-risk situation with a recurrence rate of 10–20%, treatment with one course of

carboplatinum and a recurrence rate of up to 10% seems questionable. Until we have better alternatives also high-risk patients should undergo surveillance.

Follow-up examinations should be very close for the first 3 years and close for 2 years more. Imaging is essential, because the majority of recurrences will occur within the retroperitoneum. To lower the risk of secondary malignancies caused by higher frequency of imaging, especially CT-scans, low dose CT-scans of MRTs should be preferred.

CSI Nonseminoma

In case of CSI nonseminoma, vascular invasion (VI) has been prospectively evaluated as a risk factor for occult metastases within the retroperitoneum. Also the amount of embryonal carcinoma (>80%) shows relevance, but could not be identified as an independent risk factor within multivariate analysis (Albers et al. 2003). In case of no vascular invasion, there is a 10–20% rate of micrometastases, while patients with vascular invasion show occult metastases in up to 50%. Therefore in the high-risk situation, adjuvant treatment with two courses of PEB chemotherapy was recommended (Fernandez-Ortega et al. 2000). Then data from a German study for CSI nonseminoma with one arm comparing retroperitoneal lymphadenectomy (RLA) and 1xPEB in the high-risk situation showed a recurrence rate of 7.5% after RLA and only 1% after 1xPEB after a median follow-up of 47 months, which was highly significant ($p = 0{,}0028$) (Albers et al. 2008). Consequently a randomized study was initiated to compare 2xPEB versus 1xPEB. Unfortunately the recruitment of this study was low and the study was closed. But at the same time, the SWENOTECA treated CSI nonseminoma patients prospectively with 1xPEB. The first publication with a median follow-up of 5 years reported a recurrence rate of 3.5% in the high-risk situation ($n = 157$) and 1.4% in the low-risk situation ($n = 155$) after 1xPEB and 12.6% after surveillance in the low-risk situation ($n = 461$) (Tandstad et al. 2009). The recent publication with a median follow-up of 8 years reported about 2.3% of recurrences in 517 patients, 3.2% in patients with, and 1.6% without vascular invasion. Ten-year disease-free survival was 99,6% and overall survival 99.8% (Tandstad et al. 2014).

But also for this entity, surveillance as a general strategy was tested. Kollmannsberger et al. performed surveillance in 1034 patients (886 without VI, 220 with VI, 28 unknown), and 221 patients recurred, 150 (17%) without VI and 60 (27%) with VI – median follow-up 63 months. Nearly all recurrences occurred within the first 3 years of follow-up; disease-free survival reached 98% (Kollmannsberger et al. 2015). Daugaard et al. reported about 1226 patients under surveillance. The 5-year recurrence rate was 30.6%. Seventy percent of the relapsed patients were VI positive. Median time to recurrence was 5 months. Fifty-nine percent of the relapses occurred only in the retroperitoneum, 16% only in the lungs, 7% at both sides, and 5% in the inguinal region. Relapses were detected by marker elevation and/or imaging. Daugaard also classified the relapses according to the IGCCCG classification: 94.4% were of good, 4.7% of intermediate, and 0.8% of poor prognosis. Fifteen-year disease-specific survival was 99.1% and overall survival 94.5%. Only 3.9% of the patients showed a poor compliance using the surveillance strategy (Daugaard et al. 2014).

One fact which supports surveillance for all CSI nonseminoma patients is the increased risk for cardiovascular events after chemotherapy (Kero et al. 2014; Huddart et al. 2003). Especially cisplatinum, but also bleomycin causes vascular damage. An analysis of the SEER database with 6909 patients after chemotherapy showed a standardized mortality ratio of 1,36. Especially within the 1st year after chemotherapy, it is very high with 5,31 (21,72 for cerebrovascular events and 3,45 for cardiac events) (Fung et al. 2015). It could also be shown that especially young patients will suffer from cardiovascular side effects. Van den Belt-Dusebout reported about the incidence of myocardial infarction in testis cancer patients, which reached 2,06 for patients younger than 45 years, 1,86 of those 46–54 years old, and 0,53 for those 55 years or older (Van den Belt-Dusebout et al. 2006).

Concerning secondary malignancies during long-time follow-up, there is also an increased rate after chemotherapy (Fung et al. 2012). But there exists only one report considering patients who only received one course of PEB. Among 40 high-risk patients, 3 (7.5%) developed a secondary malignancy, 2x colorectal cancer, and 1x an acute lymphatic leukemia, though the latter patient had a recurrence of his testis cancer before and received three more courses of PEB (Vidal et al. 2015).

Conclusions for the Treatment of CSI Nonseminoma

Recent data reveal a recurrence rate of about 15% for low-risk and at least 30% for high-risk patients. 1xPEB can reduce the relapse rate to 1.4% in the low-risk and 3.5% in the high-risk situation.

Therefore at least in the high-risk situation adjuvant therapy is justified. It can also be discussed for those 15% of patients in the low-risk group, because in case of a recurrence they need another three to four cycles of PEB.

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Treatment of Clinical Stage II (CS II) Disease in Testicular Cancer

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Christian Winter

Contents

Abstract

Testicular cancer represents the most common solid malignancy of young men aged 15–40 years. Germ cell tumors are best divided into those with pure seminoma and non-seminoma histology. The treatment of metastatic testicular germ cell tumors is based on risk stratification according to histological feature, clinical stages and IGCCCG classification. Clinical stage II disease (CS II) is defined by the presence of testicular cancer in the orchiectomy specimen and imaging studies of the abdomen and pelvis that show positive regional lymph nodes. Other potential sites of metastasis, such as the chest, are free of disease. About 10–30 percent of patients with seminoma and non-seminoma have stage CS II disease at clinical presentation. These patients with lymphatic metastasis should be treated with individualized risk-stratification and within a multidisciplinary approach of chemotherapy, radiotherapy and surgery at centres of excellence.

Introduction

Malignant tumors of the testis are rare, but testicular cancer is the most common cancer among men between the age of 15 and 40 years and represents the leading cause of cancer-related mortality and morbidity in this age group (Bosl and Motzer 1997; Winter and Albers 2011).

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Nevertheless patients with testicular cancer currently show excellent cure rates. The main factors contributing to this therapeutic success are improving knowledge about the pathogenesis of testicular cancer, the exact staging at the time of diagnosis, an adequate early treatment based on multimodal strategies like combination of chemotherapy, radiotherapy, and surgery, and at least a very strict follow-up and consequent salvage therapies.

During the past decades, major progress has been made in efficacy of testicular cancer treatment. The treatment of metastatic testicular germ cell tumors is based on risk stratification according to clinical stages and IGCCCG classification.

Clinical stage II disease is defined by the presence of testicular cancer in the orchiectomy specimen and imaging studies of the abdomen and pelvis that show positive regional lymph nodes. Positive nodes are those that measure at least 10 mm on the short axis of cross-sectional imaging. Other potential sites of metastasis, such as the chest, are free of disease. About 10–30% of patients with seminoma and non-semioma have stage CS II disease at clinical presentation.

Definition of Clinical Stage II (CS II) in Testicular Cancer

After completing diagnostic procedures including histological analysis of the testicular cancer, tumor marker detection, and radiological examination, the clinical stage (CS) based on UICC/TNM classification and serum tumor markers should be defined.

Metastatic diseases are classified according to the classification of the International Germ Cell Cancer Collaborative Group (IGCCCG) including the histological features, location of primary and metastatic lesions, and tumor marker levels (after orchiectomy). The optimal individual treatment strategy is predicated on the clinical stage (CS) and the IGCCCG classification (Winter and Albers 2011; Krege et al. 2008a, b; Beyer et al. 2013; Albers et al. 2015).

Patients in clinical stage II present regional lymphatic metastasis (retroperitoneum) but have no signs of metastasis in any other distant lymph nodes or organs (any T, N1–3, M0, SX).

In clinical stage CS IIA, tumor cells have spread to retroperitoneal lymph nodes, either clinical or pathological stage N1, but none is larger than 2 cm, and, if a lymph node dissection has been done, no more than five lymph nodes contain cancer. In addition, serum tumor markers are at normal levels or only slightly high, and there are no signs of cancer having spread anywhere other than the retroperitoneum (any T, N1, M0, S0, or S1).

In clinical stage IIB, testicular cancer has spread to lymph nodes in the retroperitoneum, and the largest lymph node with cancer or lymph node mass is between 2 cm and 5 cm in size; or, if a lymph node dissection has been done, cancer has spread to at least one lymph node (or lymph node mass) between 2 cm and 5 cm or to more than five lymph nodes, none larger than 5 cm. Serum markers are at normal levels or slightly high, and there is no evidence of cancer having spread anywhere other than the retroperitoneum (any T, N2, M0, S0, or S1).

In clinical stage IIC, the germ cell tumor has spread to at least one lymph node (or lymph node mass) that is larger than 5 cm. Serum markers are at normal levels or slightly high, and there is no evidence of cancer having spread anywhere other than the retroperitoneum (any T, N3, M0, S0, or S1).

Treatment of Seminoma/Non-seminoma CS IIA/B

Stage IIA/B Seminoma

Enlargement of retroperitoneal lymph nodes <2 cm in seminoma patients with negative tumor markers offers a diagnostic problem. These lymph nodes may be benign or represent lymphatic metastases. A re-evaluation after 6–8 weeks with a further staging examination is recommended unless a biopsy verifies metastatic disease. A definitive treatment should not be initiated unless metastatic disease is confirmed.

In low-volume metastatic disease of radiosensitive seminoma CS II A/B with radiological detection of infra-diaphragmatic metastasis <2 cm (CS IIA) and 2–5 cm (CS IIB), the recommended standard therapy is radiotherapy with total doses of 30 Gy (CS IIA) and 36 Gy (CS IIB). The standard radiation field should be extended from the para-aortic region to the ipsilateral iliac field (hockey-stick field). The lateral field margin in seminoma CS IIB should be modified to the lymph node size with a safety distance of 1.0–1.5 cm. The relapse rates are moderate (5% in CS IIA, 11% in CS IIB), and overall survival of patients with seminoma CS IIA/B is almost 100% (Classen et al. 2003; Chung et al. 2004). Dose reductions to 27 Gy have been associated with 11% relapses (Tandstad et al. 2011). Another recent study has shown a high rate of relapse in this group of seminoma patients (16%) and in postsurveillance relapses treated with radiotherapy alone (Kollmannsberger et al. 2011) (Fig. 1).

Current data on long-term morbidity, such as increased risk of cardiovascular events and increased risk of second malignancies after radiotherapy, has raised concerns.

In CS IIB chemotherapy with three cycles of BEP or four cycles of EP (etoposide, cisplatin) depending on IGCCCG risk group remains an alternative to radiotherapy with comparable oncological outcome but higher acute and long-term toxicity (Garcia-del-Muro et al. 2008). One population-based study with 67 stage IIB patients reported a relapse-free survival of 100% after a median follow-up of 5.5 years (Tandstad et al. 2011). Chemotherapy treatment recommendations for stage IIB disease are the following: EP regimen for four cycles (etoposide 100 mg/m^2 on days 1–5 plus cisplatin 20 mg/m^2 on days 1–5; every 21d) or BEP regimen for three cycles (etoposide 100 mg/m^2 on days 1–5 plus cisplatin 20 mg/m^2) on days 1–5 plus bleomycin 30 mg on days 1, 8, and 15; every 21d.

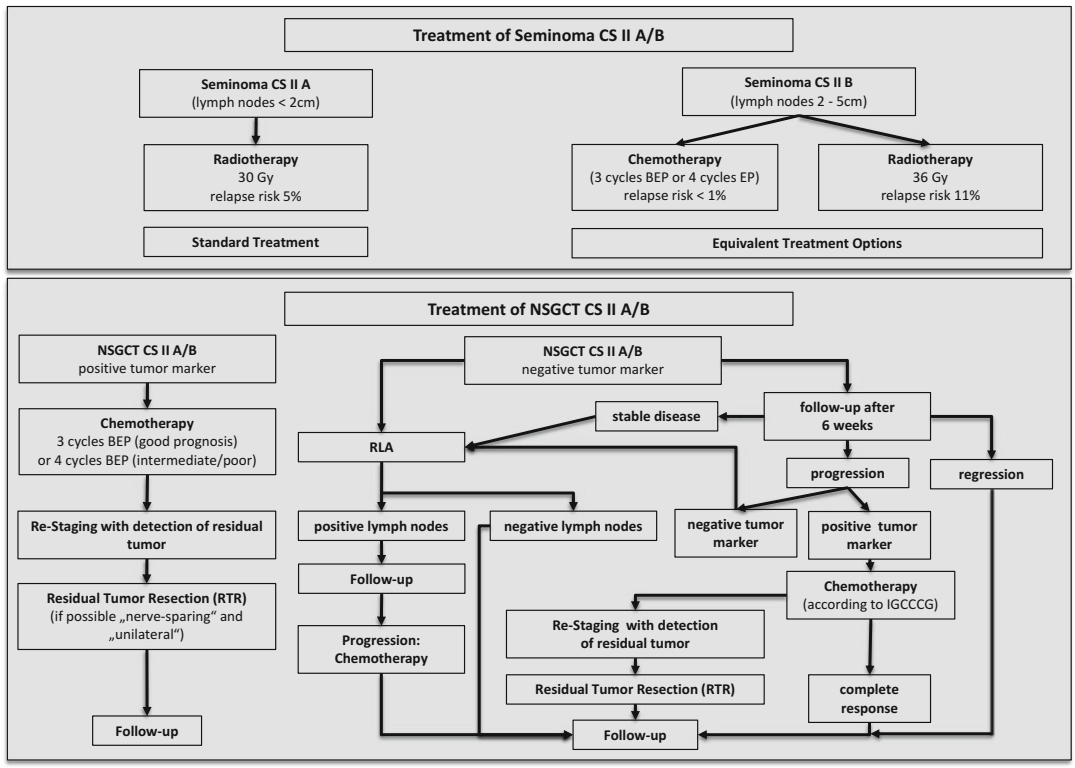

Fig. 1 Treatment algorithm of seminoma clinical stage II A/B and nonseminomatous germ cell tumors (NSGCT = Nonseminoma) clinical stage II A/B

Also in stage IIA patients, chemotherapy with three courses of BEP or four courses of etoposide and cisplatin (EP), in cases with contraindications to bleomycin, is an alternative to radiotherapy. There are no randomized studies comparing radiotherapy versus chemotherapy.

Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease (Krege et al. 2006). In CS IIA patients with seminoma, enrollment in clinical trials offering treatment options with potentially lower toxicity as compared to either radiotherapy or chemotherapy with three cycles BEP is recommended.

Recently Horwich et al. showed excellent treatment results by using a combination of radiotherapy and chemotherapy in patients with seminoma CS IIA/B (Horwich et al. 2013). The 100% recurrence-free survival rate was achieved by of a low-intensity carboplatin chemotherapy combined with partially limited dose and volume radiotherapy. The key idea behind this concept was eliminating the weaknesses of the single used therapies either radiotherapy or chemotherapy by combining both. While radiation therapy is highly effective in the para-aortal and pelvic nodal regions, relapses can occur outside the irradiated volume (Classen et al. 2003). On the other hand, carboplatin can safely combat microscopic tumor deposits, but it cannot achieve satisfactory remission in the involved lymph nodes (Krege et al. 2006). Combining both modalities may achieve optimal results without additional toxicity.

The Swiss Group for Clinical Cancer Research (SAKK) together with the German Testicular Cancer Study Group (Zengerling et al. 2014) has embarked on a prospective trial to test one cycle carboplatin (AUC7) followed by involved node radiation therapy for stage IIA/B seminoma patients (SAKK-01/10 – NCT01593241). This multicenter trial is recruiting patients since 2012.

A further alternative phase II study in Germany investigates the role of a sole operation of these small-volume metastases without any other adjuvant therapy in seminoma patients CS IIA/B with negative tumor markers (PRIMETEST – NCT02797626).

Stage IIA/B Non-seminoma

Patients with non-seminoma clinical stage II A/B and an elevation of tumor marker levels should be treated according to IGCCCG risk group recommendations. Specifically, those with a "good prognosis" should be treated with three cycles of BEP and those with "intermediate" or "poor prognosis" with four cycles of BEP.

In cases of detection of residual retroperitoneal tumor >1 cm, a residual tumor resection is mandatory. In residual tumor resection after chemotherapy, surgical margins should not be compromised in an attempt to preserve ejaculation ability, although nerve-sparing dissections are possible in patients with marker normalization after chemotherapy and no viable tumor was assessed by frozen section histology. In these patients, nerve-sparing techniques and the reduction of the surgical field to a left-sided or right-sided template are possible to preserve antegrade ejaculation and fertility (Winter et al. 2009).

Patients with non-seminoma stage II A/B without elevated tumor markers can be treated with primary retroperitoneal lymph node dissection (RPLND), if possible using a nerve-sparing technique. RPLND represents the first treatment option and should be performed by an experienced surgeon. If undifferentiated embryonal carcinoma is detected, adjuvant chemotherapy with two cycles of BEP is indicated, depending on the extent of the metastatic disease and lymph node density. If teratoma is detected, postoperative surveillance is recommended after a complete resection. Alternatively to RPLND, a surveillance strategy with a 6-week follow-up examination is indicated to evaluate whether the retroperitoneal lesion grows, is stable, or shrinks. In patients with rapidly growing lesions and rising tumor markers, the tumor should not be resected but treated with a primary BEP chemotherapy strategy according to IGCCCG recommendations (Beyer et al. 2013).

An alternative to the surveillance strategy in marker-negative II A/B non-seminoma with suspicion of an undifferentiated malignant tumor is a CT-guided biopsy, if technically possible. There is insufficient published data on PET scans in this situation (Fossa et al. 2005).

In cases of progressive or stable disease with negative tumor markers, a teratoma or a growing, undifferentiated malignant tumor is suspected, and a RPLND is indicated. A shrinking lesion is probably of nonmalignant origin and should be monitored in further follow-up examinations (Fig. 1).

When primary chemotherapy is refused by the patient or when it has some contraindications, primary nerve-sparing RPLND represents a viable option. Primary chemotherapy and primary "nerve-sparing" RPLND are comparable options in terms of outcome, but early and long-term side effects and toxicity are different.

So Weissbach et al. (Weissbach et al. 2000) performed from 1991 till 1995 a prospective multicenter trial with 187 patients from 57 participating centers comparing RPLND plus 2 cycles of PEB chemotherapy (arm A, n = 109) with 3–4 cycles of primary PEB chemotherapy plus post-chemotherapy residual tumor resection (RTR) (arm B, n = 78). After a median follow-up of 36 months, 7% of the patients in arm A and 11% in arm B had relapsed. Two patients died due to complications of chemotherapy. Surgical complications occurred to 12% in arm A and to 27% of 26 RTRs (9% in arm B). Weissbach et al. demonstrated that primary operation is associated with less complications than that following chemotherapy.

On the other hand, Stephenson et al. from Memorial Sloan-Kettering Cancer Center (MSKCC) (Stephenson et al. 2007) demonstrated in 2007 that primary chemotherapy in patients with NSGCT CS IIA/B was associated with improved relapse-free survival compared with RPLND (98% vs. 79%; $p < 0.001$), but disease-specific survival did not differ significantly (100% vs. 98%; $p = 0.3$). Between 1989 and 2002, 252 patients with NSGCT CS IIA/B were treated at MSKCC – 136 patients underwent RPLND, and 116 patients received chemotherapy and post-chemotherapy RTR.

The therapy approach for patients with NGSCT CS IIA/IIB is still controversial because the overall survival is excellent with both approaches primary chemotherapy followed by RTR in specific cases or primary RPLND followed by two cycles of adjuvant chemotherapy also in selected patients. For these clinical stages, all European guidelines recommend starting with initial chemotherapy in all advanced cases of NSGCT except for CS II NSGCT disease without elevated tumor markers, which can be alternatively treated with primary RPLND or surveillance.

Treatment of Seminoma/ Non-seminoma CS II C

Stage II C: Seminoma or Non-seminoma

Advanced or metastatic germ cell tumors should always be considered potentially curable. Survival outcomes are better in specialized centers, which may be related to experience, case selection, volume, and the organization of multidisciplinary care (49).

In IGCCCG analysis, the 5-year overall survival of patients with intermediate prognosis and poor prognosis was 80% and 48%, respectively (de Wit et al. 1995).

In germ cell tumors of stage CS IIC and/or in stage CS III, chemotherapy with BEP, EP, or PEI (cisplatin, etoposide, ifosfamide) according to IGCCCG risk classification remains standard treatment. In patients classified as having a good prognosis, three cycles of BEP or (in cases of bleomycin contraindications) four cycles of EP are recommended, and in patients classified as having an intermediate or poor prognosis, four cycles of BEP or four cycles of PEI should be given. In several studies, other chemotherapy regimens have not proven to be more effective or less toxic (Culine et al. 2008).

Restaging examination has to be performed by imaging or re-evaluation of tumor markers after two cycles of chemotherapy. In cases of adequate tumor marker decline and stable or regressive tumor manifestation, the initiated chemotherapy should be completed. If tumor markers decline but metastases grow, a presence of growing teratoma syndrome is possible, and a resection of the tumor is obligatory at least directly after completion of chemotherapy in cases of positive markers (Andre

et al. 2000). In patients classified as having a poor prognosis whose tumor markers rise or decline slowly or inadequately after the first cycle of chemotherapy, dose intensification, a different chemotherapy regimen, or high-dose chemotherapy should be considered. After having completed chemotherapy or radiotherapy, an evaluation of tumor markers and imaging investigations is mandatory.

A residual mass of seminoma should not be resected, irrespective of the size, but should be monitored regularly by imaging investigations and tumor markers. FDG-PET is a valuable tool to evaluate whether the residual mass contains viable tumor tissue or only necrosis after treatment of seminoma (Hinz et al. 2008). In patients with residuals of >3 cm, FDG-PET should be performed more than 2 months after chemotherapy in order to get more information on the viability of these residual tumors. In patients with residual tumor less than 3 cm, the use of FDG-PET is optional. In the case of a residual mass that is positive at FDG-PET with no volume increase, a second FDG-PET should be performed 6 weeks later (Decoene et al. 2015). Only in cases of increased SUVs or progressive disease histology should be obtained, all others can be on active surveillance. Post-chemotherapy resection of residuals from seminoma can lead to a high rate of complications and additional procedures. A resection of residual seminomatous mass is a technically demanding procedure that should be performed by experienced surgeons in dedicated referral centers.

Residual tumor resection in patients with non-seminomatous germ cell tumors is necessary when residual radiographic abnormalities (lesion >1 cm) after chemotherapy are present and should be performed within 4–6 weeks after chemotherapy. The size and location of residual masses make residual tumor resection a technically demanding procedure that should be

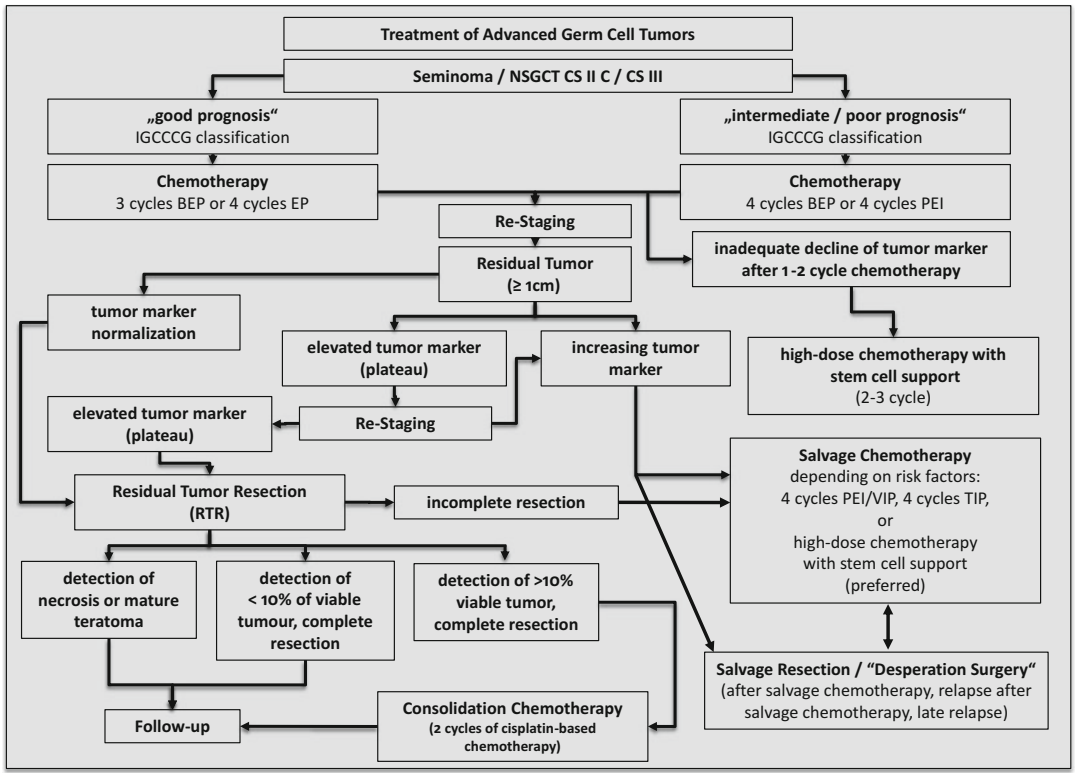

Fig. 2 Treatment algorithm of advanced testicular cancer (CS IIC/III)

performed by experienced surgeons in dedicated referral centers.

Patients with disseminated germ cell tumors who obtain a complete serologic remission and in whom no or minimal radiographic residual (<1 cm) is present after chemotherapy can be safely observed without residual tumor resection (Fig. 2). Whereas patients with initial "poor prognosis" show an increased risk of relapse, so a routinely resection of residuals <1 cm in "poor risk" patients is discussed.

Conclusion

In order to further improve outcome especially of testicular cancer patients with lymphatic metastasis, diagnostic procedures have to be optimized; patients have to be treated with individualized risk stratification and within a multidisciplinary approach of chemotherapy, radiotherapy, and surgery at centers of excellence. In early stages, treatment has to be balanced against acute and long-term toxicity, and patients in all stages need long-term follow-up not only for tumor recurrence but also for late sequelae of tumor- and treatment-related toxicity.

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Stage III Germ Cell Cancer

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Abstract

Patients with clinical high-volume disease are candidates for systemic treatment, in both histologic entities, semimona or non-seminomatous germ cell cancer. In general cisplatin, etoposide and bleomycin (PEB) is the recommended polychemotherapy scheme. According to the risk profile either three or four cycles need to be applied. Hematotoxic disorders are frequently reported acute side effects. Nevertheless the risk is still intermediate, so that no granulocyte colony stimulating factor (GCSF) is needed, except in case of previously developed neuropenic fever episodes in order to reduce morbidity in future cycles. The role of high-dose chemotherapy in the primary setting is still unclear and under investigation. High-risk patients with inadequate tumor-marker decline under PEB benefit from an intensivated chemotherapy.

There are different classification systems for metastasized testis cancer. The Lugano classification includes the localization and size of metastasis. Clinical stage III disease according to the Lugano classification is defined as metastasis above the diaphragm. Stage III described in the TNM 2009 classification combines metastatic patterns, visceral metastasis, lymph node metastasis, and tumor marker. Thus the classification of the International Germ Cell Cancer Collaborative Group into good intermediate and poor prognosis is also implemented (Table 1).

Although in general one has to distinguish between seminoma and nonseminomatous germ cell cancers in high-volume disease, stage III, in both histologic entities, chemotherapy is the treatment of choice.

Adapted to the IGCCCG classification system, the primary therapy would consist of three or four cycles of cisplatin, etoposide, and bleomycin (PEB) for good (de Wit et al. 2001) and intermediate/poor prognosis patients (Albers et al. 2015). In patients with seminoma, four cycles of etoposide and cisplatin have a favorable outcome with a 3- and 5-year overall survival of 99% (range 92–100%) and 93% (range 83–97%) (Fizazi et al. 2014a). As a consequence in patients with a good prognosis, either three cycles of PEB or four cycles of etoposide and cisplatin are the treatment of choice. In case of contraindications against bleomycin, four cycles of etoposide and cisplatin should be the preferred scheme.

In the same trial, patients with an intermediate prognosis had been treated with cisplatin, etoposide, and ifosfamide instead of bleomycin.

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Table 1 Classification system TNM 2009/ IGCCCG

Stage	T	N	M	S	IGCCCG
III	Any	Any	M1a	Sx	
IIIA	Any	Any	M1a	S0	Good
		Any	M1a	S1	
IIIB	Any	N1-N3	M0	S2	Intermediate
		Any	M1a	S2	
IIIC	Any	N1-N3	M0	S3	Poor
		Any	M1a	S3	
		Any	M1b	Any	

Modified according to EAU guidelines
N1<=2 cm/less than 5 nodes
N2 2–5 cm/more than 5; none >5 cm
N3 >5 cm
M1a nonregional lymph nodes or lung
M1b other sites
S0 tumor markers within normal ranges
Sx tumor marker not available
S1LDH<1.5× normal range/hCG<5000 IU/l/AFP<1000 ng/ml
S2 LDH1.5–10× normal range or hCG 5000–50,000 IU/l or AFP 1000–10,000 ng/ml
S3 LDH >10× normal range or hCG >50,000 IU/l or AFP >100,000 ng/ml
Modified to EAU guidelines

As more cytotoxic side effects are expected, patients are supported with GCSF. Five-year overall survival after a median follow-up of 4.5 years (range 0.4–11.6 years) was 87% (range 67–95%). Neutropenia was described in eight (36%) and a neutropenic fever in five (23%) of the patients. There was one toxicity-related death. According to the guideline recommendations in patients with seminoma and an intermediate-risk profile, either four cycles of PEB or in case of contraindications against bleomycin four cycles of VIP plus GCSF can be given.

In patients with NSGCC, either three or four cycles of PEB are the guideline recommendations. There are different application schemes for PEB. The 3-day application is oncologic equieffective but more toxic if four cycles are applied; thus the 5-day scheme should be the treatment of choice (de Wit et al. 2001). Most frequent toxicities can be found in hematologic disbalances. Neutropenic fever as an oncologic emergency is found in up to 15% of the cases. In addition sensory neuropathies and auditory defects are described in 25% of the patients. There is no general recommendation for the application of granulocyte colony-stimulating factor (GCSF). According to the NCCN Guidelines in testis cancer patients, the risk of developing an episode of neutropenic fever is intermediate; thus the application can be considered. In case of a previously developed neutropenic fever, GCSF can be considered to reduce morbidity during and after future cycles. As late complications, there are neuropathies in almost one third of the patients and auditory disorders in 15% of testis cancer patients. Although cisplatin is eliminated on a renal pathway and renal function needs to be evaluated prior to each cycle of treatment, late complications are rare in less than 5% (Albers et al. 2015).

Compared to patients with seminoma, the application of EP in good prognosis patients with NSGCC should be discussed carefully. In a large prospective trial, GETUG T93BP, patients with NSGCC and a good prognosis were randomized to either receive three cycles of PEB or three cycles of EP. There had been significantly higher rates of neutropenia grade ¾ in case of three cycles of EP (62% versus 47%, $P < 0.0001$) and higher rates of neurologic and dermatologic disorders in case of three cycles of PEB. Concerning the oncologic outcome there was no significant difference in the 4-year overall survival (97% versus 93%, $p = 0{,}082$). Although there was no statistically significant difference in overall survival, mortality rate in patients receiving PEB was 50% of patients treated with EP (4 deaths versus 11 deaths) (Culine et al. 2007) (Table 2).

Table 2 Standard chemotherapy regime in non-seminomatous germ cell cancer

Scheme	Number of cycles
PEB	3–4, 21-day rhythm
Cisplatin 20 mg/m^2 d1–5	
Etoposide 100 mg/m^2 d1–5	
Bleomycin 30 mg d1,8,15	
EP	4, 21-day rhythm
Cisplatin 20 mg/m^2 d1–5	
Etoposide 100 mg/m^2 d1–5	
PEI	3–4, 21-day rhythm
Cisplatin 20 mg/m^2 d1–5	
Etoposide 100 mg/m^2 d1–5	
Ifosfamide 1.2 g/m^{2}d1–5	

There is always a debate whether patients with intermediate or poor prognosis should be treated more aggressively or not.

Yet there is no proof that more intense regimes are associated with an improved overall survival. In a randomized European trial, EORTC 30983, there was no benefit in intermediate-risk patients treated with PEB plus paclitaxel (T-PEB) compared to PEB alone. In case of the more intense scheme, GCSF was added to reduce hematotoxicity. There was an improved 3-year progression-free survival for patients treated with T-PEB (79,4% versus 71,1%) which was at least not statistically significant (p = 0,153; hazard ratio [HR] 0,73; confidence interval [CI] 0,47–1,13). Due to poor recruitment, the trial was closed early (de Wit et al. 2012).

In another French multicenter trial, patients had been treated with poor-risk characteristics. Patients were randomized between four cycles of PEB and to a more intense scheme with two cycles of T-PEB, oxaliplatin with GCSF, and two cycles of cisplatin, ifosfamide, and bleomycin together with GCSF. There was a significant advantage in the 3-year progression-free survival (48% versus 59%; HR 0.66, 0.44–1.00, p = 0.05). Although overall survival was higher in the more intense arm (65 versus 73%; HR 0.78, 0.46–1,31; p = 0.34), the overall oncologic benefit was at least not statistically significant again (Fizazi 2014b).

Comparable results can be achieved in patients treated with PEI. In a multicenter prospective trial, patients had been randomized to four cycles of PEI or four cycles of PEB. The 2-year overall survival was 74% for VIP treated and 71% for patients being treated with PEB. The difference was not statistically significant (p = 0,78). The patients receiving PEI had a significantly higher risk for grade ¾ hematotoxic side effects (88% versus 73%, p < 0,001) (Nichols et al. 1998).

There are several trials with primary high-dose chemotherapy in addition with an autologous stem cell rescue in intermediate-/poor-risk patients (Motzer et al. 2007; Droz et al. 2007; Daugaard et al. 2011; Bokemeyer et al. 1999). In one matched pair analysis, there was an improved 2-year PFS (75% versus 59%; p = 0,0056) in patients with high-dose regimen but not in overall survival (82% versus 71%; p = 0.01) (Bokemeyer et al. 1999). This could not have been confirmed in prospective randomized trials (Motzer et al. 2007; Droz et al. 2007; Daugaard et al. 2011). There was an increase in hematotoxic and non-hematotoxic negative side effects as diarrhea, infections, fever, as well as therapy-related deaths in the patients treated with high-dose chemotherapy without achieving an overall survival benefit. In a prospective phase III trial, patients with intermediate and poor prognosis either received four cycles of standard chemotherapy, PEB, or with two cycles of PEB followed by four cycles of high-dose carboplatin-based chemotherapy. Overall this study underlines the nonsuperiority of more intense chemotherapy in the primary setting. There was no difference in patients achieving a complete response (56 versus 55%, p = 0.89). The 2-year survival rate in the high-dose versus conventional arm was 67% (95% CI 57–77%) versus 69% (95% CI 58–79%) in the poor-risk group and 85% (95%CI 70–100%) versus 83% (95%CI 68–98%) in the intermediate group. In this trial tumor marker decline during the first two cycles was a prognostic parameter. Patients with a delayed tumor marker response are considered to be chemotherapy refractory and showed a decreased overall survival. In a subgroup analysis, patients with a delayed tumor marker decrease had a worse 2-year survival rate if conventional chemotherapy continued compared to patients who switched to high-dose chemotherapy (55% versus 78%, p = 0.11) (Motzer et al. 2007). This subset of patients might profit from an early initiation of a high-dose protocol. To date the general

recommendation for primary high-dose chemotherapy cannot be given.

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Management of Residual Tumor in Testicular Cancer

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Contents

Abstract

Testicular cancer is a rare tumor but represents the most common solid tumor in patients between 20 and 30 years of age. After introduction of a Cisplatin based chemotherapy sceme in the late eighties oft he last century there was a revolutionary result with now curable patients. Nevertheless surgery still has a major impact in the multimodal treatment of patients with testicular cancer. Due to the high negative predictive value of FDG-PET in residul tumors of patients with seminoma these patients can often be followed. Compared to this in NSGCC surgery needs to be performed frequently as predictive markers with regard to the histologic specimen in the residual tumor still lack behind. Although morbidity is tried to be reduce by minimalizing the extend of resection fileds, aggressive treatment is needed in advanced cases and salvage situation with significantly increased complication rates. These points are highlighted in the following chapter.

In testicular cancer a high percentage of the patients can be cured by a multimodal therapy approach. This usually consists of a primary chemotherapy and a sequential residual tumor resection.

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Although retroperitoneal lymph node dissection is also performed in a primary setting in a selected patient population, the majority of major surgical interventions are being performed after chemotherapy or in a salvage setting. Residual tumors are mostly located in the retroperitoneum as well as in the lung (Besse et al. 2009) and liver (Jacobsen and Beck 2010). More rare sites are the central nervous system, bone (Uygun and Karagol 2006), and vessels (Johnston et al. 2013).

The position toward residual tumor resection depends on the histology of the primary tumor: seminoma versus nonseminomatous germ cell cancer.

Seminoma

Patients with seminoma and residual tumors after chemotherapy can be stratified for further interventions.

Patients with small lesions less than 3 cm have a neglectable risk of harboring vital seminoma, and surgery can be spared. The risk of vital seminoma in small lesions is neglectable. In larger lesions vital tumor is found in up to 30% (Puc et al. 1996). Compared to nonseminomatous germ cell cancer, 2-fluorodeoxy-D-glucose (FDG)-PET is the diagnostic tool in lesions larger than 3 cm. DeSantis et al. demonstrated an excellent diagnostic accuracy with a sensitivity and specificity of 80% and 100% of the cases with regard to vital seminoma or fibrotic tissue (De Santis et al. 2004). Meanwhile we are aware that the timepoint of the radiologic assessment is mandatory. False-positive results can significantly be reduced if FDG-PET is performed more than 6 weeks after completion of the chemotherapy (Bachner et al. 2012). By the prolonged interval, a reduced intralesional tracer uptake by chemotherapy-induced inflammation and thus a decreased false-positive rate can be achieved. Nevertheless, in daily clinic, a false-positive rate in lesions >3 cm of up to 60% has recently been shown (Decoene et al. 2015). In the current guidelines, a confirmatory PET is recommended in case of suspicious results. Only in case of an increased volume or SUV uptake histology should be taken, and further procedures as surgery, radiotherapy, or chemotherapy are initiated.

Compared to nonseminomatous germ cell cancer, NSGCC, in seminoma PC-RPLND desmoplastic reactions with a significant therapy-associated morbidity and even mortality in older series are described (Herr et al. 1997; Moshrafa et al. 2003; Fossa et al. 1987). As in NSGCC there is a decrease in PC-RPLND's complications and adjunctive surgeries in seminoma patients (Moshrafa et al. 2003; Pfister and Porres 2015). Retroperitoneal lymph node dissection in patients with seminoma is less frequently performed but if needed can be performed in experienced centers.

Nonseminomatous Germ Cell Cancer, NSGCC

Residual tumor resection in NSGCC used to be mandatory in all patients. This is due to the fact that we do not have radiologic imaging modalities that predict histology as in seminoma. In the final histopathology, vital carcinoma and teratoma are detected in up to 10% and 50% of the cases. In the recent years, long-term data are published describing excellent outcome in patients with complete remission after chemotherapy defined as residual tumors less than 1 cm (Kollmannsberger et al. 2009; Ehrlich et al. 2010). Longer follow-up of the patients is accompanied with a significant increase in relapses in patients with an intermediate/poor prognosis (15-year RFS 94, 7% vs. 57%; $p = 0.001$). In the last interdisciplinary consensus meeting only in patients with small residuals, defined as a complete remission of less than 1 cm and an initial good prognosis according to the IGCCCG criteria, PC-RPLND can be omitted (Beyer and Albers 2013; Oldenburg et al. 2013).

One major aspect to avoid residual tumor resection is to reduce morbidity. In this mostly younger patient cohort, antegrade ejaculation is of major importance as family planning is still ongoing. In a selected patient cohort, modified template resection is at least in Europe a standard of care. Patients with metastasis initially being

localized in the primary landing zone of the tumor-bearing testicle and the size not exceeding 5 cm can be treated with a modified template resection without affecting oncologic outcome but significantly reducing the risk of retrograde ejaculation (Heidenreich et al. 2009). Progression-free survival is roughly 95% in this patient cohort. If recurrences occur these are mostly located even outside the boundaries of a bilateral template. These so-called Heidenreich criteria are externally validated and are the standard parameter for identifying patients for a modified procedure (Vallier et al. 2014).

To achieve a complete resection of the residual tumors and thus avoid local recurrences, there is a need for adjunctive surgeries in up to 25% of the cases. The most frequent performed resection is the ipsilateral nephrectomy (Nash et al. 1998; Stephenson et al. 2006). Resections and replacement of larger vessels as mostly V. cava inferior and less frequent the abdominal aorta (Beck et al. 2001; Winter et al. 2012; Beck and Lalka 1998) are seldom. There are prognostic marker to help identifying patients with the need of a V. cava resection or graft placement. In patients with initial intermediate or poor prognosis according to the IGCCCG criteria and large residual volumes >5 cm, there is an almost fivefold increased risk of V. cava involvement (Winter et al. 2012). Concerning the abdominal aorta, multiple cisplatin-based chemotherapy regimen and again large residual tumors encaving the retroperitoneal vessels are parameters with an increased risk of aorta replacement (Paffenholz et al. 2016). These patients should strictly be operated with the needed facilities as vessel surgeons. In 73,3% of vascular interventions, either teratoma or vital carcinoma was found underlining the need of a complete resection (Paffenholz et al. 2016). In 5.8% of the patients, one finds an intraluminal thrombus. Histology in this specimen is teratoma and vital carcinoma in 28.6% and 12.2%, respectively (Johnston et al. 2013). Meanwhile there are data reflecting that the oncologic outcome of the patients varies significantly to the centers' experience (Capitanio et al. 2009; Fléchon et al. 2010). Guideline recommendations concerning the extension of resection are implemented less frequently compared to more experienced centers. This leads to a higher surgery-associated mortality rate and a higher tumor recurrence rate.

In case of several metastatic sites, one usually starts with the retroperitoneum.

After resecting the retroperitoneal residual tumor, other residual deposits need to be taken into account.

Pulmonary Metastases

Pulmonary metastases should always be resected as there is a poor concordance between the histologic specimen in the lung and the retroperitoneum (Krege et al. 2008). In case of a bilobal decay, one should start with the more appropriate side. If histology demonstrates fibrosis, the contralateral side can be spared from surgery as there is a high concordance of histology in both lungs (Besse et al. 2009).

Liver Metastases

In retrospective analysis, vital carcinoma is found in 23.3–32.4% of the cases (Hahn et al. 1999; Rivoire et al. 2001). The size of the metastases was shown to be relevant for patient outcome. All patients with metastases being larger than 3 cm died of the disease. In lesions less than 10 mm, only necrotic tissue was found (Rivoire et al. 2001). Jacobsen et al. showed in addition to the metastatic size that there is a high concordance from the pathology in the retroperitoneum to the pathology that can be expected in the liver. In case of fibrosis/necrosis in the retroperitoneum, the concordance in the liver is almost 100%. This decreases in case of teratoma and vital carcinoma to 70% and 50% but still allows an individual approach (Jacobsen and Beck 2010).

Bone Metastases

In the literature bone involvement is described in about 3% of patients with a PC-RPLND (Uygun and Karagol 2006; Paffenholz et al. 2016). In 60% bone metastases occur in relapsed disease. In some cases it is unclear whether it is an isolated

bone metastases or an infiltration from the surrounded tumor tissue. In most cases bone metastases are located in the spine and are associated with other metastatic sites. Rare locations are isolated metastases in the skull (Uygun and Karagol 2006). The experience is limited to case reports or small series (Paffenholz et al. 2016; Berglund and Lyden 2006; Hitchins et al. 1988). Resections of residual or recurrent disease in the retroperitoneum with resection of the corpus of one or more vertebrae are described as complex residual tumor resection. In this case usually a dorsal stabilization is performed in a first session. In a second step, the PC-RPLND is completed. The corpora are resected, and the defect is filled with a CAGE system. The complexity of these interventions is even underlined that in addition to the bone resection, there is a need of vascular surgery with replacement of V. cava and/or aorta in 40%. Nevertheless resection of bone metastases seems to be indicated as there is a significant histology with teratoma and vital carcinoma in 80% (Paffenholz et al. 2016). In case of seminomatous histology, a radiotherapy in bone metastases is an option with good long-term results (Collins and Eckert 1985).

Brain Metastases

About 10% of the patients with advanced germ cell tumors have brain metastases. Long-term survival with brain metastases at initial diagnosis is 30–40% according to the poor prognosis defined by the IGCCCG criteria (Oechsle and Bokemeyer 2011; Fizazi et al. 2001, 2008). There is no standardized therapy sequence. As usual chemotherapy is a main integral part of the therapy. By additional radiotherapy a survival benefit could have been demonstrated. The therapeutic effect of radiotherapy in case of complete remission after chemotherapy is unclear. In addition there are no long-term results of secondary resections of residual lesions in the brain. Iida et al. (2014) describe one case of resection and one isolated late relapse in the brain with elevated AFP values of 539 ng/ml. In a short follow-up, there was no recurrent disease after surgery only.

Exceptions in the retroperitoneal lymph node dissections are redo-RLAs and desperation surgery. Redo-RLAs are usually relapses outside the primary surgery field. Desperation surgery is patients' refractory to chemotherapy with the possibility to resect all visible tumor. In both cases there is an increased risk of finding vital carcinoma in the histologic specimen. Histology is correlated with prognosis of the patients. Vital carcinoma has a significantly decreased 5-year survival rate (30%) versus teratoma (82%) and fibrosis (85%) ($p = 0.0001$) (Becks 2005). As relapses are located in more complex anatomic sites (retrocrural, behind the aorta and V. cava), there is an increased risk of adjunctive surgeries and postoperative complications in these so-called complex RLAs (Paffenholz et al. 2016).

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50 Postchemotherapy Retroperitoneal Lymph Node Dissection in Advanced Germ Cell Tumors of the Testis

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Abstract

Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) plays an integral part of the multimodality treatment in patients with advanced testicular germ cell tumors (TGCT). According to current guidelines and recommendations, PC-RPLND in advanced seminomas with residual tumors >3 cm in

diameter is only indicated if a PET scan is performed 6–8 weeks after chemotherapy demonstrates a positive lesion.

In nonseminomatous TGCT, PC-RPLND is indicated for all residual radiographic lesions >1 cm in diameter and with negative or plateauing serum tumor marker concentrations following systemic chemotherapy. Based on the location and the size of the primary and the residual lesion, it has to be decided if a modified or bilateral template resection needs to be performed. Loss of antegrade ejaculation represents the most common long-term complication which can be prevented by a nerve-sparing or modified template resection.

Patients with residual masses <1 cm and an initially good prognosis can undergo active surveillance. PC-RPLND is only indicated in men with intermediate/poor prognosis or a testicular lesions containing teratoma predominantly.

Patients with increasing markers should undergo salvage chemotherapy. Only select patients with elevated markers who are thought to be chemo-refractory might undergo desperation PC-RPLND if all radiographically visible lesions are completely resectable. PC-RPLND requires a complex surgical approach and should be performed in experienced, tertiary referral centers only.

Keywords

Testis cancer · Chemotherapy · Metastases · Nonseminomas · Seminoma · Mature teratoma · Nerve-sparing surgery

Introduction

Surgical resection of postchemotherapy residual retroperitoneal lymph nodes or residual visceral metastatic deposits represents an integral part of the multimodality treatment for patients with advanced testicular cancer undergoing systemic chemotherapy (Albers et al. 2015; Oldenburg et al. 2013; Daneshmand et al. 2012). The rationale for postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) is to remove persistent retroperitoneal lymph nodes that may contain mature teratoma in approximately 30–40% and vital cancer in about 10–20% of the patients (Albers et al. 2015; Oldenburg et al. 2013; Daneshmand et al. 2012; Woldu et al. 2018; Flechon et al. 1979; Friedman et al. 1985).

In nonseminomatous germ cell tumors (NSGCT), PC-RPLND is currently indicated in men with normalized or plateauing serum tumor markers and residual masses >1 cm (Oldenburg et al. 2013). In patients with residual lesions <1 cm and predominant teratoma in the orchiectomy specimen or intermediate/poor prognosis, there is an increased risk of residual teratoma, so that these patients are further candidates for PC-RPLND. The rationale to resect even small residual masses with mature teratomas lies in their disposition for progressive local growth, their risk of malignant transformation, and their risk of late relapse. Residual masses with viable germ cell tumor elements reflect intrinsic or extrinsic chemoresistance, and these lesions will definitely progress when left in situ despite second-line or salvage chemotherapy. Patients with normalized serum tumor markers and complete resolution of all metastatic disease do not need to undergo PC-RPLND since only 3–5% of these men will relapse when undergoing active surveillance.

In men with residual disease after primary chemotherapy for advanced seminomas, PC-RPLND is only indicated if the residual mass is >3 cm in diameter and demonstrates positive findings in the FDG-PET scan. In all other cases, the masses should not necessarily be resected, but should be closely followed by imaging investigations and tumor marker determinations (Albers et al. 2015; Oldenburg et al. 2013; Daneshmand et al. 2012).

Although PC-RPLND is a routine surgical intervention in experienced centers, its treatment-associated complications might be substantial, since PC-RPLND will require additional surgical procedures of adjacent organs in about 25% of the cases (Albers et al. 2015; Oldenburg et al. 2013; Daneshmand et al. 2012). PC-RPLND should be performed in experienced high-volume centers since significantly higher survival rates in advanced TGCT have been demonstrated as compared to low-volume centers (Woldu et al. 2018).

The purpose of this article is to review the current role of PC-RPLND in patients with residual tumor lesions after primary or salvage chemotherapy with specific attention to the indication, the surgical technique, its complications, and the oncological outcome.

PC-RPLND in Advanced Seminomas

Following primary cisplatin-based chemotherapy, viable cancer can be demonstrated in about 12–30% of men with residual masses >3 cm and in less than 10% in those with residual masses <3 cm in diameter (Table 1). Following guideline-adapted cytotoxic protocols, however, the incidence of viable cancer in residual seminomatous masses has decreased to 20% irrespective of their size (Flechon et al. 1979; Friedman et al. 1985; Schultz et al. 1989; Fosså et al. 1987; Ravi et al. 1994; Puc et al. 1996; Mosharafa et al. 2003). Adhering to the former recommendation to resect all residual masses >3 cm diameter would result in an overtreatment rate of 80% without any therapeutic benefit for the patient reducing PC-RPLND to a mere invasive staging procedure. Furthermore, surgical resection residual seminomatous elements are technically challenging due to the severe desmoplastic reaction between the regressing mass and the adjacent vascular and visceral structures. As has been shown in retrospective studies, PC-RPLND in seminomas results in a higher frequency of additional intraoperative procedures and an increased rate of postoperative complications (Mosharafa et al. 2003). Additional nephrectomy and vascular procedures such as partial or complete resection of the v. cava and placement of aortic prosthesis are necessary in up to 38% of the patients as compared to only about 25% of men undergoing PC-RPLND for advanced NSGCT. However, in our hands, no significantly increased frequencies of surgery-related complications and adjunctive procedures have been observed when comparing PC-RPLND in 43 seminomas and in 380 nonseminomas (Pfister et al. 2015). The median diameter of the resected residual tumors was 4.6 cm and 5.9 cm in seminomas and in nonseminomas, respectively. 6% and 8.1% of patients with advanced seminomas and nonseminomas, respectively, developed surgery-associated complications following PC-RPLND.

In order to better select patients who might benefit from PC-RPLND, the role of FDG-PET to predict the presence of viable tumor in residual masses of advanced seminomas was prospectively evaluated (Fig. 1). After initial positive results (De Santis et al. 2004), studies were expanded to 54 patients with 74 documented residual masses on computed tomography ranging from 1 cm to 11 cm (Becherer et al. 2005). After PET scanning the patients either underwent surgery or were followed clinically; any growing lesion was assumed to be malignant, whereas regressing lesions or residual masses remaining stable for ≥24 months were considered to contain nonviable elements only. The sensitivity and specificity to detect viability with FDG-PET were 80% and 100%, respectively; there was no false-positive scan and there were three false-negative PET scans. In accordance with the current recommendation of the EAU and the ESMO guidelines (Albers et al. 2015; Oldenburg et al. 2013),

Table 1 Histology of residual tumors following PC-RPLND for advanced seminomas. (Adapted from Pfister et al. 2015)

Author	n	Diameter	n	PC-RPLND	Vital seminoma
Friedman	15	≥3 cm/<3 cm	11/4	3/0	0
Schultz	21	≥3 cm/<3 cm	9/12	1/2	0
Fossa	16	≥3 cm/<3 cm	10/6	3/1	0
Ravi	43	≥3 cm/<3 cm	25/18	15/4	3/0
Puc and Herr	104	≥3 cm/<3 cm	30/74	27/28	6/0
Flechon	60	≥3 cm/<3 cm	31/29	15/12	2/0
Total	**259**	**≥3 cm/<3 cm**	**116/143**	**64/47**	**11 (17%)/0**

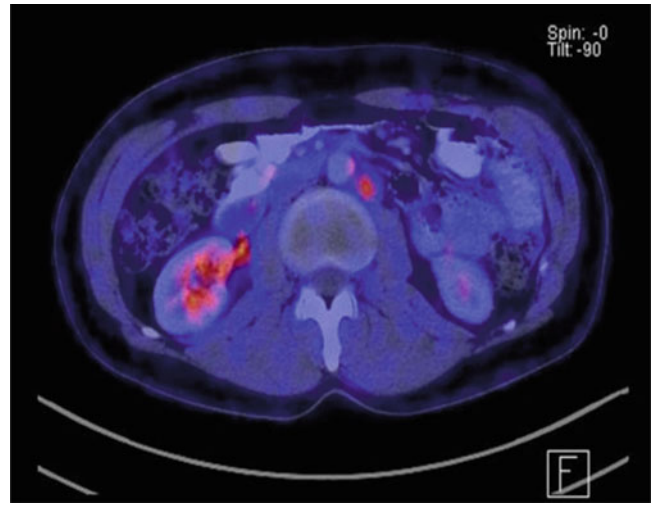

Fig. 1 FDG-PET/CT performed 8 weeks after systemic chemotherapy for metastatic seminoma demonstrating significant tracer accumulation in a residual para-aortic lymph node indicating vital seminoma

postchemotherapy as well as post-radiotherapy residual masses in seminoma patients should not necessarily be resected, irrespective of their size, but should be closely followed by imaging investigations and tumor marker determinations (Albers et al. 2004a, 2015; Oldenburg et al. 2013; Kamat et al. 1992; Hofmockel et al. 1996; Herr et al. 1997). No resection or any other treatment modality besides further active surveillance is necessary in patients with a negative PET scan, while a positive PET scan, if performed more than 6 weeks after day 21 of the last chemo-/radiotherapy, is a strong and reliable predictor of viable tumor tissue in patients with residual lesions. In FDG-PET-positive patients, histology should be obtained by biopsy or resection. Further treatment should be based on the results of histology and may include observation, surgery, radiation, or further chemotherapy.

PC-RPLND in Advanced NSGCT

In patients who achieve complete remission, i.e., normalized tumor markers and no residual lesions after chemotherapy, postchemotherapy surgery is not required (Albers et al. 2015; Oldenburg et al. 2013; Daneshmand et al. 2012).

In patients with residual masses >1 cm and normalization of tumor markers, the residual masses should be resected (Albers et al. 2015; Oldenburg et al. 2013; Daneshmand et al. 2012). Histology of residual masses after first-line chemotherapy will be necrosis, mature teratoma, and vital cancer in about 50%, 35%, and 15% of patients, respectively.

In patients with residual lesions <1 cm, PC-RPLND should be strongly considered if the primary orchiectomy specimen harbored predominantly teratoma or if an intermediate or poor prognosis existed at time of initiation of chemotherapy. It has been shown in various retrospective single-center analyses that up to 20% and 8% of those patients will harbor mature teratoma and vital cancer despite the small-sized lesions. There is an even increased risk of residual teratoma, if teratoma was present in the initial histology. If technically feasible, all residual masses should be resected. In persistent retroperitoneal disease, retroperitoneal surgery should include all areas of initial metastatic sites.

In residual lesions <1 cm, PC-RPLND can be omitted in patients without predominant teratoma in the orchiectomy specimen and in patients with good prognosis according to recent reports (Kollmannsberger et al. 2010; Ehrlich et al. 2010; Pfister et al. 2011). Kollmannsberger et al. (2010) analyzed 276 patients who underwent systemic chemotherapy for metastatic NSGCT. One hundred sixty-one (58.3%) achieved a complete remission which was defined by the presence of residual lesions <1 cm, and all patients were

followed without surgical resection. After a mean follow-up of 40 (2–128) months, relapses were observed in 6% of the patients, and none of them died after appropriate salvage therapy. However, 94% of the patients belonged to the good prognosis group according to the IGCCCG classification, and only 3% belonged to the intermediate- and the poor-risk group. In a similar approach, Ehrlich et al. (2010) evaluated 141 patients who were observed after systemic chemotherapy and residual lesions <1 cm. After a mean follow-up of up to 15 years, 9% of the patients relapsed and 3% of the patients died due to testis cancer. IGCCCG risk group classification predicted the outcome best: recurrence-free survival and cancer-specific survival were 95% and 99%, respectively, in men who belonged to the good-risk group, whereas it dropped to 91% and 73% if the patients belonged to the intermediate- and poor-risk group. However, only 6 out of 12 relapses developed in the retroperitoneum so that only 50% of the patients would have had a potential benefit from PC-RPLND. Quite recently, the German Testicular Cancer Study Group (GTCSG) analyzed the outcome of 392 patients who underwent PC-RPLND for residual lesions of any size, and they correlated the final pathohistological findings with the size of the residual masses and the IGCCCG risk profile (Pfister et al. 2011). 9.4% and 21.8% of the men with residual lesions smaller than 1 cm harbored vital cancer and mature teratoma in the resected specimens, respectively. These numbers increased to 21% and 25% in patients with residual lesions of 1–1.5 cm and to 36% and 42% in men with lesions larger than 1.5 cm. The IGCCCG risk profile was not identified as an independent risk to predict the final pathohistology of small residual lesions. The GTCSG draw the conclusion that all patients with any visible residual masses should be resected in a tertiary referral center.

Considerations for the Most Appropriate Surgical Strategy

PC-RPLND is a challenging surgical procedure which requires detailed knowledge of the retroperitoneal anatomy, familiarity with surgical techniques of the vascular and intestinal structures, as well as profound experience in the management of patients with testicular cancer. Depending on the size and the extent of the residual lesions, the surgeon has to modify his surgical approach to the retroperitoneal space. An abdominal midline incision from the xyphoid to the symphysis can be used in most patients with unilateral and infrahilar disease, whereas a chevron incision might be more suitable in those men with bilateral and suprahilar disease. About 10% of the patients demonstrate persistent retrocrural disease, so a thoracoabdominal approach will be best to easily and safely explore this anatomical region (Albers et al. 2004b). Especially the thoracoabdominal approach needs surgical expertise and knowledge of the retroperitoneal anatomy in order to prevent significant complications (Fujioka et al. 1993; Skinner et al. 1982). Although the morbidity of PC-RPLND exceeds that of primary nerve-sparing RPLND, modifications of cytotoxic regimes, the surgical approach, and perioperative care have resulted in a decreased incidence of acute and long-term complications. Due to the high treatment-related acute morbidity, however, surgery of residual masses should be performed at specialized centers only (Albers et al. 2015; Oldenburg et al. 2013; Daneshmand et al. 2012).

In patients with residual masses at multiples sites, an individual decision should be made regarding the number and extension of resections. Decisions on the extent of surgery should be based on the risk of relapse of an individual patient and on quality-of-life issues. Resection of residual tumors outside the abdomen or lung should also be considered on an individual basis, since discordant histology is found in 35–50% of patients (Wood et al. 1992).

Preoperative Imaging Studies

Prior to PC-RPLND, a complete metastatic and physical evaluation including (1) computed tomography of the chest, the abdomen, and the

small pelvis about 6–8 weeks following the last cycle of chemotherapy, (2) measurement of the serum tumor markers, and (3) pulmonary function testing in men with an increased risk of pulmonary toxicity (four cycles PEB, >40 years, smoking history, renal insufficiency) should be performed prior to PC-RPLND.

Especially in patients with large residual masses, imaging studies should allow an adequate assessment of the large retroperitoneal vascular structures since involvement of the inferior vena cava (IVC) and the abdominal aorta can be expected in about 6–10% and 2%, respectively (Heidenreich et al. 2017; Beck et al. 2001; Winter et al. 2012; Johnston et al. 2013). Magnetic resonance imaging represents the most appropriate imaging technique to predict infiltrations of the vessel wall and the presence of an intracaval tumor thrombus (Fig. 2). Infiltrations of the IVC wall or IVC thrombi should be completely resected since about two thirds of the patients harbor vital cancer or mature teratoma in the infiltrating masses. Usually intraoperative reconstruction or replacement of the IVC is not necessary since chronic venous sequelae are to be expected in less than 5% of all patients (Heidenreich et al. 2017; Johnston et al. 2013).

The necessity for aortic replacement is rare and usually accompanied by large residual masses involving additional adjacent structures and making additional surgical procedures necessary such as nephrectomy, IVC resection, small bowel resection, and hepatic resection (Figs. 3a–c and 4). In the majority of cases, mature teratoma or vital carcinoma was identified in the aortic wall (Winter et al. 2012; Johnston et al. 2013).

Timing of PC-RPLND

Once residual masses have been diagnosed, PC-RPLND should be initiated as soon as possible with a complete resection of all retroperitoneal and intraperitoneal masses. Complete resection of residual masses is of very important prognostic significance. In a recent retrospective analysis, Sonneveld et al. (1998) demonstrated that about 50% of all patients with locoregional recurrences after PC-RPLND had an incomplete resection at time of first surgery. Hendry et al. (2002) retrospectively analyzed the outcome of 443 patients undergoing either immediate or elective PC-RPLND once progression of the residual masses was demonstrated. A significant benefit with regard to progression-free survival (83%

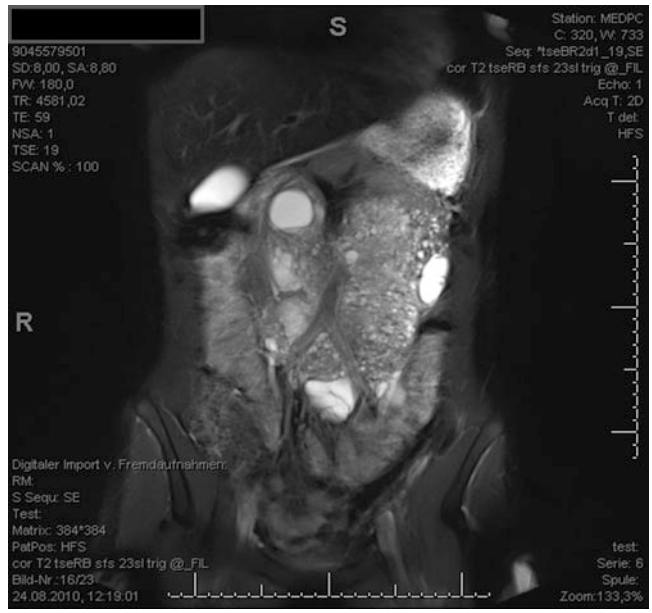

Fig. 2 Abdominal MRI of a patient with significant and large residual masses of a nonseminomatous germ cell testicular cancer with compression and infiltration of the infrarenal aorta

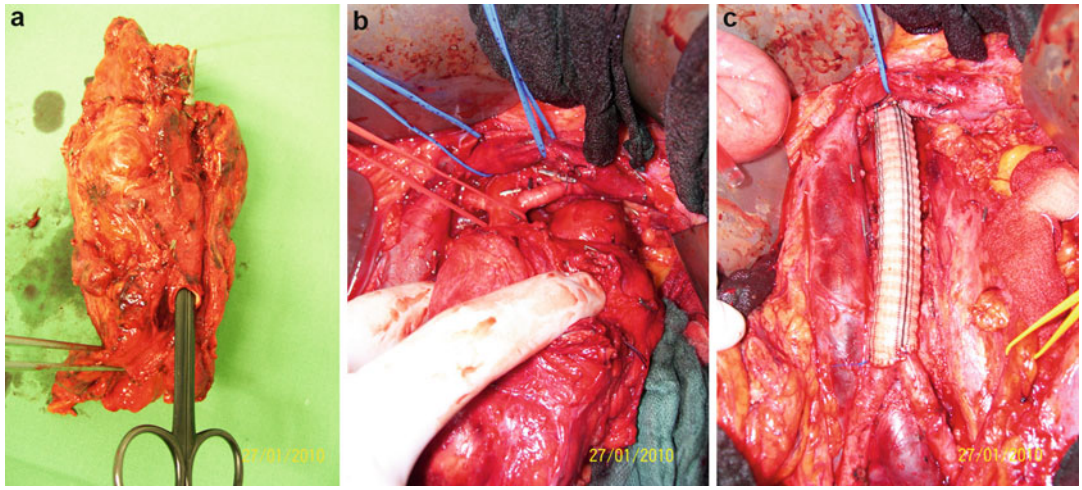

Fig. 3 Large residual mass infiltrating the aorta. (**a**) Anatomical preparation of major vascular structures, (**b**) resection of the infrarenal aorta, (**c**) replacement of the infrarenal aorta

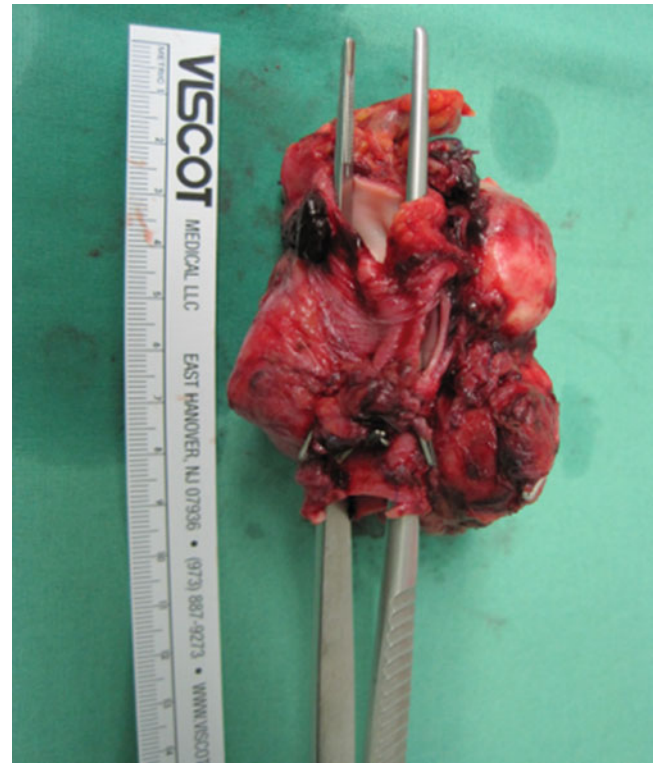

Fig. 4 Partial resection of the inferior vena cava due to infiltration of the vessel wall by teratoma with malignant somatic transformation

vs. 62%, $p = 0.001$) and cancer-specific survival (89% vs. 56%, $p = 0.001$) was identified for the immediate surgical approach. Incomplete resection and large size of the residual mass were identified as prognostic risk factors predicting poor outcome. Both parameters were observed more frequently in the group of patients who underwent elective PC-RPLND.

PC-RPLND: Extent of Surgery

The anatomical extent of PC-RPLND has been discussed controversially for many years. It has been a common practice to perform a full bilateral template dissection deriving from experiences of the 1980s when most patients presented with high-volume residual disease when undergoing retroperitoneal surgery. The boundaries of a full bilateral template include the crura of the diaphragm and the bifurcation of the common iliac arteries and the ureters, thereby including the primary and secondary landing zones of the right (paracaval, interaortocaval) and the left (paraaortic, preaortic) testicles. Wood et al. (1992) demonstrated an 8% incidence of contralateral spread among 113 patients with bulky disease undergoing full bilateral PC-RPLND after cisplatin- or carboplatin-based chemotherapy. Similarly, Qvist et al. (1991) and Rabbani et al. (1998) reported a 5.7% and a 2.6% incidence of teratomatous residues outside the boundaries of a modified template dissection. Nowadays, however, systemic chemotherapy is delivered for relatively low-volume retroperitoneal disease (clinical stage IIB) with most metastases being restricted to the primary landing zone of the tumor-bearing testicle. Although the potential of contralateral spread does exist especially from right to left, it is usually not common in low-volume residues questioning the appropriateness of full bilateral dissection for any residual disease. In a retrospective analysis, Aprikian et al. (1994) analyzed the outcome of 40 patients undergoing limited or bilateral radical PC-RPLND. A limited approach was chosen if intraoperative frozen section analysis (FSA) of the resected mass demonstrated necrosis or fibrosis, whereas a radical RPLND was used in the presence of mature teratoma or viable cancer. Twenty percent of the patients experienced recurrences (14% and 26% in the limited and radical RPLND, respectively) with none of the recurrences located in the retroperitoneum. The authors suggested to use intraoperative FSA to trigger the most appropriate surgical approach in the clinical scenario of PC-RPLND. Herr (1997) analyzed the therapeutic outcome of limited versus full bilateral PC-RPLND based on the results of FSA of the resected mass. If FSA demonstrated necrosis, a limited RPLND was performed; in all other cases, patients underwent bilateral RPLND. After a median follow-up of 6 years, 14 relapses were observed with only 2 developing in the retroperitoneum; furthermore, six major surgical complications were observed with five after bilateral RPLND. Modified PC-RPLND was considered to be a safe surgical procedure in a well-selected group of patients with advanced testicular cancer. These early retrospective and single-center studies indicate that a modified PC-RPLND might be a safe approach in men with limited retroperitoneal disease and right/left primary tumors with no evidence of teratoma or viable cancer on frozen section analysis of the residual mass. However, application of the modified unilateral template to PC-RPLND still is discussed controversially among tertiary referral centers based on the 3–8% incidence of mature teratoma or viable cancer in the contralateral landing zone (Wood et al. 1992; Qvist et al. 1991; Rabbani et al. 1998). Quite recently, three experienced groups reported their experience of patients undergoing modified unilateral template PC-RPLND (Beck et al. 2007; Cho et al. 2017; Heidenreich et al. 2009). The group at Indiana University has performed a limited PC-RPLND in 100 men with low-volume retroperitoneal disease (<5 cm) confined to the primary landing zone of the primary tumor (Beck et al. 2007; Cho et al. 2017). After a median follow-up of 125 months, only seven patients relapsed, all outside the boundaries of the modified and even of the bilateral template. The 5-year and 10-year disease-free survival rates are 93% and 92%.

It was the purpose of the Cologne Study Group to assess the oncological necessity of full bilateral retroperitoneal PC-RPLND in 85 patients with normalized or plateauing serum tumor markers (Heidenreich et al. 2009). Depending on the size of the residual mass or the location of the primary testicular tumor, a full bilateral template resection ($n = 35$) or a modified template resection ($n = 50$) was performed. If patients exhibited a well-defined lesion ≤ 2 cm, modified PC-RPLND was performed, and lesions >5 cm were always

treated by a full bilateral PC-RPLND. Lesions 2–5 cm in diameter were approached dependent on the site of the primary and the location of the mass: interaortocaval residuals were always approached with a full bilateral PC-RPLND, whereas para-aortic and paracaval lesions were treated by a modified PC-RPLND if the metastatic site corresponded to site of the primary; otherwise, a full bilateral PC-RPLND was initiated. There were no significant intraoperative complications; there was, however, a significant difference with regard to postoperative morbidity between bilateral and modified PC-RPLND with more complications in patients undergoing extended surgery ($p < 0.001$). Antegrade ejaculation was preserved in 85% of patients undergoing modified PC-RPLND, whereas it could not be preserved in 75% of the cases undergoing full bilateral PC-RPLND ($p = 0.02$), respectively (Fig. 5). Four (4.7%) recurrences were observed after a mean follow-up of 48 (2–84) months: one relapse was within the retroperitoneum following modified RTR for para-aortic disease, and three recurrences developed outside the boundaries of full bilateral PC-RPLND. There was no significant correlation with the extent of surgery and frequency and location of relapses.

In a recent validation study including 59 patients, Vallier et al. (2014) observed no relapse outside the modified RPLND field and inside the untouched contralateral RPLND field. The Heidenreich criteria did therefore not misclassify a single patient.

These data are in accordance with a study assessing the clinical and pathological features of 50 consecutive patients with advanced germ cell tumors who underwent bilateral PC-RPLND in order to define a subset of patients for whom a modified template resection might be indicated (Ehrlich et al. 2006). The authors found that all low-volume left-sided primary tumors followed a predictable pattern of spread, whereas right-sided primaries demonstrated a crossover in 20% of the cases. After a mean follow-up of 53 months, no in-field recurrences have been detected, so the authors are in favor of a modified template resection in low-volume residues and left-sided primaries.

Based on the data presented, full bilateral PC-RPLND is not always required, and it should be considered as surgical approach of choice in patients with extensive residual masses, interaortocaval location, or a location of the residual mass not corresponding to the site of the primary testis tumor. In well-defined small masses <5 cm, a modified template RTR does not interfere with oncological outcome but decreases treatment-associated morbidity.

Extraperitoneal Metastases in the Lung

Pulmonary metastases should always be resected as there is a poor concordance between the histologic specimen in the lung and the

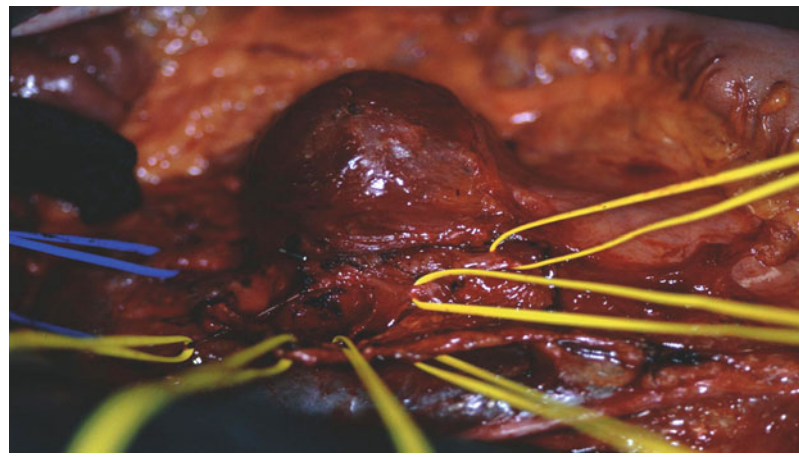

Fig. 5 Intraoperative situs of a nerve-sparing PC-RPLND with a modified template resection. The sympathetic nerve fibers are looped with yellow loops, and the residual mass is clearly visible in the center of the picture

retroperitoneum (Krege et al. 2008). But if there are residual tumors in both lungs, Besse et al. (2009) could show that one can safely spare one lung from residual tumor resection if contralaterally fibrosis is described in the pathologic specimen. In this case, the discordance decreases from 31% to 5%, and patients will be followed to reduce morbidity.

Liver Metastases

In retrospective analysis, vital carcinoma is found in 23.3–32.4% of the cases (Hahn et al. 1999; Rivoire et al. 2001). The size of the metastases was shown to be relevant for patients' outcome. All patients with metastases being larger than 3 cm died of disease. In lesions less than 10 mm, only necrotic tissue was found (Rivoire et al. 2001). Jacobsen et al. showed, in addition to the metastatic size, that there is a high concordance from the disease in the retroperitoneum to the disease that can be expected in the liver (Jacobsen et al. 2010). In the case of fibrosis/necrosis in the retroperitoneum, the concordance in the liver is almost 100%. This decreases in the case of teratoma and vital carcinoma to 70% and 50% but still allows an individual approach. With this approach, the potentially higher complication rate in liver surgery described in several series can be restricted to a minimum (Hahn et al. 1999; Rivoire et al. 2001; Jacobsen et al. 2010; Copson et al. 2004).

Bone Metastases

Bone metastases are infrequent. In the literature, bone involvement is described in about 3% of patients with a PC-RPLND (Heidenreich et al. 2017; Uygun et al. 2006). In 60%, bone metastases occur in relapsed disease. In some cases, it is unclear whether it is an isolated bone metastasis or infiltration from the surrounded tumor tissue. In most cases, bone metastases are located in the spine and are associated with other metastatic sites. Rare locations are isolated metastases in the skull (Uygun et al. 2006). The experience is limited to case reports or small series (Heidenreich et al. 2017; Berglund et al. 2006; Hitchins et al. 1988). Resections of residual or recurrent disease in the retroperitoneum with resection of the corpus of one or more vertebrae are described as complex residual tumor resection. In this case, usually a dorsal stabilization is performed in a first session. In a second step, the PC-RPLND is completed. The corpora are resected, and the defect is filled with a cage technique. The complexity of these interventions is even underlined that in addition to the bone resection there is a need of vascular surgery with replacement of v. cava and/or aorta in 40%.

Nevertheless, resection of bone metastases seems to be indicated as there is a significant histology with teratoma and vital carcinoma in 80% (Heidenreich et al. 2017). In the case of seminomatous histology, a radiotherapy in bone metastases is an option with good long-term results (Collins and Eckert 1985).

Brain Metastases

About 10% of the patients with advanced germ cell tumors have brain metastases. Long-term survival with brain metastases at initial diagnosis is 30–40% according to the poor prognosis defined by the IGCCCG criteria (Oechsle and Bokemeyer 2011; Fizazi et al. 2001). There is no standardized therapy sequence. As usual, chemotherapy is a main integral part of the therapy. By additional radiotherapy, a survival benefit could have been demonstrated.

The therapeutic effect of radiotherapy in the case of complete remission after chemotherapy is unclear. In addition, there are no long-term experiences of residual lesions in the brain. Iida et al. (2014) describe one case of resection as one isolated late relapse in the brain with elevated alpha fetoprotein values of 539 ng/ml. In a short follow-up, there was no recurrent disease after surgery only.

PC-RPLND After Salvage Chemotherapy or Previous Retroperitoneal Surgery

The presence of residual tumor masses after salvage chemotherapy is associated with a higher frequency of viable cancer, a higher likelihood of

incomplete surgical resection, and a higher risk of postoperative relapse as compared to those patients undergoing PC-RPLND after first-line chemotherapy (Eggener et al. 2007). Recently, Eggener et al. (2007) demonstrated that modern chemotherapeutic salvage regimes containing taxanes significantly reduced the presence of viable cancer from 42% to 14% ($p = 0.01$) when compared to earlier cisplatin-based cytotoxic regimes; the rates of teratoma in the residual tumors were similar with 31% and 33%. They found a 10-year disease-specific survival of 70%, so that PC-RPLND even after multiple chemotherapy regimes is indicated if the masses appear to be completely resectable.

Although rare, a subset of patients needs repeat RPLND due to metastatic tumor recurrence after primary RPLND or PC-RPLND because of incomplete tumor resection during initial surgery (Waples and Messing 1993; Cespedes and Peretsman 1999; Sexton et al. 2003; McKiernan et al. 2003; Heidenreich et al. 2005). Repeat RPLND itself represents a poor risk factor associated with a significantly lower 5-year survival rate of only 55% as compared to 86% in the group of patients undergoing adequate PC-RPLND. The long-term outcome after repeat RPLND relies on the complete resection of all residual retroperitoneal masses which will harbor viable cancer and mature teratoma in 20–25% and 35–40%, respectively. Whereas the cure rate for those with mature teratoma only approaches 100%, it decreases significantly to 44% and 20% in the presence of viable cancer and teratoma with malignant transformation, respectively. Repeat RPLND is a challenging surgical procedure associated with higher rates of adjunctive surgical procedures with ipsilateral nephrectomy and vascular procedures being the most frequent adjunctive surgeries.

Repeat RPLND represents the last chance of cure for patients with in-field recurrences, and it can be performed with an acceptable morbidity. Repeat RPLND will result in a long-term survival of 67–75%; if patients present with in-field recurrences and elevated markers, systemic chemotherapy followed by PC-RPLND should be initiated. In patients with negative markers, immediate RPLND should be performed since most masses will harbor mature teratoma only.

Desperation PC-RPLND

The term "desperation RPLND" applies to patients with persistently elevated or increasing serum tumor markers after primary inductive chemotherapy or after salvage chemotherapy due to either intrinsic or extrinsic chemoresistance. PC-RPLND in this cohort of patients is associated with a higher frequency of adjunctive surgeries and a poorer outcome. Usually, surgery alone is felt to result in a low likelihood of cure due to widespread systemic disease. However, according to the data of various groups, the 5-year overall survival is 54–67%, so that surgery might be indicated in well-selected subset cohort of patients (Albers et al. 2000; Beck et al. 2005). In a recent series, increasing preoperative ß-hCG, elevated AFP, redo RPLND, and incomplete resection had been identified as negative risk factors associated with a poor survival. Despite elevated serum tumor markers, about 45–50% of all patients harbor mature teratoma or necrosis/fibrosis in the surgical specimen resulting in a high cure rate. Patients with elevated but declining serum tumor markers and patients who had received first-line chemotherapy only had the highest likelihood to demonstrate teratoma or necrosis in the resected specimen. On the other hand, patients with incomplete resection demonstrate a poor prognosis and most likely do not benefit from extensive surgery. It is of utmost importance to identify those patients with potentially complete resection of residual masses who might benefit most from immediate surgery.

Adjunctive Surgery in Patients Undergoing PC-RPLND

Additional surgical procedures of adjacent vascular or visceral structures might be necessary in up to 25% of the patients undergoing PC-RPLND (Table 2) in order to achieve complete resection of the residual masses (Heidenreich et al. 2017; Beck et al. 2001; Winter et al. 2012; Johnston et al. 2013). En bloc nephrectomy represents the most common type of adjunctive surgery for complete tumor clearance. Additional vascular procedures such as

aortic replacement and resection of the inferior vena cava due to tumor infiltration will be necessary in about 1.5% and 10%, respectively.

Complications After PC-RPLND

Whereas the frequency of complications is low in patients undergoing primary nerve-sparing RPLND for clinical stage I NSGCT (Heidenreich et al. 2003), it increases significantly in PC-RPLND for large-volume residual disease. Although the frequency of associated complications has been decreased in recent series as compared to series of the 1990s, it still approaches 10% (Heidenreich et al. 2003; Mosharafa et al. 2004). The most common complications include minor complications such as wound infections, paralytic ileus, transient hyperamylasemia, and pneumonitis/atelectasis, whereas significant complications such as acute renal failure, chylous ascites, or obstructive ileus develop in less than 2% of the patients.

Table 2 Adjunctive surgery during PC-RPLND in a consecutive series of 152 patients

Type of adjunctive surgery	Frequency
Resection of v. cava inferior	4 (2.5%)
Replacement of v. cava inferior	3 (1.9%)
Thrombectomy of v. cava inferior	2 (1.3%)
Replacement of aorta	2 (1.3%)
Nephrectomy	6 (3.8%)
Ureteral resection	4 (2.5%)
Small bowel resection	6 (3.8%)
Resection of liver metastases	8 (5.0%)
Resection of retrocrural metastases	8 (5.0%)
Total	**43 (27.2%)**

Consolidation Chemotherapy After Secondary Surgery

After resection of necrosis or teratoma, no further treatment is required. When viable undifferentiated tumor is found, the role of further consolidation chemotherapy is uncertain. A retrospective analysis demonstrated an improved progression-free survival with adjuvant chemotherapy, but failed to show an improvement in overall survival. Therefore a "wait-and-watch" strategy may also be justified (Fizazi et al. 2001). Patients in the "good" prognosis group, according to the IGCCCG classification, with complete resection of residual masses and with <10% vital tumor cells in the resected specimens, have a favorable outcome even without adjuvant chemotherapy. If completely resected tumor presents >10% of viable cancer, or if completeness of the resection is in doubt, consolidation chemotherapy might be justified.

Summary

PC-RPLND represents a major part of the interdisciplinary management of advanced TGCT after systemic chemotherapy (Table 3). In patients with advanced seminomas, PC-RPLND is only indicated if FDG-PET scan performed 6–8 weeks after completion of chemotherapy demonstrates

Table 3 Indications for PC-RPLND

	Indication
Advanced seminoma	Positive FDG-PET scan with biopsy-proven vital residual cancer which can be completely resected
	Late relapse
NSGCT*	Any residual mass >1 cm in diameter and normalized serum tumor markers
	Any residual mass >1 cm in diameter and plateauing serum tumor markers
	Residual masses <1 cm in diameter and mature teratoma in the primary orchiectomy specimen
	Marker negative in-field recurrence after prior RPLND
	Residual marker negative or plateauing markers after salvage chemotherapy
	Desperation RPLND in patients with chemoresistant and completely respectable masses

*nonseminomatous germ cell tumors

positive findings. In advanced NSGCT, PC-RPLND should be performed in all patients with residual masses independent on size due to the high frequency of mature teratoma and viable cancer. In patients with left-sided primaries and/or low-volume disease, PC-RPLND can be performed within a modified template resection without compromising therapeutic efficacy. Complete resection of all residual masses will result in a long-term disease-free survival of 95%; in patients who undergo desperation surgery, long-term cure can be achieved in about 55%. PC-RPLND requires a complex surgical approach and should be performed in experienced, tertiary referral centers only.

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Follow-Up for Testicular Cancer

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Christian G. Ruf

Contents

Abstract

There are some specifics in testis cancer patients compared to other tumor entities. The excellent cure rates, even in advanced tumor disease, the young age, and the broad-spectrum of treatment options including reduction in treatment intensity lead to a long life expectancy with different rates of tumor relapse and side effects. Follow-up in testis cancer is worthwhile; cure rates are high even in relapsed disease. Follow-up should be frequent enough to detect relapse and side effects early enough to treat it and seldom enough to be feasible and not to harm patients, e.g., by exposure against ionizing radiation.

Therefore, anamnesis, clinical examination, different imaging procedures, and blood test should be done. Follow-up schedules are adapted to histology, clinical stage, and

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treatment modalities. Additionally, personalization of follow-up for some patients is essential, especially due to the broad-spectrum of side effect. In the vast majority of testicular cancer patients, a follow-up for 5–10 years and above is needful.

Introduction

Follow-up in cancer patients is indicated if there is an early detection of tumor relapse or side effects, and therefore an early treatment leads to better cure rates, helps to reduce treatment-associated side effects, or improves quality of life. This is especially true for testicular cancer patients. Excellent cure rates in testicular cancer patients are the results of multiparametric therapeutic approach, including active surveillance and follow-up.

Within the last decades, treatment intensity is continuously declining in almost all clinical stages. In the most common non-metastasized clinical stage I disease, active surveillance is now the treatment of choice for most of the patients. Especially in those patients, a frequent follow-up is essential to detect and treat metastatic progress in early stages.

Follow-up schedules should be frequent enough to detect tumor relapse as early as possible and rare enough to be feasible and to not harm patients by side effects, e.g., due to ionizing radiation in CT scans. Imaging procedures are therefore adapted to location and rates of tumor relapse.

Tumor relapse mostly occurs within the first 1–2 years after initial treatment. Frequency, location, and time point of tumor relapse depend on histology, clinical stage, and treatment of the patients, resulting in different follow-up schedules for different patients. There are some fix parts in follow-up program like anamnesis, clinical examination, and measuring of tumor markers, which should be done by every follow-up visit in every tumor stage. But there are also variable parts especially technique and frequency of imaging, depending on tumor stage and treatment.

Follow-up should not only detect tumor relapse but also long-term side effects of tumor therapy, typically occurring years or decades after treatment.

Side effects of tumor treatment include a broad-spectrum of diseases like treatment-associated second malignancies, metabolic syndrome, cardiovascular diseases, neurological impairment including persistent neuropathies, ototoxicity and tinnitus, renal impairment, and andrological aspects (Travis et al. 2010; Abouassaly et al. 2011; Gilligan 2011).

In over 40,576 long-term survivors, Travis et al. (2005, 2010) found 2285 secondary solid tumors after an observation period of at least 10 years. Frequency and location of secondary tumor are depending on the therapy and organ. The relative risk was 1.5–4. The diagnosis of hematologic neoplasm after radiotherapy or chemotherapy (Travis et al. 1997) succeeds in determining adequate laboratory parameters. The relative risk ranges between 3.5 and 4.5 (Fosså 2004; Richiardi et al. 2007). Solid and hematologic secondary malignancies – especially after etoposide-based chemotherapy – can be detected during follow-up (Richiardi et al. 2007).

A metachronous testicular tumor must also be expected in about 5% if primarily a GCNIS of the contralateral testis was not excluded by a biopsy or treated (Dieckmann et al. 2003).

Also psychological problems and fatigue frequently occur during follow-up (Travis et al. 2010; Fosså 2004). Incidence and frequency of side effects often depend on the intensity and modality of treatment. Due to the broad-spectrum and relatively rare incidence of particular side effects, it is impossible to screen every patient on every possible side effect. Therefore, anamnesis and clinical investigation can give a hint for side effects, often resulting in the consultation of a specialist, underlining the importance of a structured anamnesis and clinical investigation in follow-up visits.

During the course of follow-up, the focus of investigations changes from detection of tumor relapse to detection and treatment of side effects. Duration of follow-up is still under debate. While tumor relapse after 5 years is rare, long-term side effects like second malignancies typically occur after more than 10 years.

The following are thoughts and facts about follow-up in testis cancer patients:

- Follow-up should detect relapse, contralateral tumor, and side effects as early as possible.
- Most of the relapses occur within the first 2 years.
- Late relapses and contralateral tumors can occur after 10 and more years (Dieckmann et al. 2005, 2013).
- Risk for and location of relapse depend on tumor histology, stage, and treatment.
- About 50% of the contralateral tumors occur within the first 5 years.
- Long-term toxicity can occur after 10 and more years (e.g., treatment-associated second malignancies).
- Incidence and type of long-term toxicity depend on treatment.
- Long-term toxicity can be influenced by lifestyle behavior.
- Psychological side effects and fatigue should be asked for during follow-up.
- CT scans of the chest provide the best radiological information with a higher radiation exposure compared to chest X-ray.
- Follow-up schedule should be individualized for the patient concerning frequency, duration, and imaging procedures, depending on histology, clinical stage, coexisting disease, and treatment.

All standard follow-up recommendations and schedules are for standard situations and good prognosis patients only and require complete remission after therapy. All patients in intermediate and especially poor prognosis group, incomplete response, or unusual situations require individualized follow-up in experienced centers.

Anamnesis

Anamnesis should be a part of every follow-up visit. A well-performed structured targeted anamnesis has the potency to detect and treat tumor relapse as well as side effects at an early stage.

Anamnesis should ask for any relevant changes in physical and mental health since the last presentation.

Especially newly diagnosed disease and medication should be asked for.

Questions concerning pain, especially flank, bone, and back pain as well as abdominal pain, cough and expectoration, difficulty in breathing and shortness of breath, difficulties in urination and defecation, neurological abnormalities, breast swelling, any changes on the body including body weight and also noticeable fatigue, depression, and potency problems as well as prograde ejaculation should be asked (Jewett et al. 2003; Haugnes et al. 2012).

Clinical Examination

Clinical examination should initially focus on tumor relapse detection including palpation of contralateral testis, the mamae, relevant lymph node regions (groin, axilla, neck, and supraclavicular region), as well as the palpation of the abdomen and flanks. The lungs should be auscultated. A glance at the legs reveals unusual swelling.

To evaluate the risk of cardiovascular long-term side effects, blood pressure and body mass index should be measured on every visit (Krege et al. 2008).

Imaging

Ultrasound

Ultrasound of the remaining testicle must be done with high resolution, at least 7.5 MHz transducers to detect contralateral testicular tumors especially in not biopsied younger patients (<30 years) and small testicular volume (<12 ml) or untreated GCNIS.

For all follow-up visits without CT scan/MRI, ultrasound for the retroperitoneum, liver, and kidneys should be done. Devices with color Doppler are helpful for distinguishing areas of tissue with reduced perfusion and tumor tissue with

high vascular contents or identifying or delimiting large blood vessels in the retroperitoneum.

Chest X-Ray

Although chest X-ray is a standard diagnostic procedure in all guidelines, there is very limited evidence concerning its diagnostic accuracy alone (De La Pena et al. 2017). Pulmonary and mediastinal metastasis can occur in all tumor stages. In non-seminoma, there is a chance of pulmonary metastasis without retroperitoneal metastasis, which is unlikely for pure seminoma.

CT Scan

A standard method for the examination of retroperitoneal space, abdomen, mediastinum, lungs, and if necessary the pelvis and neck is spiral computer tomography with 5 mm slice distance, while magnetic resonance imaging is the superior method in the skull (Bokemeyer et al. 1997; Sohaib et al. 2009). CT scan is widely used, and there is a high level of experience also in radiologists.

Especially in patients with progress/relapse and negative tumor markers, CT scan is the diagnostic tool with the highest detection rate. Due to the disadvantages of CT scans like the exposure to ionizing radiation with its possible side effect in young men, the number of CT scans should be reduced to a minimum. Alternatives like ultrasound of the abdomen or MRI scan often show limited diagnostic accuracy or availability. Whenever possible, alternative imaging procedures should be taken into account.

MRI

The advantages of MRI of the abdomen, compared to the standard CT scan, are the lack of ionizing radiation, a contrast media with less side effects, and a more detailed imaging, especially in slim patients.

Negative aspects of abdomen MRIs are the longer scanning time with physiological bowl movement resulting in artifacts, less availability, less experience in radiologists compared to abdomen CT scans, and higher costs.

There is little evidence concerning the routine use of abdomen MRIs instead of CT scans, and results from prospective randomized trials are still pending, but there is one study showing comparable results for MRI and CT imaging of the abdomen (Sohaib et al. 2009).

Abdomen MRI instead of CT scan seems to be feasible in experienced hands.

Bone Scan

Bone scan is rarely indicated in cases of suspicion or exclusion of bone metastases (Oechsle et al. 2012) or occasionally during follow-up in successfully treated but still visible bone alterations.

Other Investigations

Other investigations like audiogram, cotransfer factor diffusion measurement, exercise ECG, or renal clearance are not used routinely but may be required during follow-up, if late toxicity is suspected (Travis et al. 2010; Abouassaly et al. 2011; Cost et al. 2012).

Tumor Marker, Hormones, and Blood Tests

Tumor markers play a central role in recurrence recognition: AFP, β-HCG, and LDH.

Due to a low specificity with a high number of false-positive results, PLAP is not used as a tumor marker for germ-cell tumors anymore.

New microRNA markers like miRNA 371 are showing a high sensitivity and specificity in diagnosis and treatment monitoring in germ cell tumors. Final results are pending, especially for the role of miRNA 371 in follow-up, but the results assume that the use of miRNA 371 as a

new tumor marker in germ-cell tumors for routine use is very likely. (Dieckmann et al. 2017).

β-HCG is the leading marker in seminoma, but it is only increased in about 10–50% of all seminomas, depending on the stage (Gerl et al. 2003). AFP is exclusively attributed to non-seminomas.

The LDH is a nonspecific tumor marker where a significant elevation may indicate advanced tumor disease. These three tumor markers are considered as prognostic factors (IGCCCG 1997; EAU 2018).

Andrological diseases like hypogonadism and infertility can occur because of the tumor or tumor treatment, also with late onset during follow-up. Therefore, the level of hormone FSH as an expression of spermatogenesis disorder and LH and testosterone as signs of hypogonadism should be monitored at least every year (Spermon et al. 2003; Nord et al. 2003; Haugnes et al. 2012). Other hormones like estradiol, prolactin, thyroid gland hormones, and others should additionally be measured if needed.

To detect side effects like renal impairment or reduce risk factors for long-term side effects like elevated cholesterin and cardiovascular disease like kidney and liver function, electrolytes and fats should be determined in the blood. Nonstandard values may imply or indicate a risk of organic complications such as cardiovascular disease due to increased blood lipids and increased creatinine or hypomagnesemia associated with impaired renal function (Haugnes et al. 2012).

Additionally, a hematuria as a hint for bladder cancer or renal failure should be excluded, especially after radiotherapy.

Schedules

The follow-up duration and the intervals are directed according to the risk of recurrence and the most vulnerable period.

The highest number of follow-up examinations per year is within the first 2 years, as the risk of relapse is the highest at that time. Within 2–5 years, the number of visits decreases. After 5 years, the likelihood of recurrence of the first-time tumor should not be greater than the occurrence of a new disease in the healthy population (Gerl et al. 1995).

The conditional risk of tumor relapse describes a dynamic change in relapse rates for primarily non-metastasized tumors depending on the time point after orchidectomy. High-risk non-seminoma of pure embryonal cell carcinoma, for example, is showing relapses in up to 50%. These relapses typically occur within the first 6 months. After 18 months of inconspicuous follow-up, the relative risk for relapse is higher in low-risk than in high-risk non-seminoma. This has to be taken into account in creating the follow-up schedule (Nayan et al. 2017).

In about 2–2.5% of cases, recurrence may occur later than after 5 years (Oldenburg et al. 2006; Buchler et al. 2011), and late relapses develop without preference from all primary stages (Dieckmann et al. 2005). If chemotherapy has been given initially, late relapses have a poor prognosis. Affected patients will have the best chance of survival if these recurrences are discovered at a time when curative therapy, usually in the form of surgery, is still possible (Flechon et al. 2005). The follow-up visits should therefore be offered once a year after 5 years for at least another 5 years, also to detect long-term toxicity. However, long-term effects are known and especially secondary malignancies occurr more than 10 years after therapy. Hence, experts advocated a lifelong one-time follow-up study for all patients who underwent chemotherapy or radiotherapy that could be combined with preventive urological checkups.

There is weak but increasing evidence in follow-up of testicular cancer patients (Cathomas et al. 2011; Souchon et al. 2011; Hartmann et al. 2011) resulting in evidence-based follow-up recommendation. Most of the actual guidelines are dividing patients into three groups with four corresponding follow-up recommendations (EAU 2018; Albers et al. 2014). For this purpose, a distinction is made between patients who have had local therapy in the retroperitoneal area or not (groups 1 and 2) and who are actively monitored in stage I (groups 3A and 3B). This results in three follow-up groups.

Table 1 Recurrence rate, target region, and duration to relapse by primary histology, clinical stage, and treatment modality

Histology	Stage	Therapy	Recurrence rate (%)	After >2 years (%)	Target region	References
Seminoma	I	Surveillance	3–31	4–6	Abdomen	Warde et al. (2002), Tandstad et al. (2011, 2016), Aparicio et al. (2011), and Dieckmann et al. (2016)
Seminoma	I	Carboplatin	1.5–6.5	1	Abdomen, lungs	Oliver et al. (2011), Aparicio et al. (2011), Tandstad et al. (2016), and Dieckmann et al. (2016)
Seminoma	I	20 Gy	2.5–4	1	Caudal field margin, lung	Classen et al. (2003), De Felice et al. (2016), and Dieckmann et al. (2016)
Seminoma	IIA/B	30/36 Gy	5–15	2	Lung	Classen et al. (2003, 2010)
Seminoma	IIC–III g.p.	3 × PEB/4 × EP	10	1	Abdomen, lungs	De Wit et al. (2001)
Nonseminoma	I low risk	Surveillance	10–15	2	Abdomen, lungs	Albers et al. (2008) and Tandstad et al. (2009)
Nonseminoma	I	RLA	8–10	2	Lung	Albers et al. (2008)
Nonseminoma	I "high risk"	2 × PEB	0–2	1	Abdomen, lungs	Oliver et al. (2004) and Tandstad et al. (2009)
Nonseminoma	IIA–III "good prognosis"	3 × PEB/4 × EP	10	1	Abdomen, lungs	De Wit et al. (2001)

Table 1 gives an overview over relapse rate and location depending on histology, clinical, stage, and treatment.

In metastatic germ-cell tumors, the recommendations in Group 1 and 2 apply only to patients of the good prognosis group according to the classification of the International Germ Cell Cancer Collaborative Group (IGCCCG) (IGCCCG 1997). In addition, the patients must be in complete remission, including resection of all remaining tumors in non-seminomatous tumors and a negative PET-CT in case of residual findings >3 cm in seminoma.

For all other patients, an individualized follow-up schedule in experienced centers is required.

Group 1

Group 1 includes all patients who receive local therapy in the retroperitoneum following adjuvant radiotherapy for stage I seminoma, curative

Table 2 Follow-up schedule for patients with local retroperitoneal treatment (Group 1)

Year	1	2	3	4	5	≥6
Follow-up rhythms (annual number of appointments)	4	4	2	2	2	1
CT abdomen (month)	12	24	–	–	–	–
Ultrasound abdomen (month)	6	18	36	48	60	–
Ultrasound testicle	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year
Chest X-ray (month)	6 + 12	18 + 24	36	48	60	–
Clinical examination RR/BMI/marker	4	4	2	2	2	1
Extended laboratory hormones/lipids	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year

Includes CT pelvis at seminom stage I after radiotherapy. In nonseminomatous GCT with initial supradiaphragmatic maninfestation (stage III) instead of chest X-ray, CT thorax; Month 6, 12, and 24

radiotherapy for stage IIA and IIB seminoma, and patients with metastatic non-seminoma and post-chemotherapy residual tumor resection. There is a low recurrence probability in the retroperitoneum resulting in only two CTs of the abdomen during follow-up (Table 2).

There are two exceptions in this group: stage I seminoma with adjuvant radiotherapy without dog leg technique receives an additional CT scan of the pelvis. In patients with initial supradiaphragmal metastatic non-seminoma, conventional chest X-ray is replaced by CT scans of the chest at 6, 12, and 24 months. The follow-up should be carried out for at least 5 years.

Group 2

Recommendations for Group 2 apply to all patients who have not received local therapy in the retroperitoneum. This includes all patients with seminoma or non-seminoma who have received systemic chemotherapy. Recurrence rates are also low in this group, especially in the first 2 years. Due to the more frequent relapse location in the retroperitoneum, additional abdominal CT is recommended at 6 months (Table 3). Excluded are patients with non-seminoma or stage I seminoma after chemotherapy with a very low risk of recurrence. In the case of supradiaphragmatic metastases, initial thorax CT scan is recommended after 6, 12, and 24 months instead of conventional chest X-ray. Follow-up should be carried out for at least 5 years.

Groups 3A and 3B

Clinical stage I patients under active surveillance undergo the schedules of Groups 3A and B. A distinction must be made between seminoma (Group 3A) and non-seminoma (Group 3B) due to the differences in timing and localization of recurrence. The recommendations for Group 3B apply for non-seminoma in the low-risk group (no lymphovascular invasion) only. In active surveillance, imaging is of special importance as in 20–25% of the recurrences tumor markers are unremarkable in non-seminoma. A large randomized phase III study (Rustin et al. 2007) provides information on the frequency of imaging in this situation: two CT scans at 3 and 12 months are preferable to more intense five CT imagings. It is important to note, however, that the other controls (hospital, tumor markers, and conventional chest X-ray) have to be monitored in the first 2 years as done in this study. There is an ongoing debate whether or not CT scans should be performed at the end of year 3 and 5. The following schedules include the minimum of CT scans which can be supplemented by addition CT scans of the abdomen after 36 and even 60 months (Table 4).

Group 3A

The extent of imaging in active surveillance patients is controversial. Recurrence rates in literature vary from 3% to 30% (Warde et al. 2002; Tandstad et al. 2016; Dieckmann et al. 2016), and the importance of particular clinical risk factors is still under debate (Zengerling et al. 2017). Currently, a randomized study (MRC study: TRISST)

Table 3 Follow-up schedule for patients without local retroperitoneal treatment (Group 2)

Year	1	2	3	4	5	≥6
Follow-up rhythms (annual number of appointments)	4	4	2	2	2	1
CT abdomen (month)	[a]6 + 12	24	–	–	–	–
Ultrasound abdomen (month)	[a]6	18	36	48	60	–
Ultrasound testicle	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year
Chest X-ray (month)	6 + 12	18 + 24	36	48	60	–
Clinical examination RR/BMI/marker	4	4	2	2	2	1
Extended laboratory hormones/lipids	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year

[a]No CT at month 6 for seminoma and nonseminoma clinical stage I after chemo, but ultrasound abdomen. In nonseminomatous KZT with initial supradiaphragmatic infestation (stage III) instead of chest X-ray, CT thorax; Month 6, 12, and 24

Table 4 Follow-up schedule for patients with clinical stage I seminoma (Group 3A) and nonseminoma (Group 3B) undergoing active surveillance

Year	1	2	3	4	5	≥6
Follow up schedule group 3A (seminoma stage I active surveillance)						
Follow-up rhythms (annual number of appointments)	4	4	2	2	2	1
CT abdomen (month)	6 + 12	18 + 24	36	–	60	–
Ultrasound abdomen (month)	3 + 9	15 + 21	30 + 36	48	60	–
Ultrasound testicle	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year
Chest X-ray (month)	6 + 12	18 + 24	36	48	60	–
Clinical examination RR/BMI/marker	4	4	2	2	2	1
Extended laboratory hormones/lipids	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year
Follow up schedule group 3B (nonseminoma stage I active surveillance)						
Follow-up rhythms (annual number of appointments)	6	6	4	2	2	1
CT abdomen (month)	4 + 12	24	–	–	–	–
Ultrasound abdomen (month)	–	24	36	48	60	–
Ultrasound testicle	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year
Chest X-ray (month)	Every 2 month	Every 2 month	30 + 36	48	60	–
Clinical examination RR/BMI/marker	6	6	4	2	2	1
Extended laboratory hormones/lipids	1x/year	1x/year	1x/year	1x/year	1x/year	1x/year

[NCT00589537] is performed to compare the necessity of CT scans versus three CT scans and their benefit in relapse detection compared to MRI (seven vs. three MRIs). Until these results are available, a total of four CT scans are recommended in the first 2 years.

As the incidence of late relapses for stage I seminoma seems to be increased, an additional CT scan of the abdomen should be done after 36 and 60 months.

Afterward, the CT should be replaced with ultrasound examinations to maintain the frequency of imaging while minimizing radiation exposure, assuming acceptable modality. Under certain conditions, the CT scan can be replaced by MRI during follow-up.

Group 3B

In non-seminoma, the risk of recurrence depends very much on lymphovascular invasion in primary tumor. For stage I low-risk tumors, the risk of recurrence is only 14–22%, whereas recurrence rate in high-risk tumors is as high as 40–50% (Albers et al. 2003). In stage I non-seminoma,

the conditional risk of tumor relapse leads to a crossover from high-risk to low-risk stages during follow-up (see above).

Under certain conditions, the CT scan can be replaced by MRI during follow-up.

Conclusion

Follow-up in testicular cancer patients is an essential part of patients' treatment. Especially in decreased treatment, intensity relapse rates might increase, and relapse therapy should start as early as possible. In long-term follow-up disease and treatment, related health impairment and side effects should be diagnosed and treated. There is low but increasing evidence for follow-up schedules and modalities resulting in follow-up recommendations for non-metastasized and metastasized patients in good prognosis group. In patients with intermediate and poor prognosis, according to the IGCCCG, the follow-up has to be adjusted individually and should be carried out by experts, interdisciplinary whenever possible. In order to record the long-term effects of the therapies in addition to recurrences and secondary tumors, the follow-up period should be extended to a minimum of 10 years, at least for chemotherapy-treated or irradiated patients. The frequency and use of diagnostic procedures especially for CT scan has been significantly reduced within the last years to minimize exposure to ionizing radiation.

Despite all standardization, only careful and if needed individualized follow-up can achieve the desired success in curing testicular cancer patients.

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Part VI

Other Rare Urologic Malignancies (Non-urological Cancers Affecting the Urinary Tract)

Urethral Carcinoma

52

Georgios Gakis

Contents

Abstract

Urethral carcinoma is a rare urogenital malignancy. Therefore, there are currently critical gaps in the understanding of the biology of the disease. Urethral carcinoma is diagnosed either as a primary tumor detected primarily in the urethra (PUC) or secondary one as a recurrence in the urethra after treatment of a urothelial carcinoma elsewhere in the urinary tract. Both primary and secondary urethral carcinomas are predominantly of urothelial

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histology. Most patients present with symptoms associated with locally advanced disease. Lymph node status is a strong predictor for outcomes in nonmetastatic PUC. In men, risk factors for the development of a SUC after radical cystectomy (RC) include non-muscle-invasive tumor stage at RC, tumor multifocality, non-orthotopic urinary diversion, superficial and invasive prostatic tumor involvement, and a positive urethral margin at RC. In women, risk factors for secondary urethral carcinoma after RC include multifocal or recurrent bladder cancer, bladder neck involvement, and a positive urethral margin at RC. In the absence of metastatic disease, urethral-sparing surgery can be utilized in distal tumors as an alternative to radical surgery provided negative surgical margins can be achieved intraoperatively. Treatment of proximal or advanced tumors most often consists of radical surgery with perioperative chemo- or chemoradiotherapy.

Introduction

Urethral carcinoma is an uncommon malignancy (Gakis et al. 2013a, b). Given this, there is a critical gap in our understanding of the biology of the disease and the choice of appropriate treatment options. This review provides an overview of the current status of the literature.

Primary urethral carcinoma (PUC) is defined as a carcinoma of the urinary tract detected primarily in the urethra, whereas a secondary urethral carcinoma (SUC) is defined as a recurrence in the urethra after treatment of a carcinoma elsewhere in the urinary tract. The estimated annual incidence of PUC was reported to be 650 new cases in Europe (Visser et al. 2012) and to be thrice higher in the United States (Swartz et al. 2006). In addition, PUC is reported to be twice likely in African Americans as in the white population (Swartz et al. 2006). There is an age-dependent increase in the incidence, with highest rates in patients aged 75 years or older and almost negligible in those <55 years of age (Swartz et al. 2006).

Etiology and Risk Factors for Primary Urethral Carcinoma

Risk factors in male patients have been reported to be chronic urethral inflammation and trauma (Saito 1981), external beam radiotherapy or radioactive seed implantation (Mohan et al. 2003), and after urethroplasty (Domino et al. 2017). In women, risk factors include urethral diverticula (Scantling et al. 2013) and chronic or recurrent urinary tract infections (Libby et al. 2010).

Etiology and Risk Factors for Secondary Urethral Carcinoma

In men, the risk of developing urethral malignancy after RC or radiotherapy for bladder cancer is low (4–10%) (Gakis et al. 2016a). The median time to recurrence ranges approximately between 13 and 30 months (Boorjian et al. 2011; Gakis et al. 2015a). In male patients, independent risk factors for SUC (RC) include non-muscle-invasive tumor stage, tumor multifocality, carcinoma in situ (Huguet et al. 2008), non-orthotopic urinary diversion (Boorjian et al. 2011), superficial or invasive prostatic tumor involvement (Huguet et al. 2008), and a positive urethral margin at RC (Gakis et al. 2015a, 2016a). In women undergoing RC, the rate of urethral recurrence was reported to range between 1 and 4% (Gakis et al. 2013b, 2016a). The most frequently reported risk factors for SUC after RC include bladder neck involvement (Stein et al. 2007) and a positive urethral margin at RC (Gakis et al. 2015a).

Histopathology of Urethral Carcinoma

Urothelial carcinoma (UC) is the predominant histological subtype of PUC (54–65%) followed by squamous cell carcinoma (SCC; 16–22%) and adenocarcinoma (AC; 10–16%), respectively (Gakis et al. 2013a, 2016b). In contrast to this, SUC are exceedingly of urothelial histology (Gakis et al. 2015a, 2016a).

Classification

The TNM staging system is recommended to classify urethral carcinoma (Sobin et al. 2010). For UC, WHO grading system of 2004 is recommended to differentiate between low-grade and high-grade carcinoma (Eble et al. 2004). It has to be noted that prostatic urethral carcinoma is staged separately. Urethral carcinoma of non-urothelial origin is graded by the three-dimensional WHO grading system of 1973 (Gakis et al. 2013a) (Tables 1, 2, 3, 4).

Table 1 TNM classification of non-prostatic urethral carcinoma (A) and urothelial cell carcinoma of the prostate (B) (Sobin et al. 2010)

A. Primary tumor (T) (men and women)	
Tx	Primary tumor not assessable
Tis	Carcinoma in situ
T0	No evidence of primary tumor
Ta	Noninvasive papillary, polypoid, or verrucous carcinoma
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following structures: Corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following structures: Corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
T4	Tumor invades other adjacent organs
B. Primary tumor (T) of prostatic urethra	
Tx	Primary tumor not assessable
Tis pu	Carcinoma in situ in the prostatic urethra
Tis pd	Carcinoma in situ in the prostatic ducts
T0	No evidence of primary tumor
T1	Tumor invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)
T2	Tumor invades any of the following structures: Corpus spongiosum, prostatic stroma, periurethral muscle
T3	Tumor invades any of the following structures: Corpus cavernosum, beyond prostatic capsule, bladder neck
T4	Tumor invades other adjacent organs
Regional lymph nodes	
Nx	Regional lymph nodes not assessable
N0	No regional lymph node metastases
N1	Metastasis in a single lymph node $\leq$2 cm in greatest dimension
N2	Metastasis in a single lymph node >2 cm in greatest dimension or in multiple nodes
Distant metastasis	
Mx	Distant metastasis not assessable
M0	No distant metastasis
M1	Distant metastasis

Clinical Presentation

The clinical onset of urethral carcinoma can be insidious. Most patients present with symptoms associated with locally advanced disease, i.e., an extraurethral mass, bladder outlet obstruction, pelvic pain, urethrocutaneous fistula, abscess formation, or dyspareunia (Gheiler et al. 1998). In women, unspecific irritative or obstructive voiding symptoms may be misdiagnosed for benign urethral conditions like urinary tract infections, diverticula, caruncles, or prolapses. Physical examination should include a digital rectal examination and palpation of the external genitalia for suspicious indurations or masses of the corpus spongiosum and cavernosum. In women, careful inspection of the external urethral meatus, palpation of the urethra, and bimanual examination under general anesthesia should be performed as well as clinical examination of inguinal lymph nodes since enlarged lymph nodes often represent metastatic disease (Gakis et al. 2013a).

Diagnostic Procedures

Urine Cytology

In a retrospective series, the sensitivity of urinary cytology for detecting PUC was reported to be low with similar detection rates for men and women (55% and 59%, respectively). Analyzed according to the underlying histological entity, varying rates were reported for UC (male to female ratio, 80%:50%) and SCC (50%:77%) (Touijer and Dalbagni 2004). In this regard, it needs always to be borne in mind that a positive urinary cytology may be related to the presence of a concomitant bladder or upper tract tumor. Urinary cytology performed at regular intervals may

Table 2 AJCC staging system of urethral carcinoma (Sobin et al. 2010)

Stage	T	N	M
0a	Ta	N0	M0
0is	Tis or tis(pd) or tis(pu)	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	N0 or N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Table 3 Histopathological grading of urothelial carcinoma (Eble et al. 2004)

Grading	
PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Table 4 Histopathological grading of non-urothelial carcinoma of the urethra (Eble et al. 2004)

Grading	
Gx	Tumor grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

be helpful in detecting secondary urethral recurrence in patients after RC, but sensitivity is impaired in patients after urinary diversion (Gakis et al. 2013b).

Bioptic Assessment

Urethroscopy with biopsy is carried out for histological confirmation of malignant disease in the urethra and should also include cystoscopy to exclude concomitant bladder cancer (Gakis et al. 2013a). Larger lesions can be resected with a resectoscope, whereas a cold-cup biopsy should be carried out for smaller lesions. If complete resection is aimed, it is recommended to mark biopsies obtained from the proximal and distal end to enable accurate histopathological assessment of surgical margins. In patients who are suspected to have PUC of the prostate, a loop biopsy of the prostatic urethra (at 5 and 7 o'clock position from the bladder neck and distally around the area of the verumontanum) has been reported to contribute to an improved detection of malignancies of the prostatic urethra (von Rundstedt et al. 2015).

Radiological Imaging

Radiological imaging aims to assess local tumor extent and detect lymphatic or distant metastatic disease. Magnetic resonance imaging is superior to ultrasonography, urethrography, and computed tomography in terms of staging accuracy due to improved soft tissue identifiability (Gourtsoyianni et al. 2011). Since clinical nodal status was found to be a critical parameter for outcomes (Gakis et al. 2016b), imaging of lymph node metastases should concentrate on the inguinal and pelvic lymphatic drainage system prior to initiation of treatment (Gakis et al. 2013a).

Treatment of Localized Primary Urethral Carcinoma

Treatment of Localized Urethral Carcinoma in Men

Treatment options for localized urethral carcinoma depend on tumor extent and location and include a variety of surgical approaches, chemoradiotherapy, and radiotherapy. Urethral-sparing techniques have become popular since they may encompass oncologic safety and functional outcomes (Fahmy et al. 2015). Most often, these techniques are applied in distal tumors as this location is associated with improved survival (Gakis et al. 2016b; Gheiler et al. 1998). Since a positive urothelial margin on frozen section analysis (FSA) is highly associated with a positive final margin, it is important to assess margins at the time of surgery (Gakis et al. 2016a). In men,

penile-preserving approaches include transurethral resection, local excision, glansectomy, distal corporectomy, distal urethrectomy, and partial urethrectomy. In a series of 18 patients treated with these types of penile-preserving surgery, no local recurrence was detected after a median follow-up of 26 months, although 8 of the patients had tumor-free margins of less than 5 mm (Smith et al. 2007).

Patients with noninvasive UC of the prostatic urethra can be treated with a urethra-sparing approach including transurethral resection and subsequent bacille Calmette-Guerin (BCG) therapy (Palou et al. 2013). Performance of a transurethral resection of the prostate before initiation of BCG immunotherapy was reported to be more effective in terms of cancer control compared to upfront BCG (Gofrit et al. 2009). Patients with extensive ductal or stromal involvement already exhibit lymph node metastases above the iliac bifurcation in up to 50% of the patients (Vazina et al. 2004). Hence, it is recommended to treat these patients with cystoprostatectomy and extended pelvic lymph node dissection (Gakis et al. 2013a).

Treatment of Localized Urethral Carcinoma in Women

Like in men, the indication for primary urethrectomy or urethral-sparing surgery in women depends on the exact tumor extent and location (Gakis et al. 2013a). Primary urethrectomy includes the removal of all periurethral tissue from the bulbocavernosus muscle with a cylinder of all adjacent soft tissue up to the pubic symphysis and to the bladder neck (Karnes et al. 2010). The importance of clinical decision-making for either urethral-sparing surgery or urethrectomy was suggested in a series of 53 women in which a local recurrence rate of 22% after partial urethrectomy was reported (Dimarco et al. 2004a). Attempting to achieve larger tumor-free margins resulted in secondary urinary incontinence in approximately 40% of the patients (DiMarco et al. 2004b). The use of ablative surgical techniques results in a considerable local failure rate of 16% with reported low cancer-specific survival rate of 50% and should therefore be discouraged (Dimarco et al. 2004a). Urethral-sparing surgery is advocated only when negative margins can be achieved without compromising the anatomical integrity of the external urethral sphincter (Gakis et al. 2013a). Otherwise, radical urethrectomy and formation of a catheterizable stoma represent a valid alternative (Karnes et al. 2010). Figure 1 depicts a urethral melanoma of the anterior urethra treated with partial urethrectomy.

Treatment of Advanced and Recurrent Primary Urethral Carcinoma

Several studies have demonstrated that modern platinum-based chemotherapeutic regimens provide prolonged survival in PUC. In a retrospective

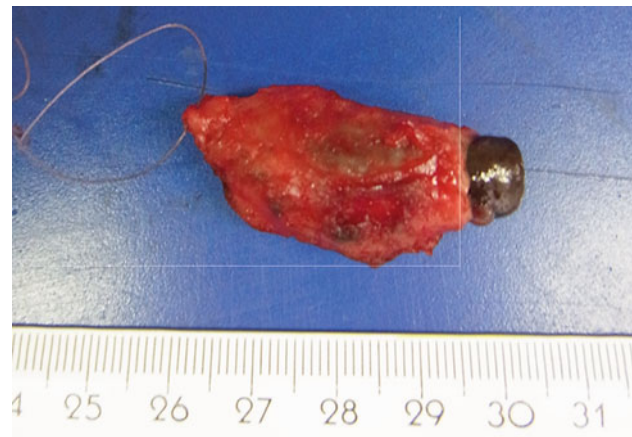

Fig. 1 Urethral melanoma of the anterior urethra treated with partial urethrectomy (suture at the proximal margin)

series of 39 patients, those who received neoadjuvant chemotherapy (NAC) or neoadjuvant chemoradiotherapy (N-CRT) for clinically advanced (≥cT3) and/or clinically node-positive PUC appeared to demonstrate improved survival compared to those who underwent upfront surgery with or without adjuvant chemotherapy (Gakis et al. 2015b). These findings are in accordance with a prior study reporting on satisfactory overall survival rates in patients with locally advanced or lymph node-positive PUC treated with a neoadjuvant approach compared to those who were managed with chemotherapy alone (Dayyani et al. 2013). The beneficial effect of radiotherapy seems to be more pronounced within a multimodal approach. In a recent series of women with PUC from the National Cancer Registry of the Netherlands, extensive surgery of the primary tumor and additional radiotherapy were found to confer a survival benefit even in patients with lymph node-positive disease. Yet, side effects included urethral stenosis, fistula, necrosis, proctitis, and hemorrhagic cystitis (Derksen et al. 2013). In case of urethral recurrence, patients undergoing salvage surgery or radiotherapy for recurrent PUC experience comparable survival rates to those who never develop recurrence after primary treatment (Gakis et al. 2018).

Treatment of Secondary Urethral Carcinoma

Urethral-Sparing Treatment for Secondary Urethral Carcinoma

The role of intraurethral instillation of BCG was investigated in a series of ten patients with Ta-T1 urethral recurrence after RC. Of these, six had CIS only and four papillary or invasive tumors. After insertion of a modified Foley catheter, three times the common dose of BCG was administered in 150 ml of 0.9% sodium chloride and applied according to a specific institutional protocol. After completion of treatment consisting of repeated instillations weekly for 6 weeks, the overall median survival in the total cohort was relatively high with 61 months (5-122). Five of the six patients (83%) with CIS only remained free of recurrence (Varol et al. 2004). These data hint at the high risk of recurrence and progression even in patients with low-stage tumors, while in those with CIS only a urethra-sparing approach with prior transurethral resection of the prostate followed by BCG instillation was reported to result in improved local control compared to BCG alone (Taylor et al. 2007).

Urethrectomy for Secondary Urethral Carcinoma

Urethrectomy is an effective treatment option for patients with early invasive urethral recurrence (Varol et al. 2004; Spiess et al. 2006). Nonetheless, to obviate the risk of urethral recurrence after RC in patients with non-heterotopic diversions, prophylactic urethrectomy in patients at high risk of recurrence may confer a survival advantage (Spiess et al. 2006). The timing of urethrectomy was analyzed in a large retrospective study of 2401 men who were initially treated with radical cystoprostatectomy for bladder cancer. Of these, 195 men (8.1%) were treated with either concurrent urethrectomy (performed within 6 weeks after cystectomy) or urethrectomy at the time of recurrence. Complication rates and intraoperative blood loss were not significantly different in patients treated with delayed or immediate urethrectomy. Yet, the use of prophylactic urethrectomy in patients with invasive prostatic tumor involvement at RC tended to confer a significant survival benefit ($p = 0.063$) compared to patients treated with urethrectomy at the time of diagnosis of recurrence (Nelles et al. 2008). Nonetheless, for women, it is suggested to perform concurrent urethrectomy in case of non-heterotopic urinary diversion at RC as it is easier in women to be performed at the time of cystectomy compared to men (Gakis et al. 2016a).

Follow-Up

Given the low incidence of primary and secondary urethral carcinoma, there are no robust data to advocate an optimal follow-up regimen in an

asymptomatic patient after curative treatment for PUC and with a retained urethra after RC (Gakis et al. 2016a). Therefore, it seems reasonable to tailor surveillance regimens according to the patient's individual risk factors for recurrence as outlined above. However, there is increasing evidence that patients with asymptomatic urethral recurrences exhibit improved survival compared to those with symptomatic recurrences since they are more likely to be diagnosed at an earlier stage (Gakis et al. 2016a; Giannarini et al. 2010). Therefore, further studies are needed to elucidate the prognostic benefit of a defined follow-up regimen.

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Adrenal Tumors

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Luciano A. Nuñez Bragayrac and Thomas Schwaab

Contents

Abstract

The adrenals are two retroperitoneal organs with multiple endocrine and neurocrine functions. The most common problems are related to the function and dysfunction of them. However, they are organs that are not except of neoplasia development or metastases from other organs.

In this chapter, the diagnosis and management of the main malignant adrenal problems would be developed, which include adrenal carcinoma, malignant pheochromocytoma, and metastases to the adrenals.

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Adrenal Carcinoma

Epidemiology

Adrenocortical carcinoma (ACC) is a very uncommon and aggressive malignancy. The incidence is difficult to determine, and it was

estimated to be 0.5–2 per million populations (Wajchenberg et al. 2000; Dackiw et al. 2001; Allolio and Fassnacht 2006; Fassnacht and Allolio 2009; Zini et al. 2011). Approximately, 5% of the adrenal incidentalomas are ACC (Zini et al. 2011; Mantero et al. 2000). ACC has a bimodal distribution that is high in children in the first decade of life and adults in the fourth decades of life, but it can be presented at any age (Allolio and review 2006; Zini et al. 2011). Between gender, it is more common in females than males, with a ratio of 1.5–2.5:1 (Allolio and review 2006; Xiao et al. 1998; Roman 2006). There are differences between the pediatric and adult ACC patients, in terms of clinical presentation, staging systems, and prognosis. We are focusing on the adult population.

Pathogenesis

The tumorigeneses of different syndromes associated with ACC are well characterized, but the molecular pathogenesis of sporadic ACC is less understood. The study of clonality of adrenocortical tumors has shown that ACC are of monoclonal origin. Comparative genomic hybridization and microsatellite analysis demonstrated losses at 1p, 17p, 22p, 22q, and 11q in up to 62% of cases of ACC (Zhao et al. 1999; Gicquel et al. 2001).

TP53 gene, located on chromosome 17p13, is the most frequently mutated gene in human cancers. It was found very common germlines mutations in Li-Fraumeni syndrome, which confers susceptibility to breast carcinoma, soft tissue sarcoma, brain tumors, osteosarcoma, leukemia, and ACC (Hisada et al. 1998). A germline mutation in TP53 has been observed within children with ACC from Southern Brazil (Stojadinovic et al. 2002; Latronico et al. 2001), North America, and Europe (Varley et al. 1999). Specifically in the pediatric Brazilian population, this germline mutation was identified in exon 10 of the TP53 gene (R337H) in almost all the cases (Latronico et al. 2001).

There is a role for TP53 in sporadic ACC that is suggested by the loss of heterozygosity (LOH) at the 17p13 locus in sporadic ACC (Bourcigaux et al. 2000). LOH is present in 85% of malignant tumors and <30% of benign adenomas (Gicquel et al. 2001). Nevertheless, in sporadic ACC, TP53 is present in 30% of the cases (Libe et al. 2007; Reincke et al. 1994; Ohgaki et al. 1993). The discrepancies between the frequencies of TP53 mutation and LOH on 17p13 suggest that there is another tumor suppressor gene in this locus (Libe et al. 2007).

The insulin-like growth factor 2 (IGF-II) gene located at 11p15 encodes an important fetal growth factor maternally imprinted and expressed only from the paternal allele (DeChiara et al. 1991). Abnormalities on the 11p are implicated on the Beckwith-Wiedemann syndrome, which present with Wilms' tumor, neuroblastoma, hepatoblastoma, and ACC (Sullivan et al. 1978). IGF-II is overexpressed in malignant adrenocortical tumors and it is approximately 90% of ACC (Gicquel et al. 1997, 2001; Ilvesmaki et al. 1993). Also, LOH of the 11p15 is associated with a higher risk of recurrence and is more frequent in ACC (Gicquel et al. 2001). However, other growth-related tumor suppressor genes at this locus may also be involved (Bourcigaux et al. 2000).

The Wnt/β-catenin pathway has an important role in the adrenal cortex development (Kim et al. 2008). Genetic alterations on this pathway were identified in familial adenomatous polyposis coli (APC) (Smith et al. 2000; Kikuchi 2003). The increased occurrence of adrenal tumors in patient with APC suggested that the Wnt/β-catenin pathway should be related to de development of ACC (Smith et al. 2000; Blaker et al. 2004). Mutations of the β-catenin gene, specifically at the glycogen synthase kinase 3-β (GSK3-β) phosphorylation site, are common in about 30% of ACCs (Tissier et al. 2005; Bonnet et al. 2011). Somatic CTNNB1 mutations may explain only about 50% of beta-catenin accumulation observed in adrenocortical tumors, indicating that other components of the Wnt pathway may be involved

(Tissier et al. 2005; Bonnet et al. 2011; Tadjine et al. 2008).

Clinical Presentation

ACC can be presented asymptomatic as an incidental mass, due to the increased routine images, however, the majority of patients still present with advance disease and symptomatic. In approximately 60% of ACCs are presented with symptoms of hormone excess (mostly Cushing's syndrome or androgenisation) (Allolio and review 2006; Luton et al. 1990; Crucitti et al. 1996; Icard et al. 2001).

The most typical presentation of adults with secreting ACCs is with symptoms of Cushing's syndrome, which is present in around 45% with central obesity, rounded face, muscle weakness, skin atrophy, menstrual alterations, osteoporosis, hypertension, and diabetes mellitus, with a rapid onset. The symptoms of Cushing-associated virilization are usually more pronounced with overproduction of both glucocorticoids and androgens (Wajchenberg et al. 2000; Dackiw et al. 2001; Ng and Libertino 2003; Koschker et al. 2006; Abiven et al. 2006). Around 10% of patients present with virilization and/or feminization alone, affected women show signs and symptoms of androgen excess, in men gynecomastia and atrophic testicles are rare and consequence of estrogen-producing adrenal tumors (Ng and Libertino 2003). More uncommon is hyperaldosteronism associated with ACCs, when present, hypertension and hypokalemia are more related to overproduction of different hormones than aldosterone (Latronico and Chrousos 1997; Johanssen et al. 2010).

In contrast, nonfunctioning tumors usually present with signs and symptoms of local mass effect of the tumor, such as abdominal pain, back pain, nausea, vomiting, and it occurs more frequently with tumors larger than 10 cm, or these tumors are found incidentally on radiographic imaging performed for a different reason (Johanssen et al. 2010).

Diagnosis

All patients with suspected AAC should have a detailed history and physical examination to exclude signs and symptoms of endocrine overproduction, an endocrine workup and imaging studies to define the extent of the disease.

Hormonal Workup

Endocrine evaluation of all suspected ACCs and adrenal masses is mandatory, not only to establish the origin on the adrenal gland but also to use them as markers of presence of residual tumor or recurrence after resection. The endocrine evaluation is useful to prevent adrenal failure after resection. European Network for the Study of Adrenal Tumors (ENSAT) recommends the evaluation of glucocorticoid excess, evaluation of sexual steroids and precursor, mineralocorticoid excess should be assessed in patient s with hypertension and hypokalemia through the aldosterone-renin ratio (Fassnacht and Allolio 2009; Arlt et al. 2011; Zeiger et al. 2009).

Pheochromocytoma should be excluded before surgery by measuring plasma metanephrines or urinary metanephrines and catecholamines (Zeiger et al. 2009; Lacroix 2010).

Imaging Studies

Imaging evaluation is important not only because the radiographic characteristic of an adrenal mass provide information regarding the malignant potential but also because it helps to stage the ACCs. It has been determinate the equivalence between CT and MRI to characterized this lesions (Ilias et al. 2007).

Most ACCs are nonhomogeneous, with irregular margins and irregular enhancement of solid components after intravenous contrast media. ACCs tend to be greater than benign masses and with an average size of 10 cm at presentation (Fassnacht and Allolio 2009; Ng and Libertino 2003).

A complete metastatic evaluation should be done and include imaging of the chest, abdomen, and pelvis. On the presence of site-specific

symptoms, evaluation for bone and central nervous system is indicated (Bharwani et al. 2011).

Measurement of the Hounsfield Units (HU) in unenhanced CT helps to differentiate benign from malignant lesions. A threshold value of 10 HU has a sensitivity of 71% and specificity of 98% (Boland et al. 1998). On consideration is that 30% of lipid-poor benign adenomas have an unenhanced HU value >10. Delayed contrast-enhanced CT scan helps to discriminate these lipid-poor benign adenomas from ACCs, through the evaluation of the contrast washout. Adrenal lesions >10 HU in unenhanced CT, a washout <50%, and an absolute value >35 HU 10–15 min after contrast media are highly suspicious for malignancy (Boland et al. 1998; Park et al. 2007).

Useful is the use of MRI, ACCs appear isointense on T1-weighted images to the liver but intermediated to high intensity in T2-weighted images. Enhancement after gadolinium is different and washout is slow. The differentiation between benign and malignant lesions with MRI has a sensitivity of 81–90% and specificity of 92–99% (Boland et al. 1998). MRI is superior to CT in evaluate invasion into adjacent organs and vascular structures.

The use of positron emission tomography (PET) scanning with fluorodeoxyglucose (FDG) is also useful, especially in the situation that an MRI and/or CT scan cannot distinguish between a benign or malignant lesion of the adrenal gland (Mackie et al. 2006; Leboulleux et al. 2006). However, FDG uptake was seem in some benign lesions, in particular the ones hormonally active, the reason why 18 FDG-PET is not recommended as a primary diagnostic instrument (Groussin et al. 2009; Caoili et al. 2007). Alternatively, the integration of CT scan and PET images can improve the detection of PET scan for the differentiation of malignancy on adrenal masses with a sensitivity of 83.3% and specificity of 85.4% (Metser et al. 2006).

Fine-Needle Biopsy Aspiration

Nowadays, the information obtained by imaging studies and hormonal workup is enough to not use a fine-needle biopsy, which is associated with risk of needle-track seeding (Schteingart et al. 2005). However, in case of metastatic disease and not indication of surgical resection, a diagnostic biopsy previous an endocrine workup it is justified to clear pathological evidence (Jhala et al. 2004).

Staging

The first contemporary staging system was proposed by the UICC/World Health Organization (WHO) in 2004, which was based on the Sullivan modification of the original McFarlane staging system (Sullivan et al. 1978). Later, the combined AJCC (American Joint Committee on Cancer)/UICC (International Union Against Cancer) staging system based on tumor, node, and metastasis (TNM), which was similar as the one proposed by the WHO, was available on 2009.

A modified stage system has been proposed by the European Network for The Study of Adrenal Tumors (ENSAT), which improves the accuracy of the TNM staging system (Fassnacht et al. 2009). In the ENSAT staging system, stage III disease includes patients with positive lymph nodes (N1), tumor infiltration on surrounding tissues, or tumor thrombus in vena cava/renal vein, whereas the stage IV is defined only by distant metastasis. It has been shown the superiority of the ENSAT staging system for predicting oncological outcome over other different systems (Lughezzani et al. 2010).

Management

Most of the patients with ACCs present with advance disease and those who present with localized disease are at a high risk for progression and metastasis. The management of ACCs should be multimodal, with adjuvant therapy administered frequently.

Surgery

For patients with stage I-III disease, complete surgical resection is a crucial key for the treatment with curative intent. In case of locoregional involvement of other organs, en-block resection should be done, and resection of invading tissues

(kidney, liver, spleen, pancreas, stomach, and colon) should be considered every time if there is suspicious of invasion (Kuruba and Gallagher 2008). Even with stage I, presumption of micrometastasis is high, the reason why a well-performed operation is not curative for many (Abiven et al. 2006).

The evidence in favor of lymphadenectomy is scarce and its benefit has not been proven. One study showed a significantly reduced risk of recurrence and disease-related death in patient who underwent lymphadenectomy versus those who did not (Reibetanz et al. 2012). Suspicious lymph nodes should be resected anytime.

The standard of care for ACCs remains the open approach. However, there is a crescent evidence for the use of minimal invasive approaches; multiple retrospective studies have shown comparable outcomes from laparoscopic and open adrenalectomy, especially in tumor less than 10 cm in high volume centers (Brix et al. 2010; Porpiglia et al. 2010; Sgourakis et al. 2015). A recent publication recommended the laparoscopic approach for selected cases of ACC without adjacent organ involvement and the robotic approach may be considered as an alternative to the laparoscopic approach, but it requires further studies (Ball et al. 2016).

In case of advance disease with metastasis, cytoreductive removal of the primary tumor should be considered as well as resection of all metastases whenever it is feasible (Schulick and Brennan 1999). Resection of locally recurrent disease may also be performed in patients in whom operation will be able to remove most of the tumor. Resection of recurrent or distant disease seems to prolong survival in some patients (Schulick and Brennan 1999; Datrice et al. 2012), but at the present time, the evidence is scarce and associated to delayed administration of any systemic therapy (Schteingart et al. 2005).

Radiotherapy

There is a limited role for radiation in the management of AACs. However, it should be considered as adjuvant treatment in patients with high risk of local recurrence and in the setting of palliation for control of local symptoms (Fassnacht et al. 2006).

The German ACC registry recommend adjuvant radiotherapy for all patients with microscopically incomplete (R1 or R2) or uncertain (Rx) margin status, and those with stage III disease (according to ENSAT criteria) even if the resection has been. Adjuvant radiotherapy should be considered for patients who have had a complete (R0) resection of a tumor >8 cm in size with tumor invasion of the blood vessels (but not large tumor thrombus in the vena cava) and a Ki67 proliferative index of >10% and for patients who have intraoperative violation of the tumor capsule, tumor spillage, or dissemination of "necrotic" fluid (Allolio and review 2006; Polat et al. 2009).

The efficacy of the adjuvant radiotherapy was seemed in retrospective studies but without a significant improvement in disease-free or overall survival (Fassnacht et al. 2006; Sabolch et al. 2015).

Consideration for palliative radiotherapy in unresectable disease was investigated with some kind of response in 57% of the patients, especially in the setting of bone and brain metastasis (Polat et al. 2009).

Medical Therapy

Mitotane is an oral synthetic derivate of the insecticide dichlorodiphenylthrichloroethane (DDT), and it has demonstrated clinical benefit in adjuvant treatment after an operation and in patient with metastatic disease. It has been use as a single agent or in combination with cytotoxic drugs.

Several retrospective studies have evaluated the efficacy of adjuvant mitotane (Schteingart et al. 2005; Khorram-Manesh et al. 1998; Terzolo et al. 2007), which has demonstrated that adjuvant mitotane was associated with longer recurrence-free survival, better overall survival after complete resection for stage I, II, or III ACC (Terzolo et al. 2007; Fassnacht et al. 2010; Else et al. 2014). It has been suggested the use of adjuvant mitotane for patients at the highest risk of recurrence, e.g., those who have histologically high-grade disease (Ki67 staining of >10 percent of tumor cells, >20 mitotic figures per 50 HPF regardless of tumor

size), intraoperative tumor spillage or fracture, and some large tumors that are low grade but have vascular or capsular invasion (Volante et al. 2009).

Mitotane is the primary treatment in patients with ACC with incomplete or no candidates for complete debulking resection, or in whom an operation is contraindicated. As a single agent, it was noticed an overall response to mitotane from 14–36%, but with a median survival of 6.5 months, which it is similar from no treated patients (Lubitz et al. 1973).

Some cytotoxic drugs have been used in combination with or without mitotane, the most promising combination is mitotane with etoposide, doxorubicin, and cisplatin (EDP-M). On the largest trial of advanced ACC to date, the First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT), 304 patients were randomly assigned to EDP-M or mitotane with streptozotocin. Rates of response (23% versus 9%), median progression-free survival (5 vs. 2.1 months) were significantly better in the EPD-M group, but not on overall survival (14.8 vs. 12 months) (Fassnacht et al. 2012).

Several new treatments were been tested, which include target therapies, but still on clinical trial basis. Two phase 2 studies with tyrosine kinase inhibitors (sunitinib as monotherapy and sorafenib with paclitaxel) did not shown efficacy and poor response to the treatment (Butler et al. 2010; Lee et al. 2009).

The combination of erlotinib with gemcitabine shown minimal benefit with advance ACC in a study where only one in ten patients experience minor response (Quinkler et al. 2008).

Prognosis

ACCs are characterized for a poor overall survival, with a 5-year-survival of 16–47% after complete resection (Luton et al. 1990; Ng and Libertino 2003; Paton et al. 2006). There was a shift of improving survival in more contemporary series, with a 5-year-survival of 55–60% (Fassnacht et al. 2010; Vassilopoulou-Sellin and Schultz 2001), and the reason of this is not clear, but it has to be considering the increase use of mitotane in the past 20 years, which could impact on better prognosis.

Besides the tumor stage, which tend to be advanced at presentation, there are other features that are been associated with decreased survival, including the size of the tumor (diameter >12 cm), high mitotic rate, tumor necrosis, and high Ki67 (Stojadinovic et al. 2002; Morimoto et al. 2008; Assie et al. 2007).

Malignant Pheocromocytoma

Epidemiology

Catecholamine-secreting tumors can arise from the chromaffin cells of the paraganglia or the adrenal medulla, in the last case are known as pheochromocytoma. In general, pheochromocytoma is a very rare neoplasm, with an estimated annual incidence of 0.8 per 100,000 person-year (Beard et al. 1983). These tumors occur at any age, but they are most common in the fourth to fifth decade (Beard et al. 1983; Guerrero et al. 2009).

About 10% of all pheochromocytomas are malignant (Guerrero et al. 2009). There is not biochemical or histological differences between benign and malignant pheochromocytomas. Immunohistochemical markers have been evaluated to distinguish malignant from benign tumors unsuccessfully (Clarke et al. 1998). In 2004, the WHO established that the metastatic spread as the only indicator for malignancy, which may occur as long as 20 years after resection (Goldstein et al. 1999). Thus, the importance of a close and long-term follow-up in the context of benign tumors. More unusual presentation of malignant pheochromocytoma is the context of hereditary diseases.

Clinical Presentation

Malignant pheochromocytoma exhibits the same constellation of signs and symptoms as benign tumors.

About 50% of patients present with symptoms and are typically paroxysmal. The classic triad of episodic headache, sweating and tachycardia, are the hallmark of pheochromocytoma (Stein and Black 1991), which are not present in most of the patients (Baguet et al. 2004). Paroxysmal hypertension is the classic presenting symptom, but 15% of patients present with normal blood pressure (Bravo 1991). Other symptoms include palpitations, pallor, dyspnea, weakness, and panic attack.

With the widespread of the imaging studies, a number of asymptomatic pheochromocytomas have been diagnosed in asymptomatic stages, around 3% of adrenal incidentalomas prove to be pheochromocytomas (Cawood et al. 2009). Metastatic pheochromocytoma tends to be asymptomatic and is discovered during surveillance after excision of the tumor in most cases.

Diagnosis

The same as AACs, pheochromocytomas required biochemical confirmation of catecholamine hypersecretion, which could be normal, especially in adrenal incidentalomas, and imaging evaluation. Adrenal incidentalomas, family history of pheochromocytoma, genetic syndromes that predispose to pheochromocytoma and past history of resected pheochromocytomas are the indication for evaluation.

Biochemical Evaluation

The diagnosis is made by measurement of urinary and plasma metanephrines and catecholamines. There are some institutional and international differences in the initial approach of the biochemical diagnosis of pheochromocytoma. In patient who exhibits mild elevation of metanephrines levels, the clonidine suppression test can be used as a secondary test. Clonidine suppresses norepinephrine production by the sympathetic nervous system but not by the pheochromocytoma (Sawka et al. 2003; Lenders et al. 2002).

Dopamine, norepinephrine, and epinephrine are included on the studies of catecholamines. Urinary and plasma catecholamines were the mainstay evaluation in the past, but because of its low sensitivity and specificity (both around 85%), they were replaced for metanephrines levels studies, but its measurement is recommended with metanephrines testing (Lenders et al. 2002).

Controversy exists in use urine versus plasma metanephrines (Lenders et al. 2002; Guller et al. 2006). Plasma metanephrines has a sensitivity of 96–100%, but the specificity is 85–90%, with a high rate of false positive tests results (Sawka et al. 2003; Lenders et al. 2002).

Imaging Studies

CT or MRI are the first test to be performed with similar sensitivity (98–100%). The first step is to distinguish from adrenal adenomas. On CT scan pheochromocytomas usually show increased attenuation on nonenhanced CT >10 UH, which differentiated from lipid-rich adenomas. Pheochromocytomas show delayed in contrast medium washout (absolute contrast medium washout of less than 50%), which distinguished from lipid-poor adenomas (Boland et al. 1998; Park et al. 2007).

Metaiodobenzylguanidine (MIBG) is molecule analogue to norepinephrine. The iodine-123 (123-I) MIBG is the preferred agent for scintigraphy. It is indicated in case of a negative CT or MRI and positive biochemical evidence of pheochromocytoma (Bravo 1991). It is also indicated on large tumors (e.g., >10 cm) due to the increased risk of malignancy (Whalen et al. 1992). It can be omitted in solitary adrenal pheochromocytoma.

Fludeoxyglucose-positron emission tomography (FDG-PET) is useful for detection of metastatic disease and more sensitive than CT or MRI (Timmers et al. 2007, 2012). For nonmetastatic disease, it is comparable with the other imaging techniques. ^{18}F-DOPA PET/CT is an excellent diagnostic tool for head and neck paragangliomas, but its sensitivity can be lower in retroperitoneal paragangliomas. The sensitivity of ^{18}FDG PET/CT in the detection of pheochromocytomas is high, but unfortunately, its specificity is lower. In patients with known metastatic pheochromocytomas, ^{18}FDG PET/CT is preferred over ^{123}I-MIBG (Timmers et al. 2012).

Management

In the case of pheochromocytomas, the definition of malignancy is based on the identification of metastasis. Approximately 10% of pheochromocytomas are malignant, and the risk of malignancy increase with familial syndromes. Around 3–5% of pheochromocytomas related to MEN2 syndrome are malignant. Initial metastatic presentation is very unusual and tends to appear even more than 20 years after resection.

Surgery

Initial metastatic pheochromocytoma, and by definition malignant, is present approximately 28% of the times (Goffredo et al. 2013, 2015). Resection of both the primary and metastatic lesions should be performed if are possible. Surgical intervention may improve symptoms and control the hormonal secretion (Ellis et al. 2013).

The procedure should be done in experienced centers, with a medical preoperative control of the symptoms, and intraoperatively. Symptoms of catecholamines excess are the same of the benign tumors and the medical management is the same as well, with combine alpha- and beta- adrenergic blockade.

Laparoscopic approach is the recommended in case of benign tumors, and open approach for the case of suspected or proven malignancy (Adjalle et al. 2009). Nevertheless, a crescent number of studies show that the minimal invasive approach for malignant pheochromocytoma is feasible and have comparable short-term outcomes than the open approach (Goffredo et al. 2015).

Radiotherapy

Malignant pheochromocytomas were believed to be resistant to radiotherapy, but recent work suggests that EBRT can affect long-term control and relief of symptoms, including pain from bone metastases. Symptomatic control or stable disease by imaging was seen in 81% and 87% of the lesions (Vogel et al. 2014). However, the use of EBRT is still in evolution.

Medical Therapy

Approximately 60% of tumors that take up MIBG as determinate by (123-I) MIBG scintigraphy can be benefit from the treatment with MIBG (van der Harst et al. 2001). MIBG is transported into cells by the norepinephrine transporter and causes cell death by emitting ionizing radiation from the decaying (131-I) radionuclide. Many small series and systematic reviews showed tumor stabilization and/or regression, with responses that go up to 40% (van Hulsteijn et al. 2014). Patients with good uptake of (123-I) MIBG with unresectable and progressive disease, symptoms not controlled with others methods, low number of bone metastasis should be considered for treatment. However, due to the different doses and schedules used in most studies, specific recommendations as to the best dose and schedule cannot be done (Chen et al. 2010). Given the significant toxicities, which include myelosuppression, thyroiditis, hypothyroidism, the use of MIBG has to evaluate against the risks (Gedik et al. 2008; Sze et al. 2013).

Systemic chemotherapy should also be considered in patients with unresectable disease with rapid progression, large number of bone metastasis, who failed MIBG therapy. Cyclophosphamide, vincristine, and dacarbazine (CVD) chemotherapy is the standard regimen for treating metastatic pheochromocytoma. A systematic review showed a complete or partial tumor response rate in 4% and 37%, and complete or partial response rate in 14% and 40% of patients, respectively. Toxicities were transient and include myelosuppression, neuropathy, and gastrointestinal (Niemeijer et al. 2014). A small study evaluated the use of temozolomide in patients with SDHB mutation, but it needs further research (Hadoux et al. 2014).

Investigations with target therapies are ongoing; the largest series nowadays include 17 patients treated with sunitinib, with partial response of 21% or stable disease of 36%. The most common side effect was hypertension (Ayala-Ramirez et al. 2012). Pazopanib, everolimus are also been studying.

Metastases to the Adrenal

Epidemiology

The adrenal glands are a common site for metastasis. Among patients without a cancer diagnosis, around 0.7–2.5% of adrenal incidentalomas are nonadrenal metastases (Mantero et al. 2000; Cawood et al. 2009). Renal cell carcinoma, melanoma, thyroid cancer, colon cancer, prostate cancer, non-small cell lung cancer, breast cancer, and cervical cancers are the most common primary tumors that can metastasize to the adrenal glands. Even with a known malignancy, 48% of adrenal masses turn to be a primary adrenal tumor (Lenert et al. 2001; Frilling et al. 2004).

Management

Even with the presence of a known cancer, all adrenal masses should have a complete imaging and biochemical evaluation to rule out a primary from the adrenal.

Clinically, metastases to the adrenal are asymptomatic and are found during evaluations or staging of different tumor. Adrenal insufficiency is infrequent and develops with bilateral metastasis (Lutz et al. 2000). CT scan is the initial method to evaluate metastases, as discussed previously, lesions exhibits more than 10 UH in non-contrasted imaging and fails to demonstrated significant contrast loss on adrenal wash out studies are less likely to be benign adenomas (Boland et al. 1998).

A biochemical workup is necessary to rule out functionality of the adrenal mass. Fine-needle aspiration biopsy can distinguish between an adrenal tumor and a metastatic disease, after excluding pheochromocytoma (Jhala et al. 2004).

Treatment of metastases to the adrenal depends on the control of the extra-adrenal disease, comorbidities, and benefits and risks for a surgical intervention. The overall prognosis for patients with metastatic cancer in the adrenal glands is poor (Lee et al. 1998), the survival duration in highly selected patient who undergo adrenalectomy for metastatic cancer is similar to that in patients who undergo resection of metastases in other visceral sites (Lenert et al. 2001).

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Retroperitoneal Tumors in Adults

54

Claudius Füllhase, Nina Harke, Christian Niedworok, Chris Protzel, and Oliver W. Hakenberg

Contents

Abstract

Retroperitoneal tumors are a heterogeneous group of rare tumors arising in the retroperitoneum, but not from the retroperitoneal organs. Most retroperitoneal tumors are malignant and derive from soft tissue, sarcomas being the most common. Primary extragonadal germ cell tumors and primary retroperitoneal lymphomas are rare differential diagnoses. A hallmark of malignant retroperitoneal soft tissue tumors is their large size upon diagnosis and their poor prognosis. CT scans and core needle biopsies are the mainstay of diagnosis. Extended radical and complete en bloc surgery is the only potentially curative treatment. Surgery should always be image-guided and never be exploratory. Despite surgery, local recurrence is common and accounts for most of the disease's morbidity. Even

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though the scientific evidence is weak, neoadjuvant chemotherapy and/or preoperative radiation might be of some value for selected patients and histological subtypes. Guidelines strongly recommend a multidisciplinary treatment approach at a specialized center and data collection in international registries. Since all these cases are rare, advances can only be made in collaboration.

Keywords
Soft tissue neoplasms · Sarcoma · Retroperitoneal neoplasms · Retroperitoneal space · Urology

Introduction, Epidemiology, and Classification

The retroperitoneum is anatomically defined as the space between the peritoneum anteriorly and the parietal wall of the abdominal cavity posteriorly. It is defined caudally by the pelvic brim and cranially by the diaphragm. Embedded in a loose framework of connective tissue, it contains the retroperitoneal organs: the suprarenal (adrenal) glands, aorta and inferior vena cava, duodenum, pancreas, ureters, ascending and descending colon, kidneys, esophagus, and rectum. Primary retroperitoneal tumors arise in the retroperitoneum and by definition exclude tumors arising from retroperitoneal organs (Armstrong and Cohn 1965). Compared to primary tumors of retroperitoneal organs as well as compared to secondary (metastatic) tumors of the retroperitoneum, primary retroperitoneal tumors are very rare (Table 1).

Table 1 Age-adjusted incidence rates of some primary tumors occurring in the retroperitoneum and estimated incidence rates of some secondary tumors in the retroperitoneum.

Age-adjusted incidence rates of some primary tumors in the retroperitoneum[a]	
Kidney cancer	8.7–17.0/100,000
Pancreatic cancer	10.1–14.2/100,000
Adrenal cancer	0.3–0.4/100,000
"Retroperitoneal tumors"[b]	**0.3–0.5/100,000**
Estimated incidence rates of some secondary tumors (metastases) in the retroperitoneum	
Ovarian cancer	5.7–7.5/100,000[a,c]
Prostate cancer	2.2–3.2/100,000[a,d]
Testicular cancer	1.1–1.4/100,000[a,e]
Endometrial cancer	1.0–1.1/100,000[a,f]
Colorectal cancer	0.4–6.2/100,000[a,g]

[a]the German cancer registry (Robert-Koch-Institute 2016)
[b]"Retroperitoneal tumors" refer to a heterogeneous group of rare tumors including retroperitoneal sarcomas and extragonadal germ cell tumors (diagnosed via the ICD.10 code C 48[a])
[c]Reports that 70% of ovarian cancers are diagnosed at stage FIGO III or IV (with an ovarian cancer incidence of 8.2–10.8/100000[a]) (Roett and Evans 2009)
[d]Reports that 4.5% of prostate cancer patients show metastases in the retroperitoneum (with an prostate cancer incidence of 56.0–80.4/100,000[a]) (Bubendorf et al. 2000)
[e]Reports that 19% of all seminomas (54% of testicular cancers are seminomas) and 45% of non-seminomas (45% of testicular cancers are non-seminomas) are diagnosed in a non-localized stage (with a testicular cancer incidence of 7.6–9.4/100,000[a]) (Osswald et al. 2009)
[f]Reports that 9.2% of patients with endometrial cancer have para-aortic node metastases (with an endometrial cancer incidence of 11.6–13.0/100,000[a]) (Mariani et al. 2008)
[g]Reports that in patients with colorectal cancer, 1–2% show retroperitoneal lymph node metastases, and 14% have metastases in the adrenal glands (with a colorectal cancer incidence of 24.7–44.7/100,000[a]) (Ribeiro Gomes et al. 2017)

Retroperitoneal tumors are a heterogeneous group and most are malignant (Table 2). Roughly, malignant retroperitoneal tumors are four times more frequent than benign retroperitoneal tumors (Van Roggen and Hogendoorn 2000). It is estimated that retroperitoneal tumors account for 0.1–0.2% of all adult malignancies (Armstrong and Cohn Jr. 1965; Pliess 1973). Most of retroperitoneal tumors arise from soft tissue, the non-epithelial, non-skeletal mesenchyma. Even less frequently retroperitoneal tumors can also be of neuronal, neuroglial, lymphatic, or embryonic origin (Table 2). However, there is disagreement whether or not retroperitoneal lymphomas should be defined as retroperitoneal tumors. Some authors consider them to be retroperitoneal tumors (Armstrong and Cohn 1965; Pinson et al. 1989), others do not (Pliess 1973). The widely used ICD 10 classification recommends to code lymphomas regardless of their primary site as a distinct entity. Indeed, 25–55% of all lymphomas include manifestations also in retroperitoneal lymph nodes

Table 2 Percentage of benign and malignant primary retroperitoneal tumors and origin of primary malignant retroperitoneal tumors according to some case series

	Pinson et al. ($n = 182$) (1989)	Pließ (review of 8 series, $n = 513$) (1973)	Tambo et al. ($n = 46$) (2007)	Rodriguez et al. ($n = 37$) (2010)	Gemici et al. ($n = 28$) (2015)
Benign tumors	11%	30%	48%	17%	25%
Malignant tumors	89%	70%	52%	83%	75%
Soft tissue tumors (sarcomas)	45.6% (41.3%)	65.5% (57%)	41.6% (29.1%)	100% (87.1%)	90.5% (66.7%)
Lymphomas	25.3%	–	29.1%	–	4.7%
Extragonadal germ cell tumors	4.3%	11.2%	–	–	–
Neuronal and glial tumors	3%	17.5%	20.8%	–	4.7%
Others and undifferentiated	21.6%	5.6%	8.3%	–	–

(Schmalz 2016). However, primary retroperitoneal presentation of hematologic malignancies only in the retroperitoneum is very rare (Chen et al. 2005). Similarly, the retroperitoneum is also very rarely the manifestation site of extragonadal germ cell tumors (Scholz et al. 2002). Nevertheless, these tumors have to be considered as differential diagnoses. Overall, among the retroperitoneal soft tissue tumors, sarcomas are by far the most common ones (Table 2).

Because of the rarity and heterogeneity of retroperitoneal tumors, valid epidemiological data are difficult to obtain. Similarly, it is almost impossible to give any general recommendations on treatment or prognosis since the literature is limited to small case series or case reports. In addition to their rarity, the classification of soft tissue tumors has changed dramatically within the last years (Jo and Fletcher 2014), making it hard to compare or merge literature data. Table 3 provides an overview about soft tissue tumors which have been reported to occur in the retroperitoneum, according to the current WHO classification (Fletcher et al. 2014). Furthermore, the histological diagnosis of retroperitoneal tumors is challenging for most pathologists. One quarter of all primary histological diagnoses of soft tissue sarcomas will be corrected during their clinical course. If the histological specimen is reviewed by a specialized reference center, the rate of altered diagnoses increases to 70% (Schmalz 2016). Hence, there is a strong recommendation that all retroperitoneal tumors should be treated in cooperation with a specialized center.

Due to their rarity, variety, and histopathological classification difficulties, no general epidemiological data on retroperitoneal tumors can be provided. Data on sex preference are conflicting (Armstrong and Cohn 1965; Schmalz 2016). Generally, the WHO reports a slight male predominance of malignant soft tissue tumors (Fletcher et al. 2014). Similarly, the age distribution of retroperitoneal tumors shows an extremely wide range of 20–90 years (Pinson et al. 1989), with most tumors occurring between the ages of 50 and 70 (Armstrong and Cohn 1965). Some rare tumor entities might rather affect younger patients (e.g., aggressive angiomyxomas) or preferably one gender; others might just do the opposite (e.g., myolipomas). The bottom line is that despite their rarity, retroperitoneal tumors can affect anybody anytime.

As stated above, retroperitoneal tumors are mostly malignant soft tissue tumors, and among them sarcomas are by far the most common (Table 2), accounting for at least a third of all retroperitoneal tumors (Schmalz 2016; Gemici et al. 2015; Strauss et al. 2011). Among the retroperitoneal sarcomas (RPS), liposarcomas are the most common (35–70%) and leiomyosarcomas the second most common ones (15–23%) (Van

Table 3 According to the current WHO classification of soft tissue tumors, tumors have been described to occur in the retroperitoneum (Fletcher et al. 2014)

	Benign	Intermediate (locally aggressive/ rarely metastasizing)	Malignant
Adipocytic tumors	Lipoma	Atypical lipomatous tumor	Dedifferentiated liposarcoma
	Lipoblastoma		Myxoid liposarcoma
	Myolipoma of soft tissue		Pleomorphic liposarcoma
	Hibernoma		
Fibroblastic/ myofibroblastic tumors	Cellular angiofibroma	Giant cell fibroblastoma	Adult fibrosarcoma
		Extrapleural solitary fibrous tumor	Myxofibrosarcoma
		Inflammatory myofibroblastic tumor	Sclerosing epithelioid fibrosarcoma
So-called fibrohistiocytic tumors	Deep benign fibrous histiocytoma		
Smooth-muscle tumors	Leiomyoma of deep soft tissue		Leiomyosarcoma
Skeletal-muscle tumors			Embryonal rhabdomyosarcoma
			Pleomorphic rhabdomyosarcoma
			Spindle cell/sclerosing rhabdomyosarcoma
Vascular tumors	Venous hemangioma	Kaposiform hemangioendothelioma	Angiosarcoma of soft tissue
	Lymphangioma		
Chondro-osseous tumors			Extraskeletal osteosarcoma
Tumors of uncertain differentiation		Phosphaturic mesenchymal tumor	Deep (aggressive) angiomyxoma
			Synovial sarcoma
			Clear cell sarcoma of soft tissue
			Extraskeletal myxoid chondrosarcoma
			Desmoplastic small round cell tumor
			Extrarenal rhabdoid tumor
			PEComa
Unclassified sarcomas			Undifferentiated sarcoma

Roggen and Hogendoorn 2000; Strauss et al. 2011; Brennan et al. 2014). Ten to 15% of all sarcomas occur in the retroperitoneum (Van Roggen and Hogendoorn 2000; Fletcher et al. 2014), and hence, the retroperitoneum is the second most common site for sarcomas to occur following the lower extremity (Strauss et al. 2011). Since RPS are the most common retroperitoneal tumor, the most valid data about prognosis and treatment are available on them. The following sections will therefore mainly refer to RPS as they are the only retroperitoneal tumor entity for which consensus recommendations and guidelines are available (Trans-Atlantic RPS Working Group 2015; von Mehren et al. 2014; ESMO Guidelines Working Group 2012; Murez et al. 2016). If any malignant retroperitoneal tumor other than RPS is diagnosed, the treatment has to be individualized, and in most cases (except for lymphomas and primary extragonadal germ cell tumors), it should be treated as if it were a RPS. As already stated, for best patient outcome,

it is strongly advised by the WHO as well as the RPS working group that retroperitoneal tumors are treated by an interdisciplinary team in a specialized center (Fletcher et al. 2014; Trans-Atlantic RPS Working Group 2015). This seems particularly noteworthy since retroperitoneal tumors generally have a poor prognosis – allowing no time for delayed or suboptimal treatment.

Clinical Presentation and Diagnosis

A clinical characteristic of retroperitoneal tumors and RPS is that they are usually very large when they are diagnosed. Fifty percent of all retroperitoneal tumors are larger than 20 cm in diameter at the time of diagnosis (Gemici et al. 2015; Gronchi et al. 2004). Despite their respectable size, RPS cause surprisingly only few and unspecific symptoms. Most patients (80%) present an abdominal mass (Mendenhall et al. 2005). It is said that RPS grow "silently" until they are large enough to present as abdominal masses (Hueman et al. 2008). Apart from abdominal masses, patients may complain of unspecific symptoms such as abdominal discomfort, early satiety, pain, and neurological or vascular symptoms of the lower extremity (Murez et al. 2016). Lymphomas might go along with classic B symptoms (unexplained fewer, drenching night sweats, and weight loss) (Hueman et al. 2008). Despite the fact that RPS often displace kidneys and ureters, urological symptoms are surprisingly rare in RPS patients. The median duration of symptoms before diagnosis is reported to be 4 months (Mendenhall et al. 2005). In contrast to most malignant retroperitoneal tumors, benign retroperitoneal tumors are usually incidental findings during CT scan or ultrasound (Schmalz 2016).

Computed tomography (CT) is the mainstay of diagnosis. With the ongoing development of CT technology, radiologists are more and more able to diagnose and differentiate even rare tumors. Some RPS, such as liposarcoma and leiomyoma, show specific CT radiological features (e.g., macroscopic fat or vessel involvement) which makes it possible to diagnose them by CT scan (Brennan et al. 2014). In doubtful cases, magnetic resonance imaging (MRI) can contribute distinguishing different entities. However, due to a substantial overlap of imaging features, at the moment, most retroperitoneal tumors require histological confirmation. The Trans-Atlantic RPS Working Group recommends that CT imaging is reviewed by a specialized tumor board (Trans-Atlantic RPS Working Group 2015). Next to a contrast CT scan of the pelvis and abdomen, a CT scan of the chest is recommended. Ten to 20% of all RPS show distant metastases in lung or liver at first presentation (Mendenhall et al. 2005). A CT scan of the head, brain MRI, bone scan, and positron emission tomography (PET) are usually not required. However, due to the fact that one kidney has usually to be removed during RPS surgery, the working group recommends a preoperative assessment of contralateral kidney function (Trans-Atlantic RPS Working Group 2015). The CT does not only serve diagnosis but also surgery planning which is crucial for a good surgical outcome.

Other primary and secondary tumors apart from RPS should be excluded. In men, it is mandatory to exclude metastatic testicular cancer (Strauss et al. 2011). This is in line with the guideline recommendation of the European Germ Cell Cancer Consensus Group which emphasizes that in all men with retroperitoneal masses, a germ cell cancer should always be considered (Krege et al. 2008). Laboratory tests should include α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG).

Following adequate imaging and exclusion of entities other than RPS as far as possible, the tumor should be biopsied. In the past, there has been a debate whether or not this should actually be done (Strauss et al. 2011). However, the RPS working group clearly advises that image-guided percutaneous coaxial core needle biopsy is needed (Trans-Atlantic RPS Working Group 2015). Fine needle biopsy, in contrast to core needle biopsy, is not recommended. Sampling during contrast-enhanced CT biopsy should aim at more solid and well-perfused areas. The risk of needle track seeding seems minimal and should be no reason to avoid biopsy. However, laparotomy and open biopsy or laparoscopic biopsy should definitely be avoided due to sarcoma

contamination (Trans-Atlantic RPS Working Group 2015). Interestingly, the same applies when an RPS is found incidentally during other surgery, e.g., laparoscopic hernia repair or explorative gynecological surgery for a suspected adnexal mass: no biopsy should be taken intraoperatively. Next to the risk of peritoneal sarcoma contamination, a CT-guided biopsy will better than "blind shooting" target the relevant parts of an RPS. Thus, nothing more should be done to explore or assess such an incidentally found retroperitoneal mass during that surgery because the risk of peritoneal sarcoma contamination is highly relevant. Incomplete resection is harmful and not beneficial for RPS patients. Such patients should undergo subsequent imaging and surgery planning.

As stated above, correct histological classification of soft tissue tumors is quite challenging and best performed in a reference center (Schmalz 2016). Histological characterization should be done according to the current WHO classification (Fletcher et al. 2014). Next to conventional histology, pathological assessment includes today often molecular subtyping and genomic profiling. Such details go beyond the scope of this review and are reported elsewhere (Fletcher et al. 2014). Grading is considered a morphological translation of molecular events that determine tumor aggressiveness (Fletcher et al. 2014). Conventional grading systems are mostly based on mitotic activity and necrosis. Due to its high prognostic predictive value, the FNCLCC grading system which includes a differentiation score is most widely used (ESMO Guidelines Working Group 2012) (Table 4).

Staging of RPS is mostly performed according to the AJCC/UICC system (Table 5). However, the AJCC/UICC stage grouping has been criticized. Most RPS are classified as cT2. The stage groups according to AJCC/UICC are mainly determined by histological grade. Next to histological grade, distant metastases and resection status are the major determinants of survival. According to those determinants, an alternative staging system has been proposed (Mendenhall et al. 2005) (Table 6).

Table 4 Histopathological parameters in the grading system of the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)

Histological parameter	Definition
Tumor differentiation	Score 1: sarcomas closely resembling normal mesenchymal tissue
	Score 2: sarcomas for which histological typing is certain
	Score 3: undifferentiated sarcomas
Mitotic count	Score 1: 0–9 mitoses per HPF
	Score 2: 10–19 mitoses per HPF
	Score 3: >19 mitoses per HPF
Tumor necrosis	Score 0: no necrosis
	Score 1: <50% tumor necrosis
	Score 2: >50% tumor necrosis
Histological grade	**Total score 2–3 = grade 1**
	Total score 4–5 = grade 2
	Total score 6–8 = grade 3

Modified from Fletcher et al. (2014)
HPF high-power field

Risk Factors and Prognosis

The etiology of most soft tissue tumors is unknown (Fletcher et al. 2014). Unknown environmental factors as well as genetic susceptibility may contribute to sarcoma development. Epidemiological studies, particularly on the SEER data, found interesting correlations. But as the authors state, those correlations might be rather speculative than causative (Burningham et al. 2012). For example, geographical differences have been described. Japanese migrants living in western countries show a higher incidence of certain sarcoma types than Japanese living in Japan, suggesting environmental lifestyle factors to be involved (Burningham et al. 2012). On the other hand, racial disparities seem to exist between certain sarcoma types suggesting a genetic factor. Furthermore, sarcomas have been linked to late pregnancy, medication during pregnancy (for nausea and vomiting), low birth weight, and childhood hernia (Burningham et al. 2012). However, those findings might just indicate a disruption of normal embryological development and are probably not causative as such. A problem identifying any sarcoma risk factors is that many sarcoma

Table 5 According to the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) classification and staging of soft tissue sarcomas (Fletcher et al. 2014)

T – primary tumor	Tx	Primary tumor cannot be assessed	**G – histopathological grading**		
	T0	No evidence of primary tumor	TNM two-grade system	Three-grade systems	Four-grade systems
	T1	Tumor 5 cm or less in greatest dimension	Low grade	Grade I	Grade I
	T1a	Superficial (above the superficial fascia)			Grade II
	T1b[a]	Deep	High grade	Grade II	Grade III
	T2	Tumor more than 5 cm in greatest dimension		Grade III	Grade IV
	T2a	Superficial			
	T2b[a]	Deep	**Stage grouping**		
N – regional lymph nodes	Nx	Regional lymph nodes cannot be assessed	Stage IA	T1 N0 M0	G1
	N0	No regional lymph node metastasis	Stage IB	T2 N0 M0	G1
	N1	Regional lymph node metastasis	Stage IIA	T1 N0 M0	G2, G3
M – distant metastasis	M0	No distant metastasis	Stage IIB	T2 N0 M0	G2
	M1	Distant metastasis	Stage III	T2 N0 M0	G3
				Any T N1 M0	Any G
			Stage IV	Any T any N M1	Any G

[a]Retroperitoneal sarcomas have always to be staged T1b or T2b but cannot be staged T1a or T2a

Table 6 The Dutch/Memorial Sloan-Kettering Cancer Center classification system (Mendenhall et al. 2005)

Classification	Definition
Stage I	Low grade, complete resection, no metastases
Stage II	High grade, complete resection, no metastases
Stage III	Any grade, incomplete resection, no metastases
Stage IV	Any grade, any resection, distant metastases

subtypes exist, but since they are all rare, they are usually grouped together for statistical analysis.

Radiation is the only proven risk factor for sarcoma development (Fletcher et al. 2014), and the risk clearly increases with radiation dose. The WHO reports a total radiation dose of >50 Gy as a risk factor with a median time lag between exposure and secondary tumor diagnosis of 10 years. Most available knowledge about postradiation sarcomas is from the literature on breast cancer (Sheth et al. 2012), and incidence rates have been reported to range between a few cases per thousand to almost a few per hundred. The literature on RPS following radiation for seminoma is scarce and limited to a few case reports (Stein et al. 1997). It might, however, be an underestimated problem. A Norwegian study identified 90 patients with postradiation sarcoma over a 25-year period, 13% of which were after radiation therapy for testicular cancer (Bjerkehagen et al. 2008). To the best of our knowledge, it is not known how many percent of patients irradiated for seminoma will suffer from radiation-induced sarcoma. 0.9% of all sarcomas are reported to be radiation induced (Kim et al. 2016).

The role of chemical carcinogens is controversial. Some authors reported an increased risk after exposure to certain herbicides, but others could not confirm this (Fletcher et al. 2014). Similarly, dioxin exposure might be a factor; however, this has not been proven. Some viral infections have

been linked to sarcomas, for example, HHV8 and Kaposi sarcoma. However, Kaposi sarcomas have not been reported to occur in the retroperitoneum (Fletcher et al. 2014). Patients suffering from the Li-Fraumeni syndrome a very rare autosomal dominant disease with TP53 tumor suppressor gene mutations are predisposed to sarcoma development. Similarly, inherited retinoblastoma, a germline mutation of the RB1 gene, might also be associated with sarcoma development particularly following radiation (Fletcher et al. 2014).

Poor prognosis is a hallmark of all malignant retroperitoneal tumors. The overall 5-year survival rate of RPS ranges from 36% to 58% (Porter et al. 2006). The sarcoma subtype is a prognostic factor, with liposarcomas showing the worst survival rates (Anaya et al. 2009; Lewis et al. 1998). Despite resections with curative intent, local recurrence is almost the natural history of RPS and accounts for 90% of disease-related mortality (Anaya et al. 2009). Complete macroscopic resection is achieved in less than 70% of primary RPS (von Mehren et al. 2014). The resection status and tumor grade are significant variables predicting local recurrence. Median survival has been reported to be 103 months for completely resected tumors and 18 months for incompletely resected ones (Lewis et al. 1998). High-grade RPS have a median survival of 33 months, whereas low-grade RPS have a median survival of 149 months (Lewis et al. 1998). Tumor size is another variable of prognostic value (Bremjit et al. 2014). Overall, 70% of all RPS patients will suffer from local recurrence within 5 years (Anaya et al. 2009). The median time to local recurrence development is 22 months (Mendenhall et al. 2005). Distant metastases will occur in around 18%, particularly with leiomyosarcoma (Bremjit et al. 2014). Metastases occur mainly in the lungs and liver (Lewis et al. 1998). Median time to distant metastases diagnosis is 19 months (Mendenhall et al. 2005). The median RPS survival was reported to be 72 months for patients with primary disease and 10 months for patients with metastases (Lewis et al. 1998). According to the French guidelines on RPS, the quality of first surgical treatment, sarcoma subtype and grading, the quality of initial biopsy and thereby the risk of peritoneal sarcoma contamination, and the volume of RPS cases treated in a center are the four most important prognostic factors (Avances et al. 2013), three of which can be influenced by physicians.

Treatment

Macroscopically complete surgical resection with negative surgical margins is the only potentially curative treatment for malignant retroperitoneal soft tissue tumors.

Surgery

As for many other malignant tumors, surgical resection with negative resection margins is a main prognostic factor for survival. The main problem with retroperitoneal tumors is that they are usually diagnosed in an advanced stage where the tumor has reached a substantial size, involving vital structures (in 50% tumors are larger than 20 cm in diameter (Gemici et al. 2015)). Therefore, complete resection cannot be achieved in over 70% of RPS patients (von Mehren et al. 2014). It has been shown for RPS that incomplete resection and contiguous organ resections are independent prognostic factors for survival (Singer et al. 2003). Multivisceral en bloc resection is necessary in over 80% to achieve negative margins (Jaques et al. 1990). Three tiers of surgical resection have been described for primary RPS (Bonvalot et al. 2009). Complete compartmental resection was performed in patients with uninvolved contiguous organs. Simple complete resection was used in advanced tumors. The third group involved patients where contiguous organs had to be removed due to invasion. The rate of recurrence was threefold lower in compartmental resections than in simple complete resections (Bonvalot et al. 2009). Several analyses of large single institution databases have consistently shown that the survival rate depends mainly on the negative margin status (Bremjit et al. 2014; Erzen et al. 2005). As such, the current treatment recommendation is not only to remove the RPS but to ensure by wide and extensive resection that

negative margins are achieved (Porpiglia et al. 2016). It has been reported that with extended resections compared to simple complete resections, the 5-year local recurrence rate dropped from 48% down to 28% (Gronchi et al. 2009).

Since the best possible surgery is the key factor for survival, the Trans-Atlantic RPS Working Group points out the importance of proper preoperative planning with CT scan and tumor board review (Trans-Atlantic RPS Working Group 2015). Low-grade liposarcoma might intraoperatively appear like normal fat tissue – therefore the surgeons should know in advance "where to cut." Intraoperative frozen section evaluation of suspicious tissue is not recommended because it rather leads the surgeons to be too close to the malignant tumor and as such bears the risk of tumor contamination. As said, the surgery should be guided by preoperative imaging, and it should not be exploratory (Trans-Atlantic RPS Working Group 2015). The RPS working group recommends furthermore that surgery is performed by a specialized team with special training and technical expertise throughout the abdominal and pelvic cavity including the handling of large vessels and nerves, full-thickness thoracoabdominal wall resection and reconstruction, and diaphragmatic and bone resection (Trans-Atlantic RPS Working Group 2015). According to the French guidelines, RPS should be resected en bloc with the surrounding organs, often a kidney, adrenal gland, colon, duodenum, pancreas, or the spleen (Avances et al. 2013). Laceration of the tumor is a technical mistake with severe consequences for the prognosis (Avances et al. 2013). In the same way as the demands are challenging for the surgical team, they are also high for the anesthesiological and postoperative intensive care – illustrating once again the need for treatment in a specialized center (Trans-Atlantic RPS Working Group 2015).

Radiation

Radiation therapy alone is no treatment option in patients with RPS. However, radiation therapy might be considered in patients with unresectable disease (von Mehren et al. 2014). Usually, the role of radiation therapy in RPS is limited to multimodal therapy regimen in combination with surgery. It is either used preoperatively (neoadjuvant) in order to reduce tumor size and to obtain negative margins or intra- or postoperatively (adjuvant) for better local control. A main problem with radiation for RPS is the close proximity of RPS to radiosensitive organs.

Preoperative Radiation

Even though the value of preoperative radiation in RPS is not proven, there exist treatment guidelines for preoperative radiation therapy for RPS based on a consensus from an international expert panel (Baldini et al. 2015). Currently, the data of an EORTC study (STRASS trial) on preoperative radiation therapy plus surgery versus surgery alone for patients with RPS are awaited (EORTC 62092-22092).

Preoperative radiation is expected to downsize the primary tumor, allowing it to become amenable to proper surgical resection and to improve negative margin outcome (Porpiglia et al. 2016). So far, only few trials assessed preoperative radiation in RPS. Some small series from Toronto, Canada, and Houston, Texas, USA, reported a median survival of >60 months in patients with intermediate and high-grade RPS in patients who received preoperative radiation (+doxorubicin) and surgery. Those data compared favorably to historical data for similar patients treated with surgery alone (Pawlik et al. 2006). However, other retrospective studies could not show any survival benefit for preoperative radiation (Bremjit et al. 2014). An American College of Surgeons Oncology Group study assessing the value of preoperative radiation in RPS (ACOSOG Z9031) was closed due to poor recruiting. As stated above, an EORTC study is currently ongoing. Readers of this review who are about to treat an RPS patient are encouraged to actively contact participating study centers (http://www.eortc.be/protoc/Details.asp?Protocol=62092 as accessed Nov. 2016).

According to the preliminary radiation oncologist's expert consensus, in analogy to the Trans-Atlantic RPS working group, the treatment plan

for an RPS patient should be managed by a multidisciplinary team in a specialized center. Patients eligible for preoperative radiation should meet the following criteria: tumor must be resectable with intent for complete resection, there should be an absence of symptoms requiring immediate surgery (e.g., bowel obstruction), the patient should be suitable for radiotherapy, and the tumor should be localized and unifocal or at most two sites in close proximity (Baldini et al. 2015). Most of the expert consensus guideline on RPS radiation deals with technical radiation details which go beyond the scope of this review (Baldini et al. 2015). 50 Gy in 25 fractions seems to be a reasonable fractionation scheme. Organs at risk portions that are contained within the planning target volume should not be subtracted. Intensity-modulated radiotherapy (IMRT) is the preferred technique. And surgery should, following new CT imaging, be performed 4–6 weeks after radiation therapy completion (Baldini et al. 2015). According to the RPS working group, preoperative radiation is a therapeutic option and should be considered (Trans-Atlantic RPS Working Group 2015).

Intraoperative Radiation

The rationale for intraoperative radiation therapy is to better spare radiosensitive structures from radiation (e.g., bowel that falls postoperatively into the space that was previously occupied by the tumor). In addition, the biological effects of directly and intraoperatively applied radiation are much higher than the effects of the same dose applied externally (Avances et al. 2013). However, the same structures that limit extended surgery (e.g., large vessels and neurons) do also limit the applicability of intraoperative radiation (Avances et al. 2013). Small series with only few patients have reported an improved local control in RPS patients with intraoperative beam radiotherapy compared to postoperatively irradiated patients. However, no benefit in median survival was reported (Porpiglia et al. 2016). The RPS working group states that intraoperative radiation is not of proven value. The margins considered at risk are usually too large for practical application (Trans-Atlantic RPS Working Group 2015).

Postoperative Radiation

The evidence for postoperative radiation in RPS is equally of limited value. A French retrospective study compared surgery alone ($n = 56$) vs. surgery plus adjuvant radiation therapy ($n = 42$) in RPS. Patients who received additional radiotherapy usually had an R1 or R2 resection. Still, they found a lower local recurrence rate for postoperatively irradiated patients than for surgery only (Local recurrence at 5 years was 22% for surgery plus radiation vs. 36% for surgery only. However, those findings were statistically not significant) (Le Pechoux et al. 2013).

There have been several epidemiological analyses of the SEER database to assess the value of postoperative radiation in RPS (Porpiglia et al. 2016). However, the SEER data give no information on the resection status (R0 vs R1, R2) which makes it difficult to draw conclusions about the value of radiotherapy. Most likely, patients with advanced tumors and positive margins were more likely to have received radiation than patients with completely resected tumors. As well, patients with high-grade tumors were probably more likely to have received radiation than patients with low-grade tumors. Therefore, since treatment groups are different, these epidemiological data are of limited value to assess the value of adjuvant radiation therapy in RPS as such. Out of 2348 RPS patients identified, 1654 underwent surgery (70.1%), and radiotherapy was used in 25.9% of these patients whereby the most common application was postoperatively (85.5%) (Porter et al. 2006). Patients who received additional radiotherapy were in general 5 years younger than patients who received surgery only and were mostly white. The authors concluded that most patients in the USA receive surgery only and that if radiotherapy might be beneficial – which could not be assessed by the SEER database research – practice patterns would require significant change (Porter et al. 2006). Other authors using SEER data assessing adjuvant radiotherapy in RPS reported no reduction in the hazard of death, no difference in disease-specific survival, and no difference in overall survival (Porpiglia et al. 2016).

Postoperative radiation is accompanied by a substantial toxicity. A study from Gainesville,

Florida, comparing pre- vs. postoperative radiation reported that median time to local recurrence was 2.5 years for preoperative and 1 year for postoperative radiation. At the same time, postoperative radiation was associated with a significantly higher rate of radiation complications (infections, hemorrhage, bowel obstruction). The authors concluded that preoperative radiation seems to be the better way to go (Zlotecki et al. 2005). Similarly, data from Ann Arbor, Michigan, showed that the rate of local recurrence was lower in preoperative than in postoperative irradiated patients (Feng et al. 2007).

The RPS working group concluded that postoperative radiation is not of proven value in RPS treatment and is associated with significant toxicities (Trans-Atlantic RPS Working Group 2015). Only for a minority of patients can a therapeutic radiation dose be achieved (Trans-Atlantic RPS Working Group 2015). In summary, if radiotherapy is considered, it is best administered preoperatively and in the context of a registered clinical trial.

Chemotherapy

Since most of retroperitoneal tumors are very large at first presentation and margin-negative surgery is a key prognostic factor for survival, the concept of neoadjuvant chemotherapy for downsizing the tumor preoperatively seems attractive. A retrospective analysis of the National Cancer Database identified 8653 patients with RPS, 17.6% of whom had received chemotherapy (Miura et al. 2015). 10.6% of chemotherapy patients had received it in a neoadjuvant setting ($n = 163$). Factors associated with chemotherapy administration were poor tumor differentiation, leiomyosarcoma or pleomorphic sarcoma histology, and R2 resection status. The study reported a worse median survival for the chemotherapy group (40 months) than for the surgery only group (52 months). The authors concluded that chemotherapy did not improve survival for resected RPS (Miura et al. 2015). However, in analogy to retrospective database analyses assessing radiation for RPS, the value of the study is limited because patients receiving chemotherapy had a worse prognosis than those who did not receive chemotherapy. As such, a definitive statement whether or not neoadjuvant chemotherapy is of use in RPS can't be given.

A meta-analysis evaluating 18 studies with a total of 1953 patients reported a small survival benefit for adjuvant chemotherapy (Pervaiz et al. 2008). Doxorubicin plus ifosfamide reduced the absolute risk for local recurrence by 5%, the absolute risk for distant recurrence by 10%, and the absolute risk for death by tumor by 11%. This amounted to the risk of death being 30% with chemotherapy compared to 41% without chemotherapy. The number needed to prevent one death was 17 (Pervaiz et al. 2008). However, overall the evidence in support of adjuvant chemotherapy is scarce. The RPS working group concludes that postoperative/adjuvant chemotherapy after complete macroscopic resection is of no study-proven value (Trans-Atlantic RPS Working Group 2015).

According to the French RPS guidelines, chemotherapy is a treatment option in patients with unresectable metastases (Avances et al. 2013). Hereby, the choice of drug depends mainly on the histological sarcoma subtype. Doxorubicin and ifosfamide regimens seem to have the best response rates (11–38%) (Avances et al. 2013).

A major problem assessing the value of chemotherapy in RPS is that RPS are a heterogeneous group of tumors (Table 3). Some histological subtypes, for example, the synovial sarcoma, might respond very well to chemotherapy; others will not. The RPS working group states that although no randomized trials of neoadjuvant chemotherapy versus resection alone have been reported, neoadjuvant chemotherapy is safe for well-selected patients and may be considered after careful review by a multidisciplinary tumor board (Trans-Atlantic RPS Working Group 2015).

Recurrence and Follow-Up

Despite complete surgical resection and multimodal treatment, the risk of recurrence is high. Overall, 70% of all RPS patients will suffer from local recurrence within 5 years. Particularly the

liposarcoma subtype is associated with a high rate of local recurrence. Local recurrence accounts for 90% of disease-related mortality (Anaya et al. 2009). The median survival for patients with an RPS local recurrence is 28 months (Lewis et al. 1998). Only 52% of patients with local recurrence can be resected completely (Lewis et al. 1998). As for the primary tumors, complete resection is the main prognostic factor. However, the resection rate decreases after each subsequent local recurrence. Resection rates were reported in 22% for the second and in 10% for the third local recurrence (Lewis et al. 1998). High-grade malignancy and local recurrence after primary surgery are associated with the worst survival (Gronchi et al. 2004). A retrospective study on the combined series of eight high-volume reference centers evaluated the recurrence patterns of 1007 RPS patients following primary resection (Gronchi et al. 2016). Predictors for overall survival were patient age, tumor size, completeness of surgical resection, malignancy grade, multifocality, and histological subtype. Interestingly, at 8 years, the crude cumulative incidence of local recurrence for well-differentiated liposarcoma was 42% in a center, where surgery was more limited, and 5% in a center, where extended surgery was used (Gronchi et al. 2016).

The Trans-Atlantic RPS Working Group published an additional consensus paper in which they provide statements how recurrent RPS should best be treated (Trans-Atlantic RPS Working Group 2016). They recommend that a recurrent RPS should be biopsied again and treatment planned in a multidisciplinary team of RPS experts. In analogy to primary RPS, complete surgical resection is the only curative option. However, in multifocal disease, recurrence can almost be taken for granted, and surgery is most likely of no oncological benefit. For the same reason, synchronous resection of local recurrence and distant metastases is not recommended. Neoadjuvant chemotherapy and radiation might be individual options. In patients who are not eligible for curative resection, cytotoxic and targeted systematic therapies may be of benefit in prolonging life and improving quality of life, but this is completely hypothetical. Radiotherapy might be used for pain control related to nerve compression. Readers are encouraged to enter eligible patients into an international collaborative registry (Trans-Atlantic RPS Working Group 2016).

The risk of recurrence after complete resection does not seem to follow a distinct time pattern. Recurrence can occur 15–20 years following primary surgery. Therefore, RPS patients should be followed for the rest of their lives (Trans-Atlantic RPS Working Group 2015). The RPS working group recommends CT scans every 3–6 months within the first 5 years. After then, annual follow-up evaluation is appropriate (Management of primary retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group 2015).

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Urologic Tumors in Childhood: Nephroblastoma and Wilms Tumor

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Raimund Stein and Norbert Graf

Contents

Abstract

Around 6–7% of all childhood cancers are renal tumors with almost 90% of them are nephroblastoma – the so called Wilms tumor. Females are slightly more effected than males and 75% of the patients are diagnosed before the age of 5 years, 15% are younger than one year and up to 2% of WT develop in adult, whereas bilateral WT are found in up to 10% and up to 15% are metastasized at the time of diagnosis. In around 10% WT is associated with congenital malformations or syndromes such as the Denis-Drash Syndrom, WAGR-syndrome or the Beckwith-Wiedemann syndrome.

The ultrasound is the first imaging modality. Magnet Resonance Imaging (MRI) is the first choice after ultrasound, as it avoids ionizing radiation and gives an excellent soft tissue contrast an a computer tomography should be only performed If an MRI could not be performed within an acceptable timeframe.

In the current SIOP RTSG UMBRELLA protocol All patients between the age of 7 months and 16 years at the time of diagnosis and with the radiological suspicion of a WT receive chemotherapy before surgery. In the first 2 months of life the prevalence of

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congenital mesoblastic nephroma (CMN) is higher compared to WT. However, thereafter the percentage of WT increases rapidly and bilateral tumors below the age of 6 months are usually WT. The best therapeutic approach in infants should be discussed within a multidisciplinary team to weight out the risk of intraoperative tumor rupture during primary surgery (e.g. in WT) versus the risk of unnecessary chemotherapy (e.g. in CMN). In adult patients with a WT using the paediatric protocols improved the survival rate of up to 90%. Surgery should be performed an experienced surgeon and should includ lymph node sampling of at least seven or more lymph nodes to guarantee a precise postoperative staging. Due to the excellent imaging modalities today, exploration of the contralateral kidney is no longer necessary. Nephron sparing surgery should be performed in bilateral WT and unilateral syndromic and patients with smaller tumors (e.g. < 300 ml at diagnosis) may benefit from NSS.

Patients receiving an adequate stage and risk group-oriented treatment are cured in 90%, Those with metastasis have a 80% survival rate.

The WT is a great example, how multidisciplinary treatment mad e a former lethal tumor to a curable tumor.

Introduction

In 1814 Rance recognized nephroblastoma for the first time (Rance 1814); however, it was the German surgeon Carl Max Wilhelm Wilms who described this tumor in detail in 1899 (Wilms 1899). Today this tumor is well known as the "Wilms tumor" (WT). The WT is a paramount example demonstrating that multidisciplinary treatment (pediatric oncology, pediatric urology/surgery, radiology, pathology, biology, and genetics) and randomized trials (International Society of Paediatric Oncology (SIOP) and the National Wilms Tumor Study (NWTS) – today Children's Oncology Group (COG)) could improve the outcome dramatically. Improvements in chemotherapy, anesthesia, and surgery contributed to this success. The major difference between these two study groups (COG and SIOP) is that patients with a WT after confirmation of the diagnosis by MRI or CT were treated with preoperative chemotherapy in the SIOP protocol, whereas in the NWTS/COG primary surgery is the method of choice. The final survival rates are almost the same (Graf et al. 2016).

Due to the rarity of this disease, these patients should be treated in pediatric oncology centers only, together with surgeons who have a high expertise with pediatric renal tumors. The 10-year survival has increased over the last 25 years and is now over 90% (Graf et al. 2006; Kaatsch and Spix 2015) (Fig. 1). Despite this successful outcome, there is a subgroup of high-risk patients who need more effective treatment. Today the aim of the studies is to improve the survival rate especially in the high-risk group and to minimize acute and late toxicity. The new UMBRELLA protocol of the SIOP Renal Tumor Study Group (RTSG) gives guidelines for standardized diagnostics, integrated research, and standard therapy. The aim of this protocol is to improve short- and long-term outcomes for children and young adults with Wilms tumor (WT) and all other childhood renal tumors. Up to now only in the COG WT studies molecular markers (loss of heterozygosity (LOH) of 1p and 16q) are used for risk stratifications.

Epidemiology

Around 6–7% of all childhood cancers are WT, which is the most common primary kidney tumor in childhood (Graf et al. 2016). In Germany, around 100 children are diagnosed with a WT annually, which represents an incidence of 7–8 cases per million (Graf et al. 2016) and the same as in the United Kingdom and the United States (Breslow et al. 1993; Gundeti 2010). In the East Asian population, the incidence is lower and, in the black population, a little bit higher compared to North America and Europe (Breslow et al. 1994; Fukuzawa et al. 2004). These differences are most likely due to genetic and epigenetic factors. Females are slightly more affected than

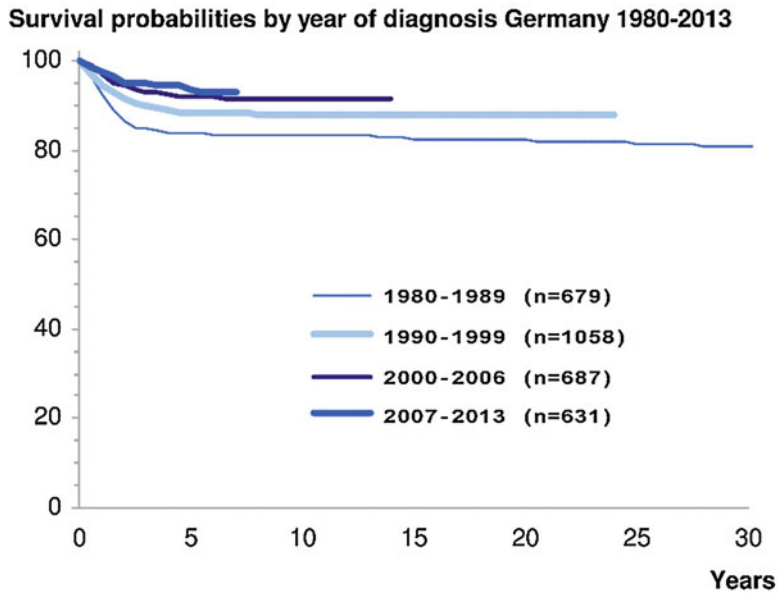

Fig. 1 Survival rates of WT treated in Germany between 1980 and 2013 (Kaatsch and Spix 2015)

males (Kaatsch and Spix 2015), and 75% of the patients are diagnosed before the age of 5 years, 15% are younger than 1 year, and up to 2% of WT develop in adults (Kalapurakal et al. 2004). Bilateral WTs are found in up to 10% and up to 15% that are metastasized at the time of diagnosis, mainly to the lung (Graf et al. 2016; Breslow et al. 1994). WTs occur earlier in patients with bilateral tumors (Breslow et al. 1994).

Of all renal tumors, almost 90% are nephroblastomas, and 11% have another histology including clear cell sarcoma of the kidney (3%), renal cell carcinoma (1%), malignant rhabdoid tumor of the kidney (1%), congenital mesoblastic nephroma (3%), oncocytoma, angiomyolipoma, sarcoma, and other rare tumors (Graf et al. 2016).

Associated Syndromes/Risk Factors

Around 10% of WT is associated with congenital malformations or syndromes. Urogenital anomalies include hypospadias, cryptorchidism and fusion anomalies of the kidney, which can be found in up to 4.5% of the patients (Breslow and Beckwith 1982). There may also be an increased incidence of Müllerian duct anomalies (such as duplication of the uterus or cervix or uterus bicornis) (Byrne and Nicholson 2002).

The Denys-Drash syndrome includes disorders of sexual development, renal mesangial sclerosis, and WT (Drash et al. 1970; Dumoucel et al. 2014). Patients with genital anomalies associated with mental retardation, aniridia, and WT–. The WAGR-syndrome – have also an increased risk for WT (Breslow et al. 2003). Aniridia is very rare in the normal population; however, up to 30% of these patients may develop a WT. Another well-known syndrome with aniridia is the Beckwith-Wiedemann syndrome (BWS) (Beckwith 1969; Wiedemann 1964), which includes also macroglossia, nephromegaly, omphalocele, and hemihypertrophy. Also patients with the Sotos and Perlman syndrome and the Klippel-Trénaunay-Weber syndrome or those with a neurofibromatosis Recklinghausen have an increased risk for WT. Around 1% of patients with a WT have a familiar background (Graf et al. 2016). Therefore, patients with a high risk to develop a WT should undergo a close ultrasound screening every 3–4 months within the first years of life. However, so far no study demonstrated a better survival due to earlier detection (Choyke et al. 1999; Green et al. 1993), despite the fact that these tumors are discovered at an earlier stage

and smaller size. Therefore, nephron-sparing surgery may be feasible in these patients to avoid renal insufficiency later in life as they have a high risk to develop bilateral tumors.

Biology/Histopathology/Stage

Wilms tumors have been and will be extensively studied to search for genetic alterations as well as for a better molecular genetic risk stratification for treatment. WT1 was the first detected Wilms tumor gene and shows in patients with WAGR syndrome a gross deletion at chromosome 11p13 (Riccardi et al. 1978). It is also associated with the Denys-Drash and Frasier syndrome. The WT2 gene is associated with, e.g., the Beckwith-Wiedemann syndrome (Koufos et al. 1989). Today there are much more genes discovered which are associated with a WT. As the loss of heterozygosity (LOH) von 1p and 16q is associated with a worse outcome (Grundy et al. 1994; Wittmann et al. 2007), these molecular markers are used for risk stratification in the current COG WT studies in North America. Such patients are treated more intensively. Today it is important to collect tumor material for molecular genetic investigations after the pathologist classified the tumor macroscopically.

The WT is in most cases a mixed tumor. The classic triphasic WT includes three cell types: blastemal, stromal, and epithelial. The percentage of each component varies from patient to patient. These components response differently to preoperative chemotherapy with regressive changes, and, in up to 5–15%, the tumor gets completely necrotic (Graf et al. 2016). The current classification by Vujanic et al. includes these changes in the histopathological classification (see Table 1) (Vujanic et al. 2002). Patients with viable blastemal cells after primary chemotherapy with actinomycin D and vincristine are resistant to these drugs and are classified as high risk needing more aggressive treatment (Graf et al. 2016).

The staging classification differentiates between stages I and V (Table 2). The pathologist determines the local tumor stage (Graf et al. 2016).

Table 1 Classification of renal tumors without and after primary chemotherapy (Vujanic et al. 2002)

A. For pretreated cases
I. Low risk tumors
Mesoblastic nephroma
Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma
II. Intermediate risk tumors
Nephroblastoma – epithelial type
Nephroblastoma – stromal type
Nephroblastoma – mixed type
Nephroblastoma – regressive type
Nephroblastoma – focal anaplasia
III. High risk tumors
Nephroblastoma – blastemal type
Nephroblastoma – diffuse anaplasia
Clear cell sarcoma of the kidney
Rhabdoid tumor of the kidney
B. For primary nephrectomy cases
I. Low risk tumors
Mesoblastic nephroma
Cystic partially differentiated nephroblastoma
II. Intermediate risk tumors
Non-anaplatsic nephroblastoma and its variants
Nephroblastoma-focal anaplasia
III. High risk tumors
Nephroblastoma – diffuse anaplasia
Clear cell sarcoma of the kidney
Rhabdoid tumor of the kidney

Table 2 Table stage according to the SIOP classification (Graf et al. 2016)

Stage	
I	Tumor is limited to the kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney and completely resected
II	Viable tumor extends beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected
III	Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopical tumor remains), and/or any abdominal lymph nodes are involved and/or any tumor rupture
IV	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
V	Bilateral renal tumors at diagnosis

Diagnosis

Despite easy access to ultrasound examinations (Fig. 2), most children with a WT present with an asymptomatic abdominal mass. In Germany 15% are discovered during an obligatory preventive medical examination. Other symptoms include abdominal pain in around ¼ of the cases and gross hematuria in less than 20% (Gutjahr 1990).

Laboratory investigations include a blood cell count, liver and renal function test, and electrolyte test. To exclude a neuroblastoma, catecholamine in the urine or blood should be determined.

Beside a thorough physical examination, the ultrasound is the first radiological examination in children with a suspected renal mass. It is the modality of choice to search for an intravenous tumor thrombus in the renal vein and inferior vena cava with 2D ultrasound and color Doppler. Magnetic resonance imaging (MRI) is the first choice after ultrasound, as it avoids ionizing radiation and gives an excellent soft tissue contrast. After the administration of gadolinium, a heterogeneous signal intensity can be observed (Fig. 3). In cases with a contraindication for gadolinium (allergy or renal insufficiency), a native MRI is performed. Computed tomography (CT) of the abdominal cavity should only be performed, if an MRI is not available within an acceptable time frame. A chest x-ray with AP or PA should be performed as a baseline investigation for the follow-up (the chest x-ray after placing the central venous line for chemotherapy may serve as a baseline).

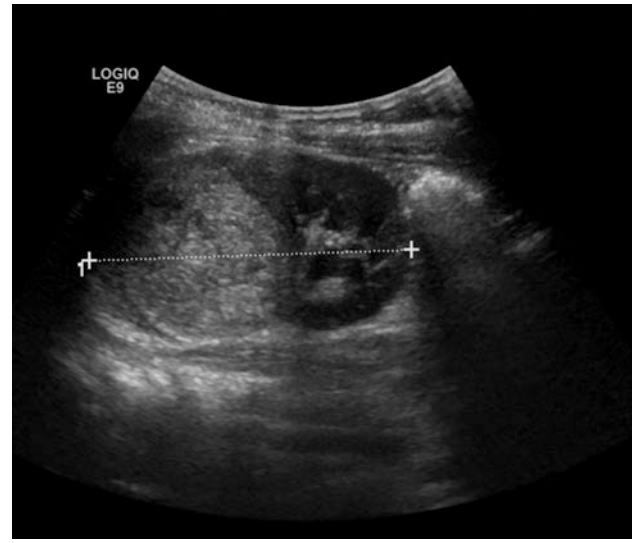

Fig. 2 Ultrasound in a 2-year-old girl with unilateral Wilms tumor

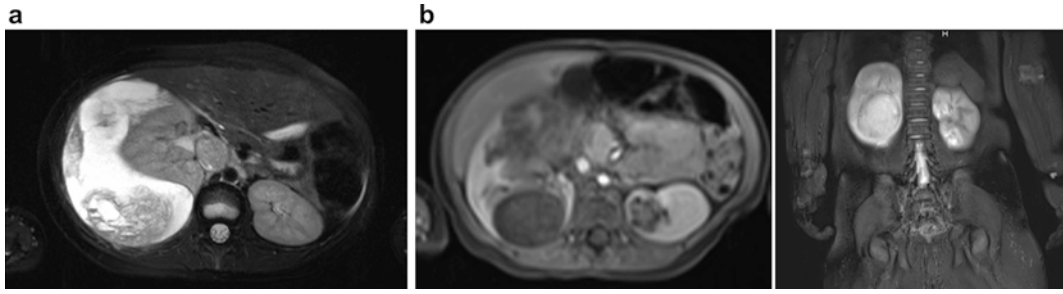

Fig. 3 (**a**) MRI in a unilateral Wilms tumor in a 4-year-old girl with lymph node metastasis. (**b**) A 2-year-old girl with bilateral WT

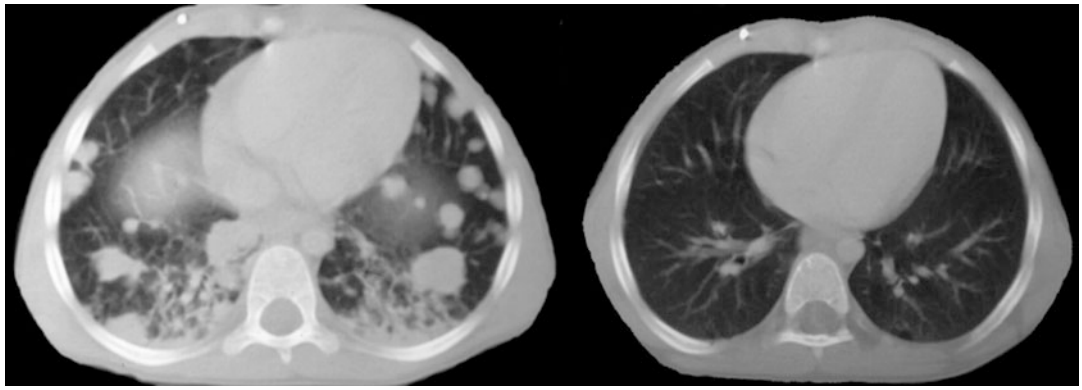

Fig. 4 Lung metastasis in a patient with nephroblastoma at diagnosis and after 6 weeks of chemotherapy with actinomycin D, vincristine, and doxorubicin. (From Graf et al. 2016, Abbildung 6 seite 2030)

However, to exclude lung metastasis, an unenhanced chest CT is performed (Fig. 4). In cases with lung metastasis, a chest CT is repeated after chemotherapy before surgery in the SIOP trial.

In children with a renal mass, other renal tumors like the congenital mesoblastic nephroma (CMN), clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor of the kidney (MRTK), and renal cell carcinoma (RCC) must be considered.

Within the current SIOP RTSG UMBRELLA protocol, in those cases, with a high uncertainty concerning the radiological diagnosis, unusual clinical presentation, or biological findings, a cutting/core needle biopsy can be considered using a retroperitoneal access under general anesthesia with a 16- or 18-gauge needle. Around 1.6% of relevant complications – such as tumor bleeding, rupture, or needle track recurrence – can occur (Vujanic et al. 2003).

Treatment

The main goal of the current SIOP RTSG UMBRELLA protocol is to find a better molecular characterization of pediatric renal tumors and to establish biomarkers for the future. The current treatment remains unchanged compared to SIOP 2001 study, except that doxorubicin is not included in treatment of stage II–III intermediate-risk Wilms tumors (Pritchard-Jones et al. 2015). All patients between the age of 7 months and 16 years at the time of diagnosis and with the radiological suspicion of a WT receive chemotherapy before surgery.

Studies demonstrated that in the first 2 months of life the prevalence of congenital mesoblastic nephroma CMN is higher compared to WT. However, the percentage of WT increases rapidly with age thereafter. Bilateral tumors below the age of 6 months are usually WT, and tumors with metastases in such infants at diagnosis are usually malignant rhabdoid tumors of the kidney (van den Heuvel-Eibrink et al. 2008). Therefore the best therapeutic approach in infants should be discussed within a multidisciplinary team to weight out the risk of intraoperative tumor rupture during primary surgery (e.g., in WT) versus the risk of unnecessary chemotherapy (e.g., in CMN).

On the other site, a WT is quite rare after the age of 16 years, and RCC are more likely; these patients are also candidates for primary surgery.

WTs in adults are usually an unexpected histological finding after nephrectomy for a renal tumor. The incidence in Europe varied between 0.17 and 0.27 per million (Mitry et al. 2006). Until recently it was suggested that adults have worse survival compared to children with this tumor type. However, using pediatric protocols, better outcomes were reported for North America and Germany (Kalapurakal et al. 2004; Kattan et al. 1994;

Table 3 Indications for interventions in the SIOP-Umbrella protocol

Intervention/surgery	
Primary surgery	Below the age of 6 months and above the age of 16 years, except those with the suspicion of a WT
Needle biopsy	Only in those with a high uncertainty concerning the radiological diagnosis and unusual clinical presentation or biological findings
Nephron-sparing surgery	In all bilateral cases, in unilateral tumors with contralateral, urological, and nephrological disorders, as well as in patients with genetic syndromes and increased risk of contralateral WT. In unilateral non-syndromatic WTs in selected cases with a tumor restricted to one pole of the kidney or peripheral at the mid-kidney, a volume <300 ml at diagnosis; no preoperative rupture, no intraluminal tumor on preoperative imaging, no invasion of surrounding organs, no thrombus in the renal vein or vena cava or multifocal tumors
Minimally invasive surgery	Acceptable in small, central tumors, if an open NSS is not feasible
Primary chemotherapy followed by radical nephrectomy	Standard procedure in all patients between the age of 7 months and 16 years with a renal tumor as well in those below or above this age limit with a suspicion of a WT

Reinhard et al. 2004). Huszno et al. demonstrated in their review article that modern treatment regimens did improve the overall survival up to 90% (Huszno et al. 2013). Therefore these patients should be treated according to the SIOP RTSG UMBRELLA protocol (Table 3; van den Heuvel-Eibrink et al. 2017).

In contrast to the COG study with primary surgery, patients with a localized WT (stage I–III) treated within the SIOP RTSG UMBRELLA protocol receive a preoperative chemotherapy with vincristine and actinomycin D over 4 weeks. Surgery is planned after another MRI during weeks 5–6. The advantage of this approach is downstaging. After preoperative chemotherapy, up to 60% of patients have stage I postoperatively in contrast to those with primary surgery with only around 30% (Graf et al. 2016). After primary chemotherapy, the rate of tumor rupture is lower, thus avoiding more intensive treatment postoperatively. Patients with primary metastatic disease receive 6 weeks of preoperative chemotherapy including doxorubicin. In patients with bilateral disease, preoperative chemotherapy using vincristine and actinomycin D can be prolonged up to 12 weeks to facilitate bilateral nephron-sparing surgery (NSS). However, in patients without tumor shrinkage, surgery is indicated earlier as most of them have a stroma subtype (Graf et al. 2016). Postoperative chemotherapy is mainly depending on local stage and histological subtype ranging from no postoperative treatment (low risk, stage I) to four drugs (high risk, stage II, III). In stage IV response to preoperative chemotherapy is used in addition as a stratification parameter for postoperative treatment. Patients with CR do receive less aggressive treatment than those with no CR.

Surgery for WT is performed elective in almost all cases and should always be performed by an experienced surgeon. Radical nephrectomy is performed in most WT including lymph node sampling. Seven or more lymph nodes should be removed to guarantee a precise postoperative staging. Due to the excellent imaging modalities today, exploration of the contralateral kidney is no longer necessary. Liver and/or lung metastasis should be removed in cases without complete remission after initial chemotherapy.

In all bilateral cases, NSS should be performed in very experienced centers to save as much renal parenchyma as possible.

Also unilateral cases may benefit from NSS, especially in those cases with contralateral, urological, and nephrological disorders as well as in patients with genetic syndromes with an increased risk of contralateral WT. In unilateral non-syndromatic WTs, NSS is acceptable in selected cases: tumor restricted to one pole of the kidney or peripheral at the mid-kidney, a volume <300 ml at diagnosis; no preoperative rupture, no intraluminal tumor on preoperative

imaging, no invasion of surrounding organs, no thrombus in the renal vein or vena cava or multifocal tumors.

Resection must be performed with margins of healthy renal tissue. In case of microscopically incomplete resection, further local treatment depends on a number of factors and should be discussed with the multidisciplinary team. In unfavorable subtypes of renal tumors, however, complete nephrectomy seems necessary. Positive LNs at the final pathology after NSS indicate radiotherapy but not necessarily a nephrectomy later on.

The classical open approach to the kidney in WT remains the gold standard; a laparoscopic or laparoscopic-assisted approach is acceptable, if the resection adheres to oncological principles including a sufficient lymph node sampling in small, central tumors. The tumor must be extracted in a bag without morcellation, through an adequate abdominal wall incision to guarantee no tumor dissemination and to ensure adequate histopathological staging. Whenever NNS through an open approach is feasible, this should be the preferred method.

Radiation therapy (RT) still plays a role in up to 15% of the children with WT depending on tumor stage, histology, chemotherapy response, and resection status. It is indicated in patients with intermediate risk, stage III (lymph nodes positive N+, residual disease left after surgery, tumor rupture), however, no boost irradiation to the lymph nodes in stage III with initially positive lymph nodes and complete resection and in those with high risk, stage II and III as well in stage V according to local stage. In children with diffuse intra-abdominal tumor spread or gross preoperative or intraoperative "major rupture," whole abdominal RT is indicated. Whole lung RT is indicated in patients with high-risk histology, with intermediate-risk histology with remaining vital tumor and in recurrent disease with lung metastases without prior lung irradiation during first-line treatment. In patients needing lung and abdominal RT, RT should be performed together to avoid overlapping radiation fields (Graf et al. 2016).

Prognosis

Today, if patients receive an adequate stage and risk group-oriented treatment, around 90% of patients are cured (Graf et al. 2016). Even patients with metastatic disease have a cure rate of 80% survival. Risk factors for a poorer outcome are older age (>2 years), a tumor volume above 500 ml, patients with high-risk histology/diffuse anaplasia and blastemal subtype, and poor response to preoperative chemotherapy in stage IV.

As most recurrences occur during the first 2 years after diagnosis, follow-up should be more intensive during that time period.

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Part VII

Penile Cancer

Epidemiology and Histopathology: Penile Cancer

56

Eva Compérat

Contents

Abstract

Penile carcinoma are rare, the vast majority are squamous cell carcinomas, they mainly occur in the squamous epithelium of the glans, sulcus and the foreskin. The WHO 2016 classification has introduced changes and redefined the prognostic value of the different subtypes of squamous cell carcinomas. Some of them, such as the verrucous carcinoma, have better outcome. Therefore it is important for the clinicians to know the prognostic value of these tumors, but it is also of major impact to classify from a pathology point of view the different types.

Epidemiology

The penile carcinoma affects most often patients in their fifth or sixth decade. Nevertheless it can occur in younger and also older age. Familial cases are rare, but exist. No racial predilection has been described. The highest incidence rates are in South America, Asia, and Africa; the incidence is relatively low in Europe and North America. Penile carcinoma accounts for 0.4–0.6% of malignancies (Siegal et al. 2014). Age-standardized incidence rates in industrialized countries range from 0.3 to 1/100000 cases. Incidence has been slightly decreasing in some countries, but the HPV-related tumors increase in several countries such as the USA.

Risk factors are well known such as lack of neonatal circumcision, poor genital hygiene, phimosis, human papilloma virus (HPV) infection, lichen sclerosus, and smoking (Daling et al. 2005). An American study could recently show an association between obesity and penile cancer. The group had already shown an association between obesity and higher risk of having invasive penile cancer after controlling for race and smoking status (Barnes et al. 2013). In this second study, they could clearly show a link between obesity and invasive penile cancer (Barnes et al. 2016).

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It is very important to have a good knowledge of the very complex anatomy of the penis. In the distal penis, three different epithelial mucosa compartments exist: glans, coronal sulcus, and foreskin. Different anatomic levels in the glans are the lamina propria, corpus spongiosum, tunica albuginea, and corpus cavernosum. The foreskin has an inner mucosa and a surface skin, both different from a histological point of view. The anatomical levels from the mucosa to the skin are the lamina propria, dartos, dermis, and epidermis. The penile fascia covers the shaft, inserts into the lamina propria of the coronal sulcus. The fossa navicularis corresponds to the distal penile urethra; its squamous lining is continuous with the perimeatal glans. The penile urethra is ventral and surrounded by a lamina propria, corpus spongiosum, and a penile fascia.

Histopathology

Precursor Lesions

Penile Intraepithelial Neoplasia (PeIN)

The basement membrane remains intact, but intraepithelial changes occur. PeIN is a recognized precursor of invasive SCC (Fig. 1).

Like in the invasive carcinomas, two subgroups can be distinguished: the HPV-related and non-HPV-related PeIN. Mostly there exists a good correlation between the grade of PeIN and the differentiation of the SCC. The same is true for warty/basaloid PeIN.

The patients' age is between 40 and 70 years. The size can be various, from small millimetric to broad lesions. Differentiated PeIN is frequently seen with lichen sclerosus. It affects the foreskin; the warty-basaloid type affects more frequently the glans (Chaux et al. 2012a).

Gross aspects are solitary white or pink maculae or plaques, borders can be sharp or irregular, and solitary or multifocal lesions are possible. The warty-basaloid PeIN has more velvet moisty dark brown aspects.

The differentiated PeIN looks like a thickened skin under the microscope; keratin pearl forming and parakeratosis are frequent. Atypia in simplex (differentiated) PeIN exists in the basal layer. The higher the atypia takes place in the epithelium, the higher is the risk of developing an invasive carcinoma. Grading PeIN is optional. Lichen sclerosus is often associated; it can be very difficult to make the difference between a PeIN and reactive condition.

Basaloid PeIN is characterized by a replacement of the whole thickness of the epithelial layer by small monotonous cells. Apoptosis and mitosis are common; these lesions are HPV positive (Chaux et al. 2011). Warty PeIN displays atypical parakeratosis. Cellular pleomorphism, koilocytes, and mitosis are usual. Squamous keratosis can be seen. These lesions are also HPV positive. It is

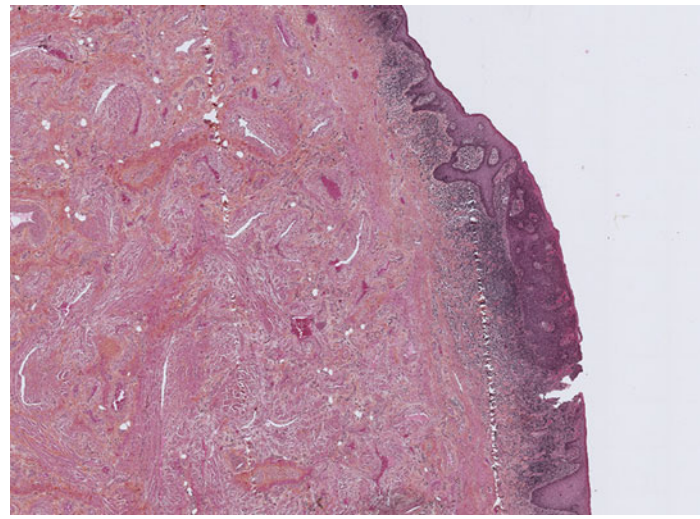

Fig. 1 PeIN with typical atypia, the basal layer is respected

unknown to which percentage these lesions evolve toward an infiltrating carcinoma.

Extramammary Paget disease can also be observed. This rare slowly growing finding adenocarcinoma can affect the penile skin or surface, mostly scrotal perianal or perineal. These erosive plaques can be misdiagnosed as eczema and can be very large lesions including the pubic region.

Under the microscope, an intraepithelial lesion can be observed, and sometimes neoplastic cells contain melanin. When excised completely, prognosis is favorable. In case of dermal invasion, the prognosis becomes more severe (Chaux et al. 2012a).

1. Non-HPV-related PeIN
   Differentiated (simplex) PeIN
2. HPV-related PeIN
   Basaloid PeIN
   Warty PeIN
   Warty-basaloid PeIN
3. Other rare patterns of PeIN
   Pleomorphic, spindle, clear cell, pagetoid

Malignant Epithelial Tumors

The most frequent entity is the squamous cell carcinoma (SCC). Most of them occur from the inner foreskin, inner lining of the glans, and coronal sulcus. The anatomic knowledge of the structure is very important for the origin but also the staging of penile carcinomas. Most penile carcinomas originate from the mucosa and not from the skin.

The pathological classification of penile squamous carcinomas distinguishes two subgroups: non-HPV-related SCCs and the HPV-related SCCs (Moch et al. 2016).

The relationship between HPV and penile carcinoma was first recognized in 1995 (Gregoire et al. 1995). HPV DNA is more frequently found in carcinomas with basal and/or warty morphology, also in the warty-basaloid penile intraepithelial neoplasias (PeIN). It is rare in usual and low-grade variants of keratinizing SCC and constantly negative in differentiated PeIN (Chaux et al. 2012a).

SCC can occur in any part of the penis and be multifocal. Few are known about genetic features. Two pathways exist in the carcinogenesis, one related to HPV-related which occurs for about 30–50% of cases. The second is non-HPV-related pathway which can be divided into two subgroups: TP53 mutations and the other with chromosomic instability (Moch et al. 2016).

Non-HPV-Related SCC

SCC Usual Type/NOS

These carcinomas display the usual aspects of SCC with different degrees of differentiation and keratinization; this diagnosis can be proposed if all the other histological variants have been excluded. Most of the time, these tumors have an exophytic gross appearance; endophytic ulcerated cases have also been described.

The grading of these carcinomas is a very important prognostic factor. The three-tiered ISUP/WHO system should be used (Moch et al. 2016). The admitted grades are from well to poorly differentiated with different nuclear polymorphisms, atypia, and keratinization. If well differentiated (grade 1), the aspect is the same as keratinizing tissue, they grow in large sheets and can have nested patterns, and the stroma reaction is limited. In moderate (grade 2) carcinomas, the nests become smaller and the tumor stroma is more abundant. In poorly differentiated (grade 3) tumors, keratinization can be difficult to find, growth is angular and irregular, and mitoses are frequent. As soon as a tumor displays anaplasia, it becomes grade 3. Grades should be given according to one high-power field (HPF) with the highest atypia. Heterogeneity is frequent.

The SCC has a tendency to invade deeply the penile tissue, two thirds of patients present inguinal metastasis, and mortality is about 30% (Fig. 2). The grade is the most important predictor of clinical behavior. Vascular invasion accounts for a third of cases; local and regional recurrence is linked to insufficient surgery. Between 28% and 39% of the patients develop inguinal lymph node metastases; the 10-year mortality rate is 78% (Guimarães et al. 2009; Cubilla et al. 2001).

Several risk nomograms exist; extranodal spread is a factor of bad outcome and is considered immediately as N3, even if a single lymph node is concerned. The more positive lymph nodes exist, the worse is the outcome.

Pseudohyperplastic Carcinoma

This tumor is an extremely differentiated SCC, mostly associated with lichen sclerosis, and occurs in older patients on the foreskin. An association with other histological types is frequent. Gross aspects are flat or slightly elevated, and multifocality is common.

In histology, borders are sharp, cells are very well differentiated, and peritumoral stroma is absent or minimal. PeIN can be observed, their grade is 1, and no vascular or perineural invasion or metastasis is reported (Fig. 3).

Pseudoglandular Carcinoma

This variant is aggressive with acantholysis and pseudoglandular spaces. Patients re younger around 50 with a distal irregular, firm whitish ulcerated mass.

Histologically honeycomb aspects are common which are filled with necrotic debris. Most

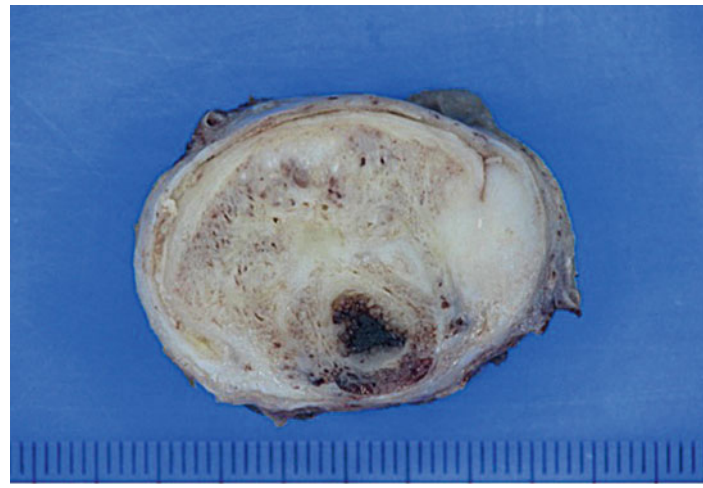

Fig. 2 Penile SCC invading deeply in the penile tissue, ureter not invaded

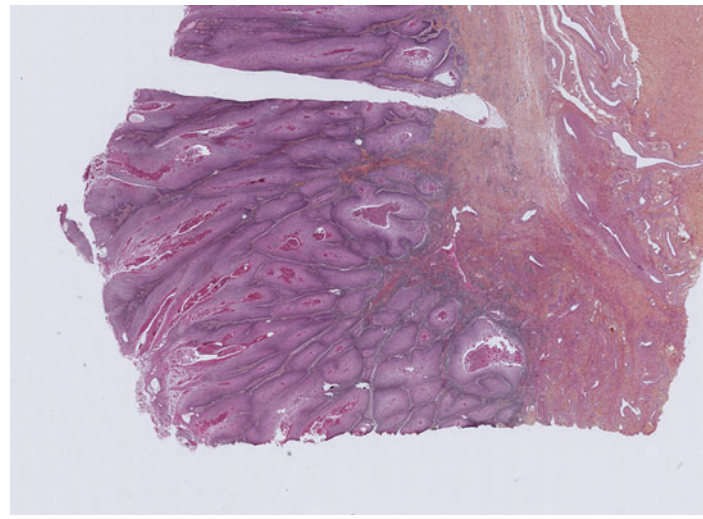

Fig. 3 Pseudohyperplastic penile carcinoma, nests are irregular, elongated with poor stroma reaction

of these cases are poorly differentiated and high-grade tumors. Lymph node metastases occur in more than two thirds, and mortality rate is high (Cunha et al. 2009).

Verrucous Carcinoma

This tumor is, like in other organs, extremely well differentiated with papillomatous aspects, the tumor base is broad, and the tumor has pushing borders into the stroma. This carcinoma has a slow evolution and is seen in elder patients. Lichen sclerosus is frequently associated. This carcinoma accounts for 2–3% of penile cancers (Fig. 4).

On the gross the aspect is exophytic and papillomatous white to gray, and the interface between tumor and stroma is sharply delineated (Cupp et al. 1995).

This well-differentiated carcinoma shows hyperkeratosis, acanthosis, and papillomatous aspects. The tumor base is broad, and the tumor does not directly invade the lamina propria, but pushes the borders into deeper tissue, making the diagnosis of invasion, especially on small biopsies, very difficult. The verrucous carcinoma is an extremely well-differentiated carcinoma; minimal atypia can be observed in the basal layers. In case of clarified cells, they should not be mistaken for koilocytes. The tumor can be focally invasive, but normally remains superficially invasive. In case of mixed features, the case should be reported as a mixed case. If combined with a SCC NOS, which is the most frequent combination. It should be called a verrucous hybrid carcinoma. Normally these carcinomas are HPV negative. Their prognosis is good, and the slowly growing tumor recurs in a third of cases, mostly because of underestimation in histology as a benign neoplasm or because of insufficient surgery (Stankiewicz et al. 2009).

Carcinoma Cuniculatum

This entity is a variant of the verrucous carcinoma, and it is a low-grade carcinoma. Men between 70 and 80 are mostly concerned; different anatomic parts can be affected, but most frequently the lesions grow from the glans into the deeper layers to the erectile corpora. The tumor is whitish gray, and deep invaginations are common.

Histologically the lesions are close to the verrucous carcinoma, no koilocytes are seen, and the lesion is extremely well differentiated. No vascular or perineural invasion has been reported, the invasion is with broad-pushing borders, and no metastasis can be found (Barreto et al. 2007).

Papillary Carcinoma NOS

This type of carcinoma is papillomatous and verruciform, no koilocytes are seen, and this tumor accounts for about 5–8% of penile carcinomas and is usually associated with lichen sclerosus. Size can be very small, but lesions to 14 cm have

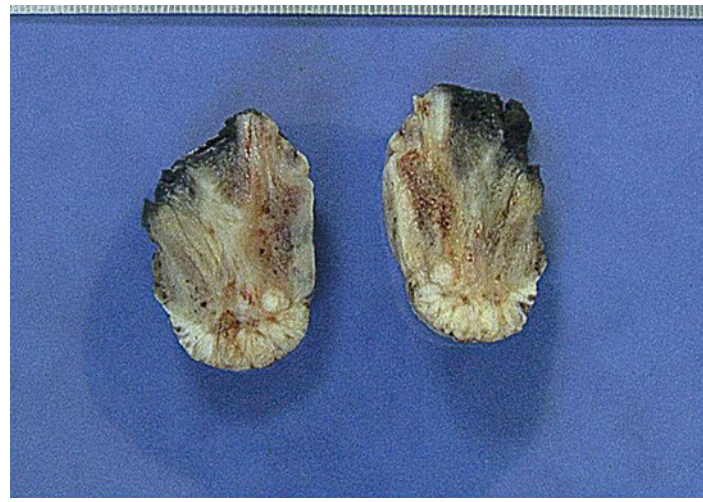

Fig. 4 Verrucous carcinoma with exophytic papillomatous aspects

been reported. The tumor has a cauliflower-like, whitish aspect which is badly limited.

Histologically we see well-differentiated hyperkeratotic lesions. Atypia is minimal and HPV negative. These tumors can recur, but mortality and metastasis are rare (Chaux et al. 2012b).

Adenosquamous Carcinoma

These carcinomas are SCC with mucinous features; they are also called mucoepidermoid carcinoma. Only few cases exist, and recurrence and lymph node metastasis are seen in up to 50%; on the other hand, mortality remains low (Romero et al. 2006).

Sarcomatoid SCC

This entity is aggressive, and focal squamous differentiation is seen. The spindle cell component should be at least present in 30%.

Predilection is the glans, and this carcinoma occurs in 1–4% (Guimarães et al. 2009). It is important to identify the tumor localization; otherwise, the difference with a sarcoma affecting the penile shaft and corpora cavernosa can be impossible.

These masses are slowly growing and frequently ulcerated; regional or systemic metastases are possible. Recurrence is possible; some of these lesions are initially SCC and go through a sarcomatoid transformation after radiation therapy. Necrosis and hemorrhage are frequent.

The histological aspects join atypia, mitosis, pleomorphisms, and sarcomatoid aspects like in other sarcomas.

These carcinomas are the most aggressive neoplasms of the penis. Bad prognostic factors, such as high-grade lesions, deep invasion, and perineural invasion, are present. Eighty percent of local recurrence exists with inguinal metastases, mortality is high with up to 75%, and most patients die within a year (Chaux et al. 2009).

Mixed SCC

Mixed carcinomas contain at least two variants of SCC. Patients are older in their seventh decade; mostly they are located on the glans. The tumor presents as a white exophytic grayish mass replacing the distal penis, which invades deeply the erectile tissue.

Most frequent is the combination of warty and basaloid carcinomas. Adenosquamous tumors also fall into this group. HPV- and non-HPV-related tumors can also be found in the same tumors.

Low-grade tumors are most frequent in about 75%; vascular and perineural invasion is seen in about 25%. Recurrence has been reported in 20%, regional lymph nodes in 9%, but the mortality is rare with less than 5% (Chaux et al. 2009).

HPV-Related SCC

Basaloid SCC

This type of carcinoma is aggressive and solid and accounts for about 5–10% of penile carcinoma. The origin is most frequently the glans; the foreskin can also be a site of predilection. Metastasis is seen in about 50% of cases. The carcinomas present as flat ulcerated masses, deeply invasive, and sometimes necrotic.

The tumor consists of closely packed small basophilic cells, mitosis is frequent, and central keratinization can be seen. Another aspect is "starry sky"-like features; sometimes they display features close to neuroendocrine tumors. Hyalinization of the stroma is frequent. These HPV-related carcinomas are p16 positive. As they are high grade, frequently massive, and invasive with lymphovascular and perineural invasion, lymph node metastasis is seen in more than 50% (Guimarães et al. 2009). Local recurrence is high; mortality is high and depends on the extension at time of treatment.

Papillary Basaloid Carcinoma

These exo- and endophytic carcinomas resemble to urothelial carcinomas. They are rare and affect the glans, hyperparakeratosis is frequent, and condylomatous features are frequent as well as a central fibrovascular core. Like other HPV-related carcinomas, p16 is positive. In case of doubt of an urothelial origin, urinary-related immunostains are helpful (Guimarães et al. 2009).

Warty Carcinoma

These exophytic carcinomas look like condylomas and account for 5–10% of the penile carcinomas. They have a macronodular cauliflower-like

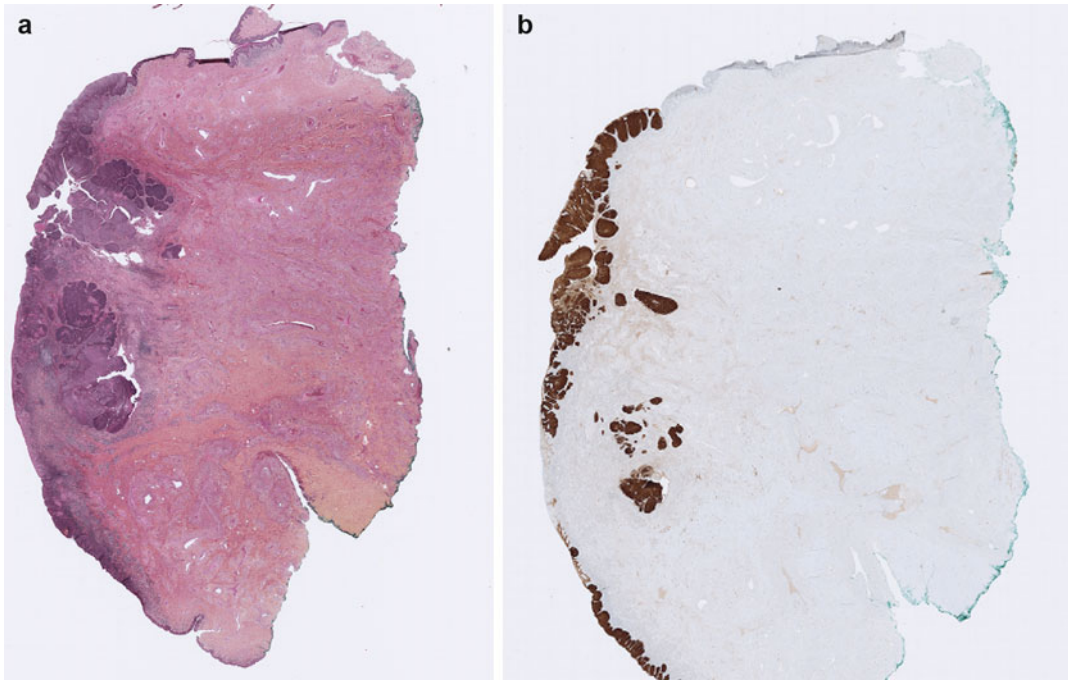

Fig. 5 (**a**) Warty carcinoma invading deeply in an exophytic manner into the underlying penile tissue (**b**) The same tumor with p16 staining

appearance; the papillae have a dark fibrovascular core which the tumor surrounds with a whitish aspect. Endophytic growth may be present (Fig. 5a and b).

The histological aspect shows pleomorphic koilocytes, hyper- and parakeratosis, nuclear pleomorphism, and cellular clarification which are frequent; the clear cell features predominate in the invasive areas. Individual cell necrosis is observed. HPV is positive in these carcinomas, p16 expressed.

These carcinomas, invading the corpus cavernosum and the dartos, usually do not display intravascular or perineural invasion. Nodal metastasis is seen in less than 20%. The mortality rate is low (Cubilla et al. 2000; Manipadam et al. 2013).

Warty-Basaloid Carcinoma

This HPV-related SCC shows both warty and basaloid features. Normally these carcinomas present as voluminous masses growing from the glans and foreskin.

From a histological point of view, these tumors are mixed with a papillomatous warty-like surface and a solid basaloid invasive component. Nested growth patterns have been described. Small basaloid cells in the periphery are frequent; p16 is strongly expressed. Invasion into deeper structures is frequent, the grade is mostly high, and vascular and perineural invasion is frequent. They are more aggressive than the warty counterpart. Around 50% will develop lymph node metastasis, and 30% will die of disease (Sanchez et al. 2016).

Clear Cell Carcinoma

The clear cell SCC is aggressive and HPV related and occurs as large masses of the glans and foreskin.

The tumor develops in sheets; necrosis is frequent. Staining of the clear cells is positive with p16.

These tumors are highly aggressive, and deep vascular and perineural invasion is frequent. The tumor-related mortality is around

20%. Distant metastasis is frequent (Chaux et al. 2010).

Lymphoepithelioma-like Carcinoma

This carcinoma is poorly differentiated, resembling to the lymphoepithelioma-like carcinoma of the nasopharynx. It occurs in men around the sixth decade. The tumor growth starts most of the time at the glans and extends to the foreskin.

The tumors are more or less circumscribed; sheets with lymphocytic or plasmacytic cells mixed with tumor cells are common. They are P63 and p16 are positive. Prognosis is adverse; too few cases have been described (Mentrikoski et al. 2014).

Other rare carcinomas such as carcinomas with medullary features or desmoplastic variants have been described. Neuroendocrine and Merkel cell carcinomas are exceedingly rare. Skin tumors like melanoma also exist. Mesenchymal tumors, such as leiomyomas, but also sarcomas and even Kaposi sarcomas have been described (Moch et al. 2016).

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Advanced Disease and Recurrent Disease in Penile Cancer

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Abstract

Management of advanced penile carcinoma remains a complex and challenging mission due to its rarity and poor prognosis. Although organ-confined disease is often curable, the high-grade and aggressive nature of disease progression highlights the difficulties of treatment. Diagnosis is typically made with a thorough physical exam and/or cross-sectional imaging. Surgical treatment with lymph node dissection is the standard treatment for locoregional disease. However, progression to bulky and/or fixed nodal disease requires different management strategies as single modal treatment is often incurable. Combination chemotherapy with surgical consolidation is recommended in this case with radiation therapy reserved for the palliative setting. Although local recurrence is typically amenable to surgical resection, nodal recurrence often requires more aggressive treatments, similar to cases with bulky disease. The subject of this chapter discusses the pathogenesis, diagnosis, treatment strategies, and available therapies for advanced penile carcinoma and recurrent disease.

Introduction

Tumors of the penis are rare cancers that represent only 0.4–0.6% of all malignancies in the United States and Europe (Siegel et al. 2016). It can lead to devastating outcomes and often present with significant challenges in management. The majority of penile cancers are organ confined, which is associated with excellent chance for cure. However, it is not unusual for its presentation to be delayed, which can lead to progression of disease before treatment is initiated. Advanced disease occurs in a predictable manner from the primary site, starting with involvement of the inguinal lymph nodes, and spreads to the pelvic lymph nodes prior to distant metastasis. Due to the rarity of disease, the limited data investigating this disease present challenges in treatment despite the availability of the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines (Clark et al. 2013; Hakenberg et al. 2015). In this chapter, we review the natural history of advanced penile squamous cell carcinoma and imaging modalities for diagnosis and treatment planning. We will also discuss strategies in therapy including surgical resection, chemotherapy, and radiation therapy. Furthermore, we will review management of recurrence in local and locoregional disease.

Natural History

Squamous cell carcinoma of the penis typically begins at the glans and can extend to the penile shaft. Buck's fascia serves as a barrier to local tumor extension, but invasion allows involvement of the corporal bodies and potential lymphatic spread. Lymphatic spread is predictable, starting from the connecting lymphatic channels draining the shaft skin to the superficial inguinal nodes, which drain to the deep inguinal nodes. Next, lymphatic drainage continues to the pelvic lymph nodes. Interestingly, drainage from inguinal to pelvic lymph nodes does not cross to the contralateral side. Without treatment, enlarged regional metastasis can progress to skin ulceration, necrosis, infection, or femoral vessel hemorrhage (Burgers et al. 1992). It's notable that the pathogenesis of penile carcinoma has a prolonged regional phase prior to distant metastatic spread. Uncommonly, distant metastatic disease can occur in 1–10% of patients based on most case

series. Advanced disease may also result in bulky or unresectable lymph node metastasis or visceral metastasis. Prognosis in advanced cases is generally poor with high mortality rates. In these patients, surgery or radiotherapy is often unsuccessful for cure given its aggressiveness resulting in high mortality rates (Ornellas et al. 1994; Ravi et al. 1994; Hegarty et al. 2006).

Presentation

Advanced disease is typically found during the staging workup with physical exam and imaging after a patient has been diagnosed with penile carcinoma. It is unusual for advanced penile cancer to present without evidence of a primary penile lesion due to its mode of pathogenesis. Occasionally, phimosis may keep a primary lesion hidden resulting in gradual progression of disease without raising suspicion. This can lead to progression to an enlarged inguinal mass with associated ulceration or necrosis as the initial presenting sign. Systemic symptoms such as fevers, weight loss, fatigue, and malaise can occur with distant metastasis but are rarely found at presentation. Due to the predictive lymphatic spread of penile carcinoma, distant metastasis typically occurs late after significant advancement of local and nodal disease.

Diagnosis

Physical Exam

Physical exam on the primary tumor on the penis and inguinal lymph nodes remains reliable for the initial assessment of stage for the nonobese patient. This provides important staging implications regarding a patient's risk and potential management. In addition to examination of the penis, it is important to rule out advanced disease through inspection of the scrotum and perineum. Palpation of the inguinal areas for lymph node enlargement is important to evaluate for metastatic spread. A rectal exam can also provide evidence for a pelvic mass. However, more infiltrative primary tumors and a non-ideal body habitus may preclude a sufficient physical examination. This results in the need for more accurate methods for evaluation of stage such as imaging modalities.

Magnetic Resonance Imaging and Ultrasonography

For primary tumors, magnetic resonance imaging (MRI) and ultrasonography have been shown to have higher clinical utility than computed tomography (CT) (Vapnek et al. 1992). Penile ultrasonography was evaluated in a cohort of 16 patients, and although tumor thickness was often underestimated, sensitivity for detecting corporal body invasion was 100% (Horenblas et al. 1994). Lont et al. compared MRI and ultrasonography in 33 patients prior to surgery and found similar precision in assessing infiltration depth and corpus cavernosum infiltration (Lont et al. 2003). Furthermore, the use of artificial erections via prostaglandin E1 (alprostadil) with imaging may also have significant utility in evaluation. In a study of 55 men, MRI accurately predicted corporal body invasion in all patients of pathologically proven disease (Kayes et al. 2007).

The evaluation of the inguinal and pelvic nodes also remains critical for assessing prognosis and overall survival. Because physical exam may be difficult in the patient who is obese or has had prior inguinal surgeries, cross-sectional imaging is recommended for evaluation. With palpable inguinal lymph node involvement, additional imaging is also helpful in treatment planning as central necrosis and irregular nodal borders of reginal lymph nodes have been found to be highly accurate in identifying high-risk node-positive penile cancers (Graafland et al. 2011a).

Positron Emission Tomography with Computed Tomography (PET/CT)

Positron emission tomography with computed tomography (PET/CT) has shown promise in detecting metastasis in penile carcinoma. PET/CT showed a sensitivity of 88% and specificity of 98% in assessing inguinal lymph node

involvement in a prospective study of 35 patients with invasive squamous cell carcinoma of the penis (Schlenker et al. 2012). Another prospective study with invasive squamous cell carcinoma also found utility in subclinical inguinal lymph node involvement (Souillac et al. 2012). This study found PET/CT to have a sensitivity of 75% and specificity of 87% in 22 clinically node-negative patients. In another study of 18 patients with known tumor-positive inguinal disease, PET/CT was found to have high sensitivity (91%) and specificity (100%) in detecting pelvic nodal involvement (Graafland et al. 2009). This study also detected distant metastasis in four patients that were previously unsuspected. It's important to note that PET/CT seems to have limited clinical utility in clinically node-negative patients. A recent meta-analysis reported PET/CT to be of low sensitivity for inguinal lymph node involvement, especially for clinically node-negative patients (Sadeghi et al. 2012). However, sensitivity for palpable lymph nodes remains high with PET/CT and continues to be a reasonable modality for staging.

Treatment

Inguinal Lymph Node Dissection

The presence and extent of inguinal lymph node metastases are the most important prognostic factors for survival in patients with penile cancer, and there is evidence that early inguinal lymph node dissection leads to a better prognosis compared to delayed dissection (Ornellas et al. 1994; McDougal 1995; Johnson and Lo 1984a). Therefore, for those patients with high-risk disease features (TIG3, $T \geq 2$), aggressive management of the lymph nodes is indicated with the goal of preventing regional and distant metastases (Clark et al. 2013). Given the unique pathogenesis of a prolonged locoregional phase in penile carcinoma, removal of metastatic inguinal nodes can be curative. If nodal involvement is confirmed on frozen section, a standard extended inguinal lymph node dissection is recommended, which includes the superficial and deep inguinal lymph nodes (Clark et al. 2013). The superior boundaries are the superior margin of the external ring to the anterior superior iliac spine. The lateral boundary includes the anterior superior iliac spine and extends 20 cm inferiorly. The medial boundary is defined by the pubic tubercle extending 15 cm inferiorly.

Pelvic Lymph Node Dissection

Pelvic lymph node dissection is recommended in patients with two or more positive inguinal lymph nodes, extracapsular extension, or poorly differentiated metastasis (Clark et al. 2013). This is based on a series of 79 chemotherapy-naïve patients undergoing prophylactic pelvic lymph node dissection with findings of pelvic node positivity to be associated with inguinal extranodal extension or two or more inguinal positive lymph nodes (Djajadiningrat et al. 2015). A pelvic lymph node dissection entails removal of the external iliac, internal iliac, and obturator lymph nodes. Prognosis is poor compared to metastasis confined to the inguinal region with reported 5-year disease-specific survival to be 17% associated with pelvic nodal involvement (Djajadiningrat et al. 2015). In a multi-institutional study, the detection of four or more positive inguinal lymph nodes was shown to be an independent predictor of bilateral pelvic lymph node metastasis (Zargar-Shoshtari et al. 2015). Therefore, bilateral pelvic lymph node dissection has been recommended in this case. In addition, bilateral pelvic lymph node dissection has also been shown to improve overall survival by 8.6 months compared to unilateral dissection after controlling for potential confounders (Zargar-Shoshtari et al. 2016).

Chemotherapy

Chemotherapy is recommended for bulky disease as it is known to have low cure rates and is highly lethal. Single modality treatments are often incurable with surgery and radiation therapy alone. However, there are not many clinical trials reporting the effects of chemotherapy in advanced disease. Although earlier studies investigated

single-agent chemotherapy as a primary treatment modality, multimodal treatment is now recommended in the neoadjuvant and/or adjuvant setting (Clark et al. 2013; Hakenberg et al. 2015). No randomized clinical trials have yet been reported for chemotherapy in penile carcinoma.

Primary Chemotherapy

Early studies report responses observed in small cohorts treated with cisplatin, bleomycin, or methotrexate. Cisplatin was studied as a single-agent study by the Southwest Oncology Group for advanced carcinoma of the penis (Gagliano et al. 1989). In 26 patients treated with cisplatin (50 mg/m^2), there were an overall response rate of 15% and median overall survival of 4.7 months. A smaller study also looked at response to cisplatin in 12 patients with extensive disease (Ahmed et al. 1984). Varying doses of cisplatin were given (70–120 m^2), and significant tumor regression was observed in 25% of patients. Bleomycin has also been reported as a potential single-agent therapy in a cohort of 14 patients (Ahmed et al. 1984). In this study, one patient had a complete response but subsequently died secondary to bleomycin pulmonary toxicity. Significant tumor regression was observed in 3 of 13 (21%) of these patients with a median response duration of 3 months. Methotrexate was also used in advanced disease as a single agent in a cohort of 13 patients (Ahmed et al. 1984). Sixty-one percent of patients produced responses with one complete response. Median duration was also only 3 months. Interestingly, three of these patients received previous cisplatin.

Adjuvant Chemotherapy

There are studies that have examined the role of combination chemotherapy in the adjuvant setting for inguinal metastases. Vincristine, bleomycin, and methotrexate were used to treat 12 patients after radical resection of inguinal lymph node metastases (Pizzocaro and Piva 1988). A 12-week course of this combination chemotherapy was used, and only one patient relapsed after a 42-month median follow-up. Combination chemotherapy was studied by the Southwestern Oncology Group using bleomycin, methotrexate, and cisplatin for locally advanced or metastatic disease (Haas et al. 1999). Forty-five patients were enrolled in this phase II evaluation, which resulted in a 32.5% response rate (five complete and eight partial responses). The median overall survival was 28 weeks. A European Organization for Research and Treatment of Cancer (EOC) phase II study followed 28 patients receiving a combination of irinotecan and cisplatin (Theodore et al. 2008). These patients had either locally advanced or metastatic disease and were treated in the neoadjuvant setting before surgery. Out of 26 patients eligible for response evaluation, there were two complete responses and six partial responses. Interestingly, three patients were found to have no evidence of residual disease at time of surgery. However, this study was considered a negative study as it failed to demonstrate a response rate significantly above 30%. A smaller study followed six consecutive patients treated with paclitaxel, cisplatin, and 5-fluorouracil with either unresectable or recurrent nodal metastasis from penile carcinoma (Pizzocaro et al. 2009). Two patients had a complete response and are disease-free over 2 years after chemotherapy. One patient underwent early surgical resection secondary to chemotherapy intolerance and remained disease-free 46 months after therapy. Two patients achieved complete responses but did not complete the chemotherapy regimen and found to have recurrence at 4 and 10 months. One patient had no response and died within 4 months of treatment. Finally, a recent study found adjuvant chemotherapy to be associated with improved overall survival in pelvic node-positive patients in a multi-institutional review (Sharma et al. 2015). The authors found an improvement of 11 months with adjuvant chemotherapy in overall survival in a cohort of 84 patients.

Neoadjuvant Chemotherapy

A study by the MD Anderson Cancer Center evaluated response to neoadjuvant chemotherapy in patients with N2 or N3 disease without distant

metastases (Pagliaro et al. 2010). A total of 30 men received neoadjuvant paclitaxel, ifosfamide, and cisplatin and underwent subsequent resection. Fifteen patients (50%) had an objective response and nine patients (30%) had a complete response. Median follow-up was 34 months in surviving patients. Twenty deaths occurred during the study, with 17 secondary to progressive penile cancer. A third phase II trial studied the effects of docetaxel, cisplatin, and 5-flurouracil chemotherapy in 20 patients with locally advanced or metastatic penile cancer (Nicholson et al. 2013). This study reported an objective response in 10/26 patients (38.5%) and 2 patients with locally advanced disease achieving complete response. Unfortunately, this trial did not reach the predetermined threshold of a response rate of 60%, and so the authors do not support routine use of this regimen in treatment of advanced disease. A more recent study followed six consecutive patients treated with paclitaxel, cisplatin, and 5-fluorouracil with either unresectable or recurrent nodal metastasis from penile carcinoma (Pizzocaro et al. 2009). Complete response was achieved in two patients after two courses of treatment. However, due to refusal to complete chemotherapy, both patients relapsed.

Surgical Consolidation

In patients with an observed response to systemic chemotherapy, surgical consolidation is considered. This may be attempted to render a patient to be disease-free or for palliative intent. This is mainly based on small individual series in patients with metastatic penile carcinoma. In patients who have not responded to chemotherapy, surgery is not recommended in these patients as this typically represents aggressive, rapidly recurring, or metastatic disease.

A series of eight patients with advanced penile carcinoma were treated with cisplatin and 5-fluoruracil prior to surgical consolidation (Shammas et al. 1992). Two patients achieved a complete response, while one patient achieved a partial response. One of the complete responders required a further operation, while the other required surgery and radiation. They were disease-free at 32 and 57 months, respectively.

A phase II trial reported response to methotrexate, cisplatin, and bleomycin for locally advanced or metastatic disease (Corral et al. 1998). Nine of 30 patients in his study were disease-free with a median survival of 34.4 months. Six of those patients became disease-free after consolidation surgery or radiation. It's important to note the limited duration of response. This study reported an objective response for 16 total patients, but median duration was 4.7 months. The patients achieving the longest duration of response underwent consolidation surgery after chemotherapy. Six patients had duration of response of over a year, and four of these patients underwent consolidation surgery.

A review of 20 patients with unresectable metastatic squamous cell carcinoma was performed over a 34-year period (Leijte et al. 2007). Five different chemotherapy regimens were used to evaluate tumor response and clinical outcome. The chemotherapy regimens included single-agent bleomycin; bleomycin, vincristine, and methotrexate; cisplatin and 5-fluorouracil; bleomycin, cisplatin, and methotrexate; and cisplatin and irinotecan. Of these patients, 12 responded with 8 long-term responses without recurrent disease after surgical consolidation after chemotherapy. Three patients who did not respond to chemotherapy underwent surgery for palliation but all died within 3 months after surgery.

Bermejo et al. reviewed a cohort of ten patients with advanced penile carcinoma treated with surgical consolidation after demonstrating a response to chemotherapy (Bermejo et al. 2007). Three different chemotherapy regimens were used including ifosfamide, paclitaxel, and cisplatin; bleomycin, methotrexate, and cisplatin; and paclitaxel and carboplatin. There were four complete responses and one partial response after chemotherapy. The remaining five patients had stable disease. After surgical consolidation, three patients had no nodal disease (pN0), and seven patients had nodal involvement (pN1–3). Three patients who had greater than three metastatic nodes died with a median survival of 23 months.

The overall 5-year survival rate was 40% with these patients with a median survival of 26 months.

Radiation Therapy

Primary Radiation Therapy for Nodal Disease

As lymph node status in penile carcinoma provides key prognostic information in management, surgical evaluation remains widely accepted as first-line therapy whenever feasible. Evidence for primary radiotherapy of lymph nodes is not robust and is not recommended (Hakenberg et al. 2015). A prospective nonrandomized trial found lymph node dissection to have superior results to radiation therapy in nodal disease (Kulkarni and Kamat 1994). Therefore, surgical resection is recommended over radiotherapy with treatment of enlarged nodes suspicious for metastatic disease.

Adjuvant Radiation Therapy

Radiation therapy in the adjuvant setting has suggested some benefit. A cohort of 23 patients who received inguinal adjuvant radiation therapy after positive lymphadenectomy was reviewed (Franks et al. 2011). This study showed better overall survival (66% vs. 11%) and locoregional relapse-free survival (56% vs. 22%) in patients receiving adjuvant radiation therapy. In another small retrospective study, regional failure rates after node-positive inguinal lymph node dissection were found to be 11% in patients who received adjuvant radiation therapy and 60% in those who did not (Chen et al. 2004). Interestingly, analysis of 2458 patients with penile cancer from the Surveillance, Epidemiology, and End Results (SEER) Program database did not report a positive effect in patients receiving adjuvant radiation therapy compared to surgery alone (Burt et al. 2014). However, confounding factors of the SEER database should be noted as lymphovascular invasion, margin status, extracapsular extension, and radiation treatment fields are not recorded.

Radiation for Unresectable Disease and Palliation

There are cases in which patients present with unresectable disease and may benefit from radiation therapy. Ravi et al. reported one of the largest series of penile cancer patients treated with radiation therapy for lymph node and/or distant metastasis (Ravi et al. 1994). This was a cohort of 120 patients where 33 patients with mobile lymph nodes over 4 cm received preoperative radiation therapy and subsequent lymph node dissection. The incidence of extranodal extension and groin recurrence was statistically lower than a previous study reported during this time. Radiation therapy was found to result in 8% of patients with extranodal extension and 3% groin recurrence compared to 33% and 19%, respectively, in the contemporary report without radiation therapy. This suggests preoperative radiation therapy for large inguinal lymph nodes (>4 cm) improved local control. However, pelvic and/or para-aortic radiation therapy did not show any benefit in patients with pelvic metastasis. In addition, radiation therapy in the palliative setting may also be of clinical utility. Radiation therapy was reported to improve symptoms in 56% of patients with fixed inguinal lymph nodes, all five patients with painful bony metastasis, and one out two patients with cord compression (Ravi et al. 1994). As a result, radiotherapy is, namely, recommended in advanced stage penile cancer and in the palliative setting (Clark et al. 2013).

Nodal and Local Recurrence

Once a local or inguinal recurrence develops, the prognosis is quite poor, and optimal management remains unclear with few options available such as chemotherapy, radiation, or surgery, either alone or in combination. Others have found the salvage rate of local failure to be about 25–85%, and the salvage rate of regional failure is only 33–50% (Chen et al. 2004; Mobilio and Ficarra 2001). Therefore, some recommend aggressive initial inguinal treatment because patients with inguinal recurrence have a relatively poor prognosis (Chen et al. 2004).

Surgery

Although patients treated with penile preservation experience more local recurrences, this has not been associated with worse cancer-specific survival (Djajadiningrat et al. 2014). Thus, more organ-sparing surgeries have been performed in recent years (Djajadiningrat et al. 2014; Pietrzak et al. 2004). Invasion of the corpora cavernosa and basaloid and sarcomatoid histologies have been found as adverse findings after initial organ-sparing approach and may warrant partial or total penectomy (Chaux et al. 2009). For other types of primary tumor recurrence, salvage penile-sparing treatments could still be considered (Clark et al. 2013).

Surgical management of nodal recurrence carries a higher risk as well as markedly higher morbidity when compared to prophylactic dissections (Bevan-Thomas et al. 2002). Multiple single center series have shown palliative dissections have a significantly higher complication rate compared to prophylactic dissections when it comes to the incidence of lymphedema, wound infection, skin edge necrosis, seroma formation, and even death (Johnson and Lo 1984b; Ravi 1993; Ornellas et al. 1991). A recent series from the MD Anderson Cancer Center (MDCC) group advocates careful patient selection for those palliative dissections due to a higher risk of tumor involvement of the femoral and iliac vessels (Bevan-Thomas et al. 2002). However, for isolated locally recurrent inguinal metastasis, salvage resection has been suggested to be beneficial. In a multi-institutional collaboration, 9/20 patients undergoing salvage resection with isolated nodal recurrence had no evidence of disease at a median follow-up of 12 months (Baumgarten et al. 2014). This group reported complications in 11 patients, with wound infections being the most common.

Chemotherapy

In general, there is a low chance for curative treatment for patients with non-resectable lymph node recurrence after surgical treatment. Using a cisplatin, methotrexate, and bleomycin regimen, Hakenberg et al. demonstrated three of eight patients showed response with adjuvant chemotherapy for pN+ disease, while all five patients that had recurrence after pN- status died of disease progression or therapy-related complications (Hakenberg et al. 2006).

Pizzocaro et al. reported a partial response in two of three patients with regional recurrence after inguinal lymphadenectomy using a taxane-based regimen (Pizzocaro et al. 2009). Pettaway et al. reviewed treatment strategies for those with stage IV penile cancer and recommended cisplatin-containing regimens and suggested surgical consolidation for those fit patients that show an objective response to chemotherapy (Pettaway et al. 2010). Bleomycin-containing regimes were not recommended due to significant pulmonary toxicity. The current literature shows few studies on second-line agents. One phase II trial of 25 patients by Di Lorenzo et al. showed partial response with paclitaxel in 5 patients with good tolerability (Di Lorenzo et al. 2011). In addition, targeted therapies have also been attempted for refractory penile cancer cases after chemotherapy. A small series showed one partial response and four stable diseases out of six patients treated with sorafenib and sunitinib (Zhu et al. 2010).

Radiation

Salvage radiation has not been shown to be beneficial in the setting of nodal recurrence. A prior study reviewed a series of 26 patients with inguinal recurrence after lymph node dissection and found only 2/26 patients had a successful response to salvage therapy (Graafland et al. 2011b). Thus, the role of radiotherapy has been largely palliative in recurrent penile cancer. Palliative radiotherapy of the primary tumor, lymph node, or distant metastases can be of use for a few incurable patients after chemotherapy (Pettaway et al. 2010; Mahlmann et al. 2001).

Recommendations for Isolated Inguinal Recurrence

Figure 1 shows a proposed recommendation for the management of isolated inguinal node

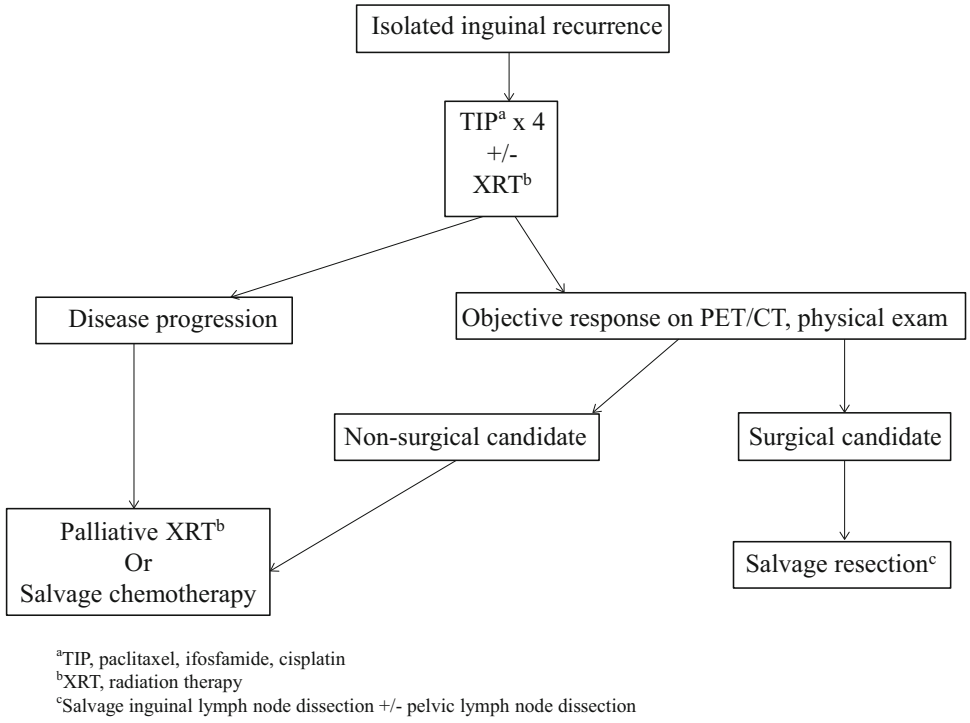

Fig. 1 Treatment algorithm for isolated recurrent inguinal lymph node

recurrence. In summary, treatment with chemotherapy with a cisplatin-containing regimen should be considered such as paclitaxel, ifosfamide, and cisplatin (TIP). In patients with a favorable response, salvage nodal resection can be attempted in those who are acceptable surgical candidates. The use of preoperative radiation therapy can also be considered prior to resection to improve resectability and decrease recurrence in patients with enlarged lymph nodes of over 4 cm. If patients progress despite chemotherapy, palliative radiation therapy or salvage chemotherapy can be considered.

Future Directions

The rarity of disease continues to result in a paucity of literature. This has resulted in no improvement in treatment outcomes in the United States or Europe in over 20 years (Verhoeven et al. 2013). However, extrapolating studies in human papilloma virus (HPV) in squamous cell carcinoma in other organs such as vulvar and head and neck cancers have given way to potential molecular targets within the HPV pathway that have been proposed to be associated with penile cancer outcomes (Spiess et al. 2016). Future studies in systemic approaches targeting the HPV pathway may pave the way to significant advances in improving the dismal outcomes reported in advanced disease.

Conclusion

Patients with bulky inguinal or distant metastases are rarely cured by a single modality alone, although a few series have demonstrated the benefit imparted by neoadjuvant chemotherapy followed by consolidative surgery in patients with cN2/3 disease. Large-scale studies are sorely needed to provide level I evidence for the treatment of recurrent and advanced disease.

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Diagnosis and Staging in Penile Cancer

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Desiree Dräger and Oliver W. Hakenberg

Contents

Abstract

Penile cancer is usually an obvious visual diagnosis but may be hidden under a phimosis and always requires histological confirmation. Superficial forms may appear as innocuous changes in color and texture of the glandular skin. A high degree of diagnostic suspicion and early biopsy are required in such cases.

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Palpation of the primary tumor will give relevant information on the local extent, and additional penile imaging is usually not needed. Since metastatic lymphatic spread occurs early in penile cancer and can quickly lead to disseminated disease, examination of the regional inguinal lymph nodes is essential. Groin palpation remains the most useful examination to detect suspicious lymph nodes. Imaging can confirm palpably enlarged lymph nodes and may only be additionally useful in obese patients or for pelvic node staging. But no imaging modality can reliably exclude micrometastatic disease in clinically normal inguinal lymph nodes which occurs in up to 25% of cases. This can only reliably be

done by invasive lymph node staging of inguinal nodes removed by sentinel lymph node biopsy or limited modified lymphadenectomy. In case of enlarged and suspicious inguinal lymph nodes, imaging to detect pelvic nodes and distant metastasis by CT, MRI, or PET/CT scanning can be required in addition to pathological staging by radical inguinal lymphadenectomy followed by ipsilateral pelvic lymphadenectomy if more than one inguinal node is affected. Thus, diagnosis and staging in penile cancer remains mostly clinical and surgical.

Introduction

Since penile cancer is relatively rare in the developed world, most physicians will have limited experience with this disease. Although penile cancer often is an obvious visual diagnosis, there are some pitfalls in diagnosing and staging it. One is the underdiagnosis and therefore often delayed recognition of superficial and premalignant disease; second, the late diagnosis of penile cancer hidden under a phimosis; and the third, the underdiagnosis of micrometastatic regional lymph node disease. A fourth pitfall is perhaps the overuse of imaging with CT or MRI which does not alter management when it often adds little additional information to what is clinically evident.

Diagnosis of the Primary Tumor

Exophytic penile cancer is usually an obvious visual diagnosis (Fig. 1). However, before any ablative treatment is undertaken, histological confirmation is required. Therefore, all suspicious penile lesions should be biopsied, and even in clinically obvious cases, histological verification must be obtained.

Superficial and noninvasive penile cancer such as penile intraepithelial neoplasia (PeIN, formerly called carcinoma in situ) and precancerous lesions are less obvious and are often fairly unremarkable changes in the color and/or texture of the skin of the glans or the sulcus coronarius (Fig. 2). Not infrequently, these lesions are not recognized as suspicious of malignancy and mistreated as unspecified inflammatory changes by anti-infective and/or corticosteroid ointments for prolonged periods of time. This is not helpful and can lead to serious delays in diagnosis and treatment. A high degree of suspicion is required and a diagnostic biopsy should be performed before subjecting undiagnosed penile lesions to prolonged empirical treatment with ointments.

A histological diagnosis with adequate local pathological staging, i.e., identifying correctly the depth of invasion, is obligatory if nonsurgical treatment with topical chemotherapy, radiotherapy, or laser ablation is considered. Without pathological staging, underestimation of the local stage can easily occur and lead to local recurrence and progression (Chipollini et al. 2018). In all cases with nonsurgical treatment, histological verification and local pathological staging must be obtained before treatment.

Biopsies must be of sufficient size. If these are too small, the depth of invasion cannot be reliably assessed and the pathological diagnosis may even be false-negative. Also, with respect to small biopsies, grading may differ between the biopsy and definitive surgical pathology in up to one-third of cases (Velazquez et al. 2004a). Therefore, a reasonably sized excisional biopsy is needed (>0.1 cm in diameter) and is generally preferable to a punch biopsy.

Penile cancer of the glans or the inner prepuce may be masked by a phimosis so that again a high degree of suspicion as well as careful palpation are required. Pain even in large and infiltrating penile cancers does not occur. Secondary inflammatory local changes and necrosis may give rise to discharge and odor.

In penile cancer, local staging regarding the extent and invasion of penile structures depends foremost on clinical examination. This requires careful palpation of the lesion which will in most cases suffice to determine the extent reliably enough for a clinical decision (Lont et al. 2003). It will give adequate information on the size, extent, texture, and infiltration of penile structures (corpora cavernosa, urethra).

Imaging of the penis is rarely necessary as it adds little relevant information. Ultrasound may

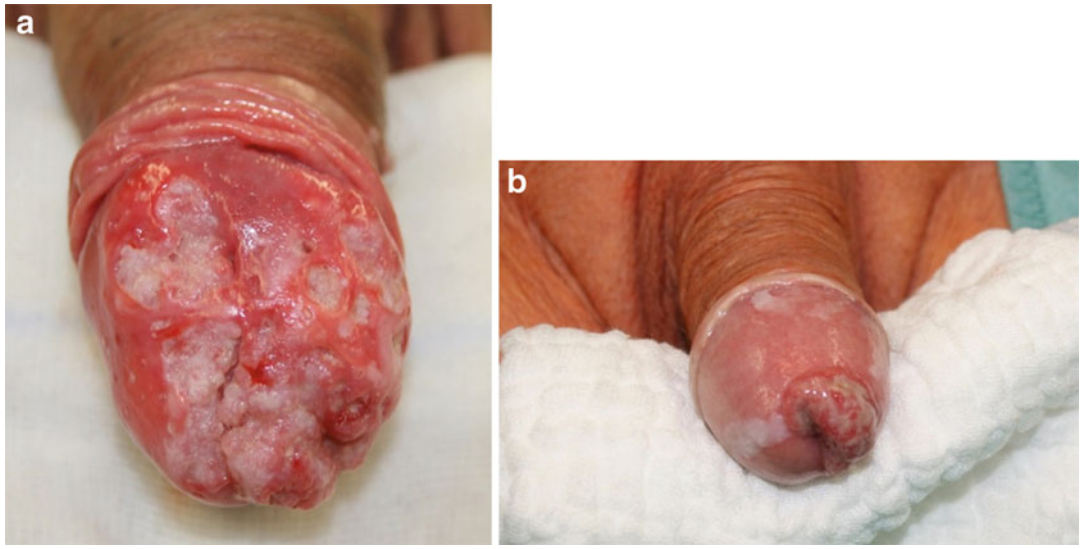

Fig. 1 (**a** and **b**) Typical appearance of penile carcinomas

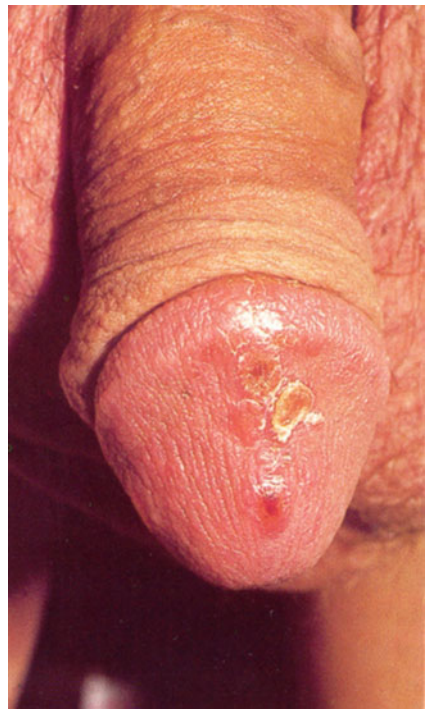

Fig. 2 Small glandular lesion representing a carcinoma in situ

be helpful in some cases but usually is not. Penile MRI can show glandular or cavernosal invasion. However, the information gained is mostly already known from palpation. MRI with an artificial erection can show whether the corpora cavernosa are invaded or not, but it is unpleasant and painful for the patient and the gain in information is minimal (Petralia et al. 2008).

With planned surgical treatment, the confirmatory biopsy can be obtained at surgery with a frozen section, followed by definitive surgery if the diagnosis is confirmed. However, in cases of condylomatous and/or highly differentiated tumors, frozen section may be unreliable and treatment must be postponed until definitive histopathology is received. Definitive surgery will then show the local extent of the disease which will become macroscopically obvious intraoperatively.

Clear (negative) resection margins must be confirmed histologically both by frozen sections and definitive histopathology (Velazquez et al. 2004b). The width of negative surgical margins required does not need to be extensive. With the recognized need for organ-sparing, it is entirely obsolete to obtain wide negative margins of one centimeter or more as was advised in the past. It is today recommended to follow a risk-adapted strategy based on tumor grade, i.e., with higher grade, the width should be larger. Around 1–3 mm based on tumor grade can be considered adequate margins (Minhas et al. 2005). Both intraoperative frozen sections and definitive pathology must confirm complete surgical resection.

Diagnosis and Staging of Regional Lymph Nodes

Penile cancer tends to metastasize early to the regional inguinal lymph nodes. Distant metastatic disease is only seen in patients who have lymph node spread. Therefore, it is of utmost importance to diagnose or exclude inguinal lymph node disease as best as possible. Indeed, the entire prognosis depends on regional lymph node disease. Undiagnosed inguinal lymph node metastasis will lead to overt inguinal nodal "recurrence" which carries an overall 5-year cancer-specific survival of under 40% while lymph node negative cases achieve long-term survival with appropriate local treatment in well over 90% of cases (Leijte et al. 2008a).

Staging of inguinal lymph nodes depends foremost on clinical examination, i.e., careful palpation of the groins. This will either be normal or show palpably enlarged nodes if not overt gross lymphadenopathy.

Normal Inguinal Lymph Nodes

Normal, not enlarged inguinal lymph nodes in invasive penile cancer pose a problem. Such patients are at considerable risk of harboring micrometastatic lymph node disease in up to 25% of cases (Leijte et al. 2008a). Surveillance after local treatment is therefore inadequate since this may lead to later local "recurrence" of overt inguinal nodal disease with a much reduced long-term prognosis (see above) (Leijte et al. 2008a).

Unfortunately, imaging techniques are of very limited value in penile cancer with normal inguinal lymph nodes since all imaging techniques rely on nodal enlargement for diagnosing nodal metastasis and enlargement can usually be diagnosed by palpation. Ultrasound (7.5 MHz) can reveal abnormal nodes with some enlargement. The longitudinal/transverse diameter ratio and the absence of the lymph node hilum have been reported to be findings with relatively high specificity (Krishna et al. 2008). Conventional CT or MRI scans similarly rely on nodal enlargement and cannot detect micrometastases (Kayes et al. 2017). Similarly, ^{18}FDG-positron emission tomography (PET)/CT imaging does not detect lymph node metastases <10 mm (Leijte et al. 2009). Imaging studies are therefore not really helpful in staging clinically normal inguinal regions. An exception can be patients with obesity in whom palpation is unreliable or not possible.

Thus, the only reliable way to diagnose or exclude micrometastatic inguinal nodal disease in penile cancer is surgical staging. For invasive (surgical) nodal staging, a limited number of lymph nodes is removed instead of performing a full radical inguinal lymphadenectomy. Invasive nodal staging can be done by identifying and removing inguinal sentinel nodes either by dynamic sentinel lymph node biopsy (DSNB) (Leijte et al. 2009) or by removing the lymph nodes of the most likely affected groin areas by (limited) modified inguinal lymphadenectomy (Neto et al. 2011).

These areas are the medial and the central (confluens) inguinal regions according to Daseler (Yao et al. 2010). Single photon emission computed tomography (SPECT CT) in penile cancer

patients has shown all inguinal sentinel nodes to be located in the superior and central inguinal zones, with most found in the medial superior zone (Daseler et al. 1948). No early lymphatic drainage seems to occur from the penis to the two inferior regions of the groin, and certainly no direct drainage to the pelvic nodes (Leijte et al. 2008b).

The indication for invasive nodal staging is based on the likelihood with which micrometastatic nodal disease is present. This likelihood correlates with local stage and grade (Riveros et al. 1967). Thus, invasive nodal staging is indicated with higher local stage and higher grade, i.e., should be guided by these pathological risk factors. Current guideline recommendations advise invasive nodal staging in all cases of pT1G3 disease or higher (Solsona et al. 2001).

Unusual with cancer classification, grading has been included in the TNM classification of penile cancer because of its prognostic relevance (Hakenberg et al. 2015). However, grading in penile cancer is often unreliable. It has been shown to be highly observer-dependent for the WHO grading system (Brierley et al. 2017). Also, penile cancers may have a heterogenous composition making grading again less reliable.

For these reasons, it seems advisable to perform invasive inguinal nodal staging for all locally invasive cases which are not highly differentiated, i.e., pT1G2 or higher (Kakies et al. 2014). Several series have identified lymphovascular invasion in addition to local stage and grade as risk factors predicting the likelihood of lymphatic metastasis (Riveros et al. 1967; Kakies et al. 2014). Therefore, with additional unfavorable local tumor features such as a very malignant type (e.g., basaloid, sarcomatoid) and/or lymphovascular invasion, micrometastatic disease is more likely. Thus, tumors with low risk of metastatic disease are those with superficial penile cancers (pTa, pTis) and low grade (G1) and high risk are those with pT2 and high grade (G2–3). pT1 tumors are a heterogenous risk group. They are only considered low risk if they are well differentiated (G1), otherwise they represent an intermediate (G2) or high risk group (G3) (Solsona et al. 2001). Invasive lymph node staging is required in patients at intermediate or high risk of lymphatic spread. However, micrometastatic nodal disease may even occur in pTa penile cancer. The indication for invasive nodal staging is based on probabilities but should not be restrictive. Nomograms are unreliable as they cannot achieve accuracy over 80%.

If DSNB or modified lymphadenectomy yields affected nodes, a complete radical lymphadenectomy is necessary both for treatment and staging. If this yields more than one affected inguinal node, then an ipsilateral pelvic lymphadenectomy is indicated (Solsona et al. 2001). Thus, lymph node staging in penile cancer remains mainly clinical and surgical.

Palpable Inguinal Nodes

In penile cancer patients, palpable, enlarged, and/or indurated inguinal lymph nodes are very likely to be metastatic and must be considered so until proven otherwise (Fig. 3). Physical examination should note the number of palpable nodes on each side, their size, and whether these are fixed or mobile.

It is entirely obsolete to treat enlarged inguinal nodes in penile cancer patients by empirical antibiotic treatment for several weeks since purely inflammatory inguinal lymph node enlargement in penile cancer does not occur. Instead, antibiotic treatment for enlarged inguinal nodes delays appropriate treatment.

Imaging techniques with enlarged inguinal nodes can confirm the enlargement but cannot definitely diagnose or exclude metastatic disease. CT, MRI, and PET/CT have all been used extensively for lymph node staging in penile cancer with enlarged regional nodes (diffusion-weighted MRI or ^{18F}FDG PET/CT). Although the sensitivities and specificities of these techniques for the detection of enlarged lymph nodes with metastatic disease are high, they are unreliable for the definitive confirmation of metastatic disease or the exclusion of micrometastatic disease (Graafland et al. 2010; Lützen et al. 2016). Thus, they are not all that helpful for the staging of the already diagnosed enlarged inguinal nodes. Instead, surgical

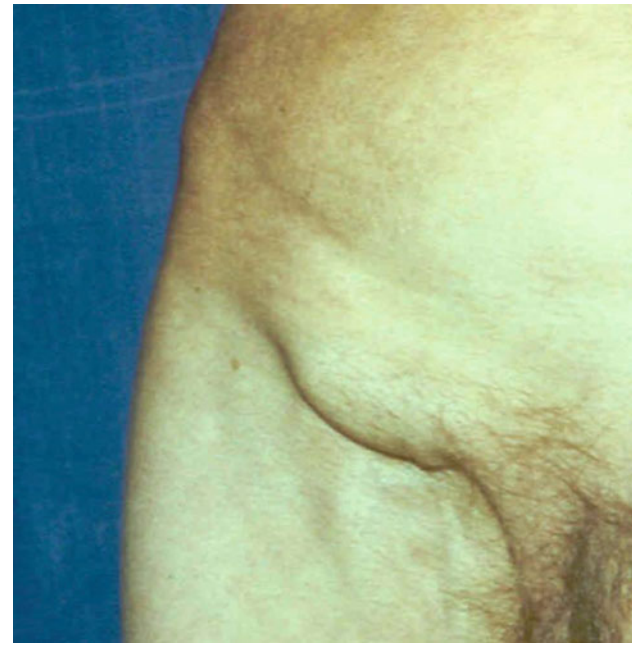

Fig. 3 Enlarged inguinal lymph node representing lymphatic metastasis

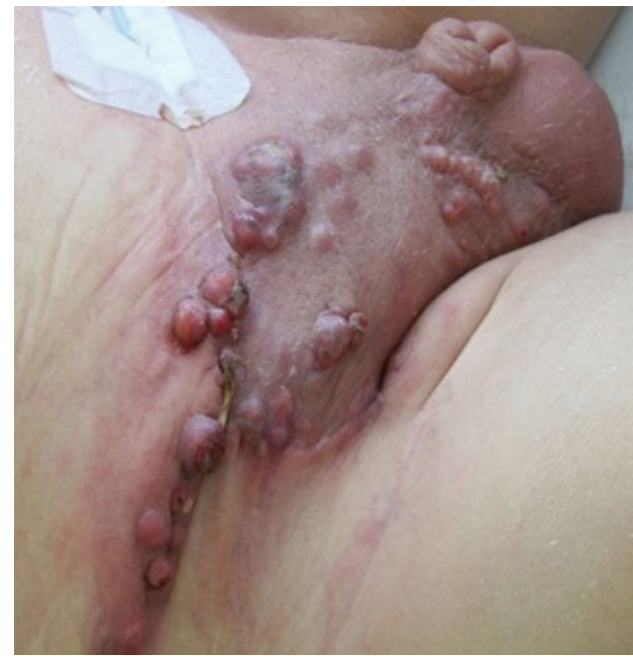

Fig. 4 Bulky disease with enlarged regional nodes together with cutaneous metastatic nodules

staging by lymphadenectomy is necessary since the enlarged inguinal lymph nodes are highly likely to be metastatic and must be excised for histopathological diagnosis. DSNB is not indicated in cases of enlarged inguinal nodes. If lymph node metastasis is confirmed by frozen section, ipsilateral radical inguinal lymphadenectomy (ILND) is required. If more than one node is found to be involved at radical ILND, an ipsilateral pelvic lymph node dissection for

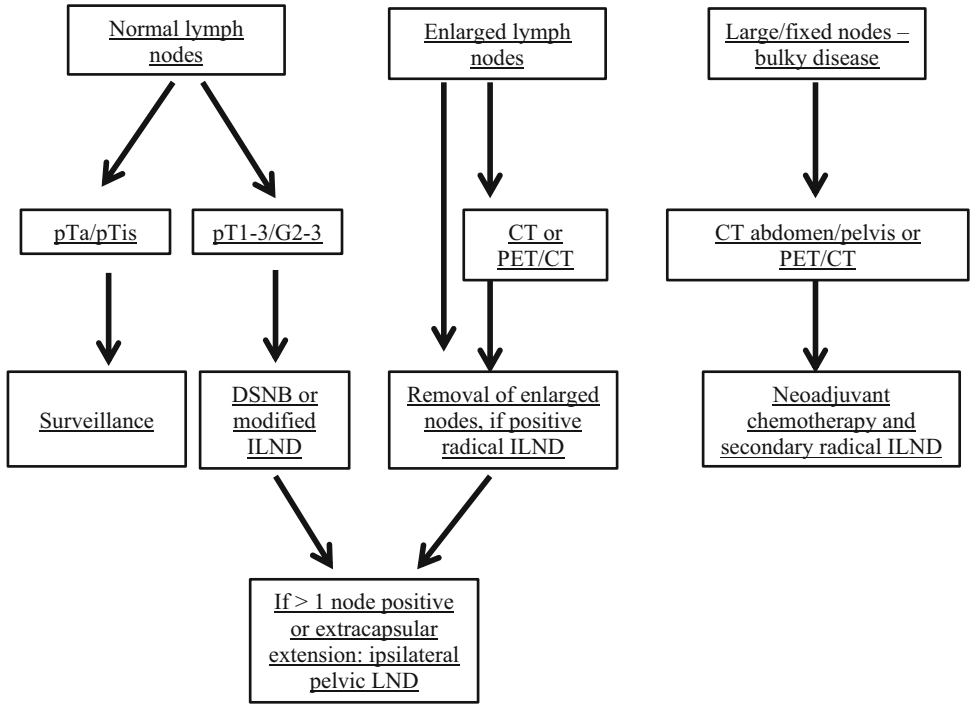

Fig. 5 Diagnostic and staging algorithm for regional lymph nodes in penile cancer. ILND = inguinal lymph node dissection

staging and treatment is required which can be done in the same session.

Thus, surgery is the definitive method of staging of enlarged inguinal lymph nodes in penile cancer. Additional imaging of the inguinal region in patients with enlarged inguinal nodes does not alter management and is usually not required except for further staging of pelvic lymph nodes or for systemic disease.

Bulky Inguinal Lymph Nodes

In cases with bulky and/or fixed inguinal lymph node enlargement, the diagnosis is clinically obvious (Fig. 4). Surgical staging of such bulky disease by excision of a node or biopsy is not necessary. Instead, treatment either by surgery or first by neoadjuvant systemic treatment is indicated. Imaging should be used in these cases to diagnose systemic disease and determine its extent.

Staging of Pelvic Nodes

In cases with inguinal nodal involvement of more than one node on one side (or extracapsular extension), ipsilateral surgical staging of the pelvic lymph nodes is indicated. Imaging is useful in diagnosing pelvic nodal enlargement as well as paraaortic lymph nodes. Involvement of the latter is, however, classified as systemic disease. CT and MRI are useful for this. PET/CT can assess nodal as well as systemic disease reliably (Lützen et al. 2016; Souillac et al. 2012).

The diagnostic and staging management for regional lymph nodes in penile cancer is summarized in Fig. 5.

Staging for Distant Metastases

A complete staging assessment for distant metastases should be done in all patients with positive inguinal nodes. This includes an abdominal CT

and a chest x-ray or a thoraco-abdominal CT or MRI (Solsona et al. 2001). An alternative is a PET/CT which is also reliable in identifying pelvic nodal and distant metastases in penile cancer patients with positive inguinal nodes (Lützen et al. 2016; Souillac et al. 2012).

Diagnosis of Recurrence

Local recurrence can be treated locally and usually does not significantly alter long-term prognosis. Regional lymph node recurrence markedly changes the patient's prognosis and indicates that micrometastatic disease was missed at first treatment. Systemic recurrence alone is very rare.

The diagnosis of local and regional recurrence is again entirely clinical. Careful inspection and palpation of the penis for local recurrence and of the inguinal regions for lymph node recurrence are necessary and should be done at regular intervals. These intervals should be three monthly for the first 3 years since most recurrences occur within the first 2 years of treatment (Solsona et al. 2001).

Routine imaging for inguinal nodal recurrence is often done but has not been shown to be superior to clinical examination. Ultrasound of inguinal nodes together with fine needle aspiration cytology has been reported to be superior to clinical examination alone for detecting inguinal nodal recurrence early (Dräger et al. 2018).

Unfortunately, there is no established tumor marker for penile cancer. Squamous cell carcinoma antigen (SCC Ag) is increased in less than 25% of penile cancer patients (Zhu et al. 2008). Thus, SCC Ag is not a predictor of occult metastatic disease but may be a prognostic indicator of disease-free survival in lymph-node positive patients (Djajadiningrat et al. 2014).

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Treatment of the Primary Tumor: Role of Organ-Preserving Surgery in Penile Cancer

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Abstract

Historically radical surgery has been the mainstay of penile cancer management, with the ability to pass urine being the predominant concern in terms of functional outcomes. As evidence has evolved, surgeons have had a greater confidence to take smaller margins in the knowledge that the oncological safety of the procedure is not compromised. Coupled with a more thorough appreciation of the psychological effects of diagnosis and treatment, this has led to a change in the surgical paradigm to include functional and cosmetic aspects. The use of new technologies and plastic surgical techniques has seen the use of organ-preserving surgery become the mainstay of penile cancer management.

Introduction

Historically, radical surgery was the mainstay of treatment for men with penile cancer. While penectomy has been shown to be oncologically safe with low recurrence rates, it has a negative impact on men's health, including impaired voiding and sexual function and psychological distress (Opjordsmoen and Fossa 1994; Maddineni et al. 2009).

A series of publications have led to a shift in our understanding of the disease and given surgeons the confidence to adopt conservative approaches that preserve function of the penis. The model of management has consequently shifted from oncological control to incorporate consideration of quality of life outcomes and "survivorship." Ideally, the goal of penile-preserving surgeries imparts excellent oncological control, together with a maintained or at least minimally impaired sexual and voiding morbidity.

Rationale for Adopting Penile-Preserving Surgery in the Management of Penile Cancer

A number of surgical techniques have evolved around the concept of penile-preserving strategies. The safe use of smaller resection margins and confirmation that local recurrence does not affect disease-specific mortality have contributed to this change.

What Margin Is Safe?

Traditionally, a 2–3 cm resection margin has been arbitrarily utilized, but this has since been questioned. The rarity of the disease in many countries often prevents large-scale randomized interrogation, forcing comparison from more common diseases to create an educated evidence base for oncological principles. Squamous cell carcinoma of the skin is an aggressive disease like penile cancer and shares the same histological subtype. Strong evidence in this condition points toward the need for wide excision margins of 15–25 mm. As a consequence it was for a long time a widely held belief that this was also the case in penile cancer and thus many patients underwent partial (PP) or total penectomy (TP) for T1–T3 disease.

In 1999 Hoffman et al. retrospectively analyzed 14 patients who had undergone partial or total penectomy with traditional margins. Microscopic pathological margins were evaluated from stored sections and a mean margin for each stage calculated. Nine patients had $\geq$T1 N0M0, of which 7 (78%) had microscopic pathological margins $\leq$10 mm. None of these patients had local recurrences after a mean follow-up of 32.4 months, and only one had inguinal metastasis (Hoffman et al. 1999).

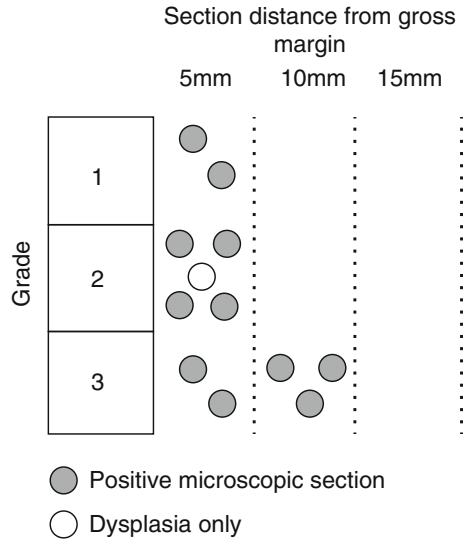


Fig. 1 Microscopic spread, beyond visible tumor

A year later Agarwal et al. reported a prospective analysis of 64 patients undergoing partial (PP) or total penectomy (TP). Specimens were processed in 10% formalin and serial 5 mm cross sections created proximal to the macroscopic limit to allow assessment of microscopic spread beyond the visible tumor. All lesion were ≥T2 ($n = 63$, T2; $n = 1$, T4). All tumors were graded 1–3 (G1, $n = 20$; G2 $n = 32$; G3 $n = 12$). The histological extent beyond the gross tumor margin per grade is shown in Fig. 1. Only 12 of the 64 specimens had evidence of microscopic spread beyond the macroscopic margin. In G1 and G2 lesions, the 10 mm section was clear in all cases. Three of 12 G3 cases had positive disease in the 10 mm section. No G3 tumors extended beyond 15 mm (Agrawal et al. 2000).

We first presented our institutional data in 2005: 51 men underwent either wide local excision (WLE), partial glansectomy (PG), glansectomy, or partial penectomy. Six percent had a positive margin, and only 4% developed local recurrence within a median of 26 (2–55) months (Minhas et al. 2005). The histology in these two cases were G3pT1 and G3T3. After review of the histopathological margins, 48% were within 10 mm and 92% within 20 mm.

In 2012 we reported on 179 patients (2002–2010) with a mean follow-up of 42.8 months. The mean distance from the excision margin was 5.23–5.78 mm (range 0–30); 12 patients (6.7%) had involved surgical margins. Importantly, these patients underwent further organ-sparing surgery, and negative margin status was achieved by repeat resection in all, with no local subsequent recurrence. However, overall, 16 (8.9%) developed local recurrence, 15 of which within 5 years (Philippou et al. 2012). These studies suggest that that PPS appeared to be oncologically safe and the concept has been incorporated into best practice guidelines.

Does Local Recurrence Translate to Increased Mortality?

One of the perceived issues with penile-preserving surgery is the increased recurrence rate above that of traditional approaches. A number of studies however have highlighted that despite this criticism the increased recurrence rate does not necessarily translate into a reduction in survival.

Shindel et al. published their data on the use of Moh's micrographic surgery (MMS) in patients with penile cancer (Shindel et al. 2007). The retrospective review of patients' charts identified 33 patients having undergone overall 44 MMS. The indications for MMS were (1) carcinoma in situ (CIS), or verrucous carcinoma, (2) distal or glanular squamous cell carcinoma of the penis with features permissible for partial penectomy, or (3) patient desire to optimize the preservation of penile tissue and function. Of 33 patients, follow-up data was available for 25 with a median of 37 months (0.5–214 months). Eight patients (32%) had recurrences at a mean of 36 months and seven were managed successfully with repeat MMS. The overall survival (OS) and disease-specific survival (DSS) were 92% and 96%, respectively, comparable to traditional techniques.

Leijte et al. in 2008 examined the records of 747 patients from two centers treated for penile cancer. Patients with Tis, Ta, and T1 tumors as well as T2 tumors <3–4 cm were treated with penile-preserving techniques. When the patients were stratified into penile-preserving surgery vs. amputation, 27.7% developed local recurrence vs. 5.3%, respectively, with a median follow-up

time of 60.6 months (3–358 months). However this high recurrence rate did not translate into a reduced survival (Leijte et al. 2008).

A large retrospective study of 1000 patients, over 56 years by Djajadiningrat et al., demonstrated that although more local recurrences occurred using penile-preserving techniques (laser, WLE, glans resurfacing, glansectomy), a 5-year cancer-specific survival was unaffected. They examined the records of patients with T1–T4 penile cancer treated between 1956 and 2012 and compared outcomes for penile-preserving surgery versus amputation. They found the 5-year cumulative incidence of local recurrence as the initial event to be 27% (95% CI 23–32) vs. 3.8% (95% CI 2.3–6.2), respectively ($p = <0.0001$). This confirmed the suspicion that the rate of local recurrence in patients with T1–T4 was higher in those treated with penile-preserving techniques. However when the cancer-specific survival was examined, they found that after adjusting for relevant co-variables, those that underwent penile-preserving surgery had no significant different CSS to those treated with amputation (HR 1.52, 95%CI 0.96–2.4, $p = 0.08$). Further on cox modeling, there was no significant association between local recurrence and CSS in the penile-preserving group (recurrence vs. no recurrence HR 0.52, CI 95% 0.21–1.24, $p = 0.14$). Interestingly this was not replicated in those patients managed with amputation (recurrence vs. no recurrence HR 5.26, 95% CI 2.6–10.5, $p < 0.0001$) (Djajadiningrat et al. 2014).

In summary the maturation of penile-preserving techniques can be attributed to the confidence to use smaller than traditionally accepted margins safely and accepting the higher recurrence rate this has no discernible impact upon survival.

Importance of Sexual Function

So what impact does radical surgery, i.e., PP or TP, have on patients with penile cancer, and thus, is there really a role for attempting penile-sparing techniques?

Unfortunately the rarity of the disease and paucity of large-scale studies again hinder our true understanding of this important aspect. There are no prospective randomized control studies comparing treatment outcome in this group of patients. Do the few studies available confirm an inherent belief that radical penile surgery affects men, sexually, socially, or psychologically?

A small follow-up study of 30 Norwegian patients from 1971 to 1990 who underwent either organ-preserving or radical surgery demonstrated that PP or TP did indeed lead to worse sexual function outcomes. Interestingly, overall well-being and social contact were better for the four patients who underwent radical surgery. An important observation, 7 of 25 patients upon questioning, would prefer to have kept their penis and risk lower long-term survival (Opjordsmoen and Fossa 1994).

A review from Maddineni et al. (2009) analyzed quality of life outcomes from 128 patients in 6 studies, 1 of which was discussed above. A plethora of quantitative tools were used, but in general they concluded that overall, radical treatments resulted in lower psychological well-being. Quite concerning was the observation that psychiatric symptoms were noted in up to 50% of patients. That said, while some of the papers showed impaired well-being (Ficarra et al. 2000; Romero et al. 2005) (measured by the General Health Questionnaire), others, such as D'Ancona et al. did not (D'Ancona et al. 1997). Despite this paper not finding a difference in well-being, 36% of their patients whom underwent PP reported no sexual function or at least a moderate to severe reduction.

Ficarra's study (Ficarra et al. 2000) of 16 penile cancer patients showed that sexual function scores were significantly lower for those undergoing radical surgery – scoring 1.3 and 1.0 for partial and total penectomy, respectively (where 4 is the best function).

Thus while there is heterogeneity in the reported outcomes from penile-preserving surgery, there seems to be an overall trend that sexual function levels (e.g., self-made activity or function scores, IIEF-15) were reduced for those patients undergoing PP (D'Ancona et al. 1997).

Surgical Management by Stage

In the following sections, we will explore the various penile-preserving surgical options – it is helpful to group these according to the suitability to various cancer stages. It is important to remember that there exist several nonsurgical treatment options; however, these will not be discussed within this chapter.

Tis Ta

Laser Ablation

The use of lasers has been employed across many different disciplines of medicine. The first description of lasers in the management of penile cancer was in 1978 by Hofstetter et al. (1978). In the treatment of penile cancer, two types have been used: (1) carbon dioxide (CO_2) and neodymium: yttrium aluminum garnet (Nd:YAG) lasers. Their individual wavelengths impart slightly different usage characteristics.

Nd:YAG are a solid-state laser that produce a beam with a wavelength of 1064 nm and penetrate between 4 and 6 mm. They lead to protein denaturation, coagulative necrosis, and in comparison to CO2 laser reduced carbonization and vaporization.

CO2 lasers on the other hand use a gas medium that generates a longer wavelength of 10,600 nm. As a consequence the energy is highly absorbed by water and has a penetration depth of 1 mm. They can also be used to excise lesions.

The strong hemostatic properties of this approach and ability to perform under a local anesthetic lend it to day-case treatment.

A number of studies have addressed the use of laser in the management of penile cancer.

Windahl et al. in 2003 prospectively collected data on 67 men with a mean age and follow-up of 60-year-old and 42 months, respectively, treated with a combination of Nd:YAG and CO_2 laser (Windahl and Andersson 2003). Forty-six patients had T1–T3 disease. There were 13 (19%) recurrences in the Tis/Ta group and 10 (21.7%) in the T1–T3 group. Overall 11 went on to have penile-preserving surgery and 2 had a partial penectomy. Five (7%) patients had postoperative bleeding.

Meijer in 2007 retrospectively reviewed 44 consecutive patients treated with Nd:YAG (Meijer et al. 2007). Twenty-one patients had stage T1, 17 had T2, and 6 Tis. Recurrences occurred in 29 patients (65.9%). Twenty-one cases had the recurrence at the original site, while nine had recurrences at alternative sites (one patient had both recurrence at resection site and at another site on the penis). There was no significant difference in recurrence rate between T stage and grade ($p = 0.4$ and $p = 0.2$, respectively). There were ten nodal metastases (two at presentation). The eight delayed nodal metastases developed at a mean of 41 months, and only one had Tis on original pathology. Six were T2 disease. Nine percent of patients died of metastatic penile cancer.

A larger review by Bandieramonte et al. reported on 224 cases of early-stage penile cancer (Tis, Ta, and T1–T2) treated between 1982 and 2006 with a CO_2 laser combined with peniscopic examination at ×10–16 magnification and 5% acetic acid (Bandieramonte 2008). Over a median follow-up of 66 months (35–132 months), 32 patients experienced a recurrence(s) (14.2%), and there were a total of 52 recurrences. In those with T1–T2 disease, 12 of 118 had a recurrence (11.3%). The majority of recurrences were managed with repeat laser treatment, although nine required amputations. The 5- and 10-year cumulative risk for recurrence were 14.1% (95% CI 13.4–14.9%) and 17.5% (95% CI 16.4–18.6%), respectively.

The median healing time (by secondary intention) was 6 weeks (5–7 weeks). Of 27 patients that had meatal involvement, 2 required surgical intervention for subsequent meatal stenosis.

More recently the combination of photodynamic diagnosis (PDD) with Nd:YAG laser therapy has been retrospectively reported by Schlenker et al. (2011). Twenty-six patients (11 with Tis and 15 suffering invasive penile cancer G1 – 3T1 N0 – 1 M0) were given topical

5-aminolevulinic acid 2 h prior to surgery. The suspicious area was then observed under white light and then blue light and accordingly ablated with a 3 mm safety margin. Biopsies were taken from the tumor base and sent for frozen section. After ablation the glans was re-examined for further areas that were treated accordingly. The mean follow-up was 71.1 months (41–104 months). The overall recurrence rate was 4/26 (15.4%). In patients with Tis, none developed local recurrence or died. In patients with invasive penile cancer, there were four local recurrences (26.7%) at 16, 41, 53, and 60 months. No patients in this group died of penile cancer.

In terms of urinary and sexual function and form of the penis, there is a paucity of data. A study by Tewari in 2007 examined 32 patients having undergone laser treatment for pT1 (25 patients) and pT2 (7 patients) disease (Tewari et al. 2007). The patients were followed up at three monthly reviews and asked about micturition sexual function and form. The median follow-up was 70 months (6–120 months). Eight patients observed celibacy, and in 23 they described their sexual function as satisfactory postoperatively.

Skeppner et al. conducted a retrospective review of patients with penile cancer treated with laser (Skeppner et al. 2008). All patients had Tis–T2 N0 Mo G2–G3 and <3 cm. They conducted face-to-face interviews regarding sexual activity and life satisfaction (LiSat-11) after a median of 3 years (6 months–15 years). An ad hoc comparator group was used for the LiSat-11. Six out of 46 patients were sexually inactive prior and after treatment. Ten had not resumed sexual activity when interviewed. However, 29 (63%) patients had penetrative intercourse in the 3 months up to the interview. Of the 23 whom reported manual stimulation by their partners prior to the procedure, 65% acknowledged to have continued afterward. In terms of life satisfaction, patients' satisfaction with life as a whole was similar to that of the general population although identified somatic health and psychological health to be worse.

Glans Resurfacing

The technique of glans resurfacing was first described by Bracka in relation to the management of lichen sclerosus (Depasquale et al. 2000). Subsequently the technique has been adopted for the use in superficial penile cancer. It allows complete or partial replacement of the glans epithelium where disease is diffuse or relapsing.

The procedure is performed under a general anesthetic. The glans is marked using a permanent marker into four quadrants, which meet at the urethral meatus. The glans epithelium and subepithelial tissues are then carefully dissected away from the spongious tissue underneath (Figs. 2, 3, and 4). Frozen sections of the underlying spongious are taken to confirm complete excision. A split-thickness skin graft (STSG) can then be harvested from an appropriate donor site (e.g., the thigh) and secured carefully using sutures and appropriate dressings to immobilize the graft and encourage imbibition and inosculation. The tie-over dressing for graft application (TODGA) technique has yielded excellent results and allows early patient mobilization (Hegarty 2011).

Hadway et al. reported on their first ten patients managed for erythroplasia de Queryat and high-grade dysplasia (Hadway et al. 2006). At a median of 30 months (7–45 months) follow-up, there were no recurrences and all margins were negative. There were no postoperative complications including stenosis or graft loss. The group also examined sexual function pre- and postoperatively, using the abbreviated International Index of Erectile Function score (IIEF-5), and found that all patients whom were preoperatively sexually active remained so afterward. The median IIEF-5 was 24 of the 7 patients who responded. All seven patients reported no change or/and improvement in sensation. Five out of seven reported an improvement in their sex life and two reported no change. Patient satisfaction was universally high.

Ayres et al. reported on 33 patients with G1/G2 T1 SCC penis (Ayres et al. 2011). In total there

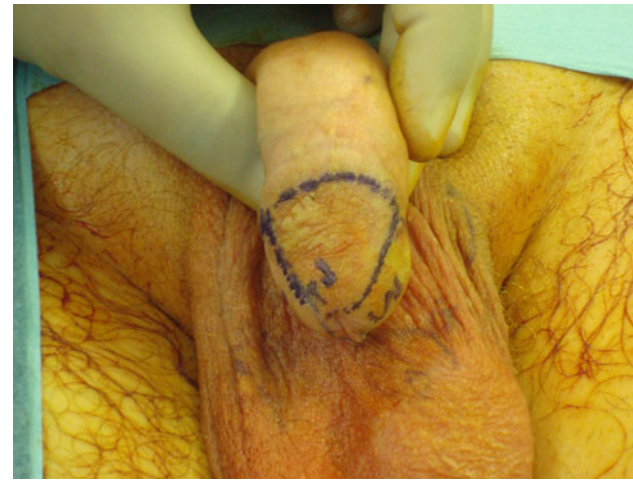


Fig. 2 Glans resurfacing: region for resection marked

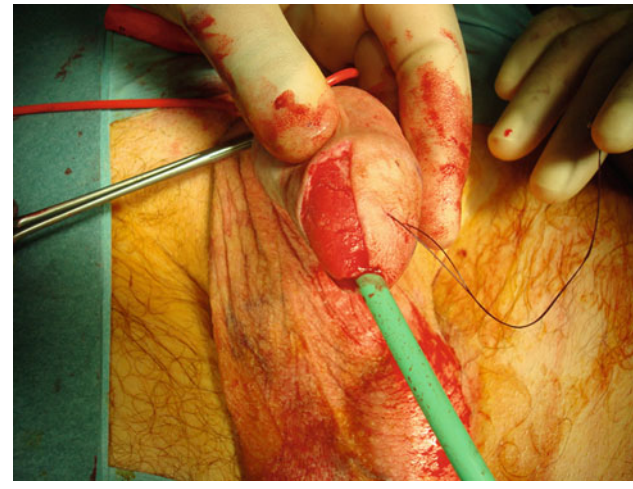


Fig. 3 Glans resurfacing: region excised to spongiosum

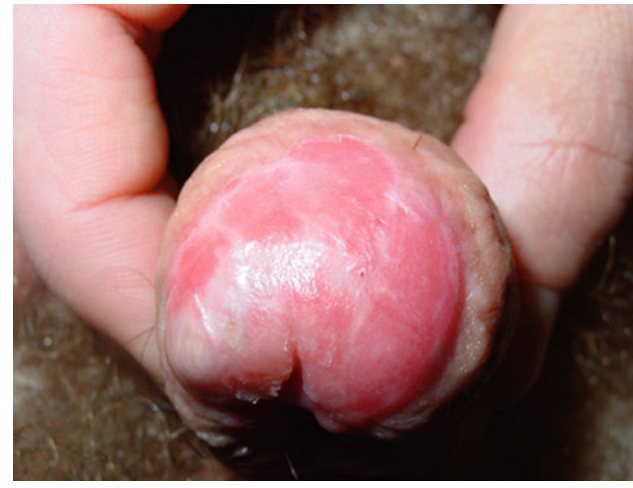


Fig. 4 Glans resurfacing: cosmetic result

were seven (21%) positive margins of which three required glansectomy as were extensive. In the remaining four, they were managed expectantly; however two had recurrences, which were excised and remained disease free. In those patients with negative margins, there were no recurrences with a median follow-up of 10 months (1–69 months) and no reported complications.

Shabbir et al. retrospectively reviewed patients undergoing glans resurfacing using split-thickness skin grafts after partial (PGR) or total glans resurfacing (TGR) for CIS (Shabbir et al. 2011). Intraoperative margins were taken so that they were visibly clear. In total 25 patients were included (10 TGR, 15 PGR). The mean follow-up was 29 months (2–120 months). Forty-eight percent of patients on review of histopathology however had positive margins, thus highlighting one of the difficulties with glans resurfacing in judging where the lesion extends. Overall seven (28%) patients went on to have further surgery (two for extensive CIS at the margin, five for unexpected invasive disease). Consequently four had further resurfacing and three had glansectomy. Overall the recurrence rate was 4% and no progression or effect on mortality observed. The group reported no complications and a graft loss rate of 4%.

Moh's Microsurgery

Moh's micrographic surgery (MMS) was first described by Frederick Edward Moh in the 1930s in relation to the management of skin cancers (Mohs 1991). It was initially termed chemosurgery as he used zinc chloride to fix the specimens in situ. Thin slices of the tumor are taken and the under surface examined to check for margins. The specimens and margins are carefully mapped to ensure complete excision of the tumor. This was a laborious procedure as the tissue had to be left to fix and could take several days. Further it was quite uncomfortable for the patient while this process occurred. In 1974 Tromovitch and Stegman described the procedure using fresh tissue (Tromovitch and Stegman 1978). This meant that the procedure could be performed quicker with less discomfort to the patient. The procedure has been logically applied to penile cancer (Mohs et al. 1985; Brown et al. 1987).

Relatively recent long-term retrospective data of patients treated between 1988 and 2000 with MMS using the fresh tissue technique (Shindel et al. 2007) was provided by Shindel et al. They identified 41 procedures in 33 patients. Tumor stage was Tis in 26, T1 in 4, T2 in 7, and T3 in 4. Median follow-up was 37 months (0.5–214 months) in 25 patients. In patients with CIS, squamous cell carcinoma, verrucous carcinoma, and epidermoid carcinoma, the recurrence rates were 3 (21%), 2 (30%), 2 (66%), and 1 (100%), respectively. The overall recurrence rate was 32%. Two patients progressed mandating more radical surgery. At near 5 years of mean follow-up, the recurrence-free survival rate was 68%, OS 92%, and DSS 96%. No association between initial tumor size and the progression or death rate was found. In terms of complications, there was one infection and one pulmonary embolism, and two had meatal stenosis.

The procedure thus has a reasonable, albeit not insignificant recurrence rate – despite this, however, the uptake of MMS for penile cancer has been poor. This is probably due to a number of factors including time constraints, need for highly specialized training, and other more accessible alternatives.

Lesions Confined to the Prepuce

Circumcision

In tumors <pT2, confined to the prepuce, circumcision offers oncological control with organ preservation. However, this procedure also enables more thorough/easier clinical follow-up up of penile tumors. Circumcision also appears to have a role in the prevention of PeIN. Guidelines recommend that a circumcision be performed for all patients undergoing nonsurgical penile-preserving techniques (Hakenberg et al. 2015).

Lesions Extending to Corpus Spongiosis or Distal Urethra (pT2 or T3 Confined to Glans)

Partial Glansectomy

When tumors are small and cosmesis less of an issue, a wide local excision essentially can be performed. When tumors are larger, or in close proximity to the urethral meatus, a split skin graft or advancement of the shaft skin can provide an acceptable cosmetic result. A distal urethrectomy can be performed for lesions arising from the distal urethra. Creation of a hypospadiac meatus is preferred, but voiding can be impaired. Alternatively, the urethra can be mobilized and reconstructed in the anatomical glans location – chordee however may result. Partial glansectomy should not be performed in cases of CIS, whereby field change may result in up to 50% local recurrence (Horenblas and van Tinteren 1994).

Glansectomy

Anatomically the glans spongious is contiguous with the spongious of the urethra but distinctly separate from the corporal bodies (Fig. 5).

Pisani and Austoni et al. rationalized that lesions anatomically confined to the glanular spongiosus unit could be separated, leaving the corpora functionally intact (Pisani et al. 1994; Austoni et al. 1996). Bracka refined the technique using STSG to improve cosmetic outcomes and subsequently described his improvements in 1996 and later in 2010 (Fig. 6) (Bracka 1996, 2010).

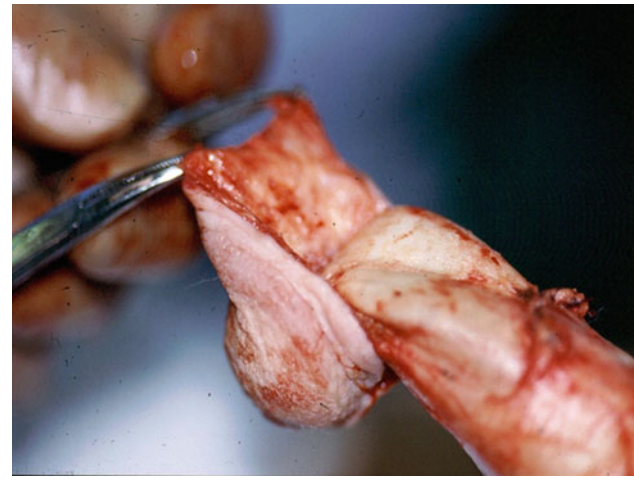
Briefly the patient is placed in a supine position and the thigh on the operating surgeons side shaved. The patient is prepped leaving the thigh and penis exposed. A subcoronal incision is made with an adequate margin to allow safe excision of the penile lesion. Dissection proceeds down to Buck's fascia. The dissection then proceeds distally over Buck's taking care not to enter the spongious until only the urethra remains. In cases where there is concern regarding invasion, the dissection can be performed beneath Buck's and frozen sections taken to confirm margins. The urethra is then transected and splayed over the corporal heads. The penile shaft skin is then sutured to the corporal bodies to create a glans-shaped recipient bed for the graft. A STSG can then be taken from the prepped thigh with a thickness between 0.014 and 0.018 in. and applied carefully using interrupted dissolvable sutures (Fig. 7). There is a variation in techniques adopted for immobilization of the graft; however either quilting the graft or the TODGA dressing (as previously described) has produced excellent results.

Other donor sites have been used including prepuce, urethra, and oral mucosa (Gulino et al. 2007). In cases where the patient has expressed a disinterest in cosmesis or has comorbidity that precludes graft application, the penile skin can be brought up to the urethra with adequate cosmetic results.

Smith et al. prospectively collected data on 72 patients with T1 and T2 penile cancer treated with glansectomy and STSG with a mean follow-up of 27 months (4–68 months) (Smith et al. 2007a). Thirty-seven (61%) patients had resection margins less than 5 mm including 6 (9.8%) with positive margins. Of the six with positive margins, four were observed with no evidence of recurrence up to 23 months. The remaining two showed early recurrence and underwent local excision. There were three (4%) local recurrences (late), all of which were managed with local excision. Only two patients with metastatic disease at presentation died without evidence of local recurrence. Complications included two (3%) patients requiring resurfacing due to graft loss and one patient with stenosis requiring formal urethral dilatation.

O'Kane et al. reported on the results of 25 patients with CIS ($n = 6$), T1 ($n = 15$), T2 ($n = 3$), and T3 ($n = 1$) disease and a mean follow-up of 28 months (10–66 months) (O'Kane et al. 2011). DSS was 92%, and there was only one recurrence (4%) in a patient with G2 pT1 disease. Eleven patients were evaluated regarding their sexual function in a non-validated manner. Nine (82%) of patients reported being

Fig. 5 Glansectomy



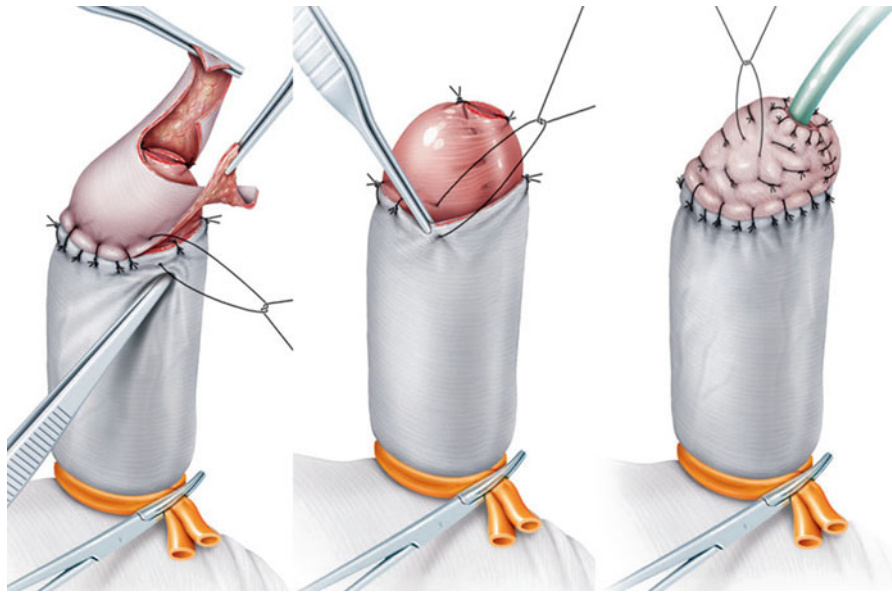


Fig. 6 Placement of split skin graft to neo-glans (Aivar Bracka. Glans resection and plastic repair. BJUI. 2010)

able to achieve erections, and six (55%) continued to be sexually active. The rate of graft failures was 0% – two patients required urethral dilatation for stenosis.

Parnham et al. published a large cohort of patients undergoing glansectomy and STSG alongside a video description of the procedure in 2016 (Parnham et al. 2018). They retrospectively reviewed the records of 177 patients with T1–T3 disease, with a median follow-up of 41.4 months (1.9–155 months). In 17 patients out of 171 patients with known margin status, the margin was positive. Ten were managed with revision surgery, as had overt margins or high-risk features. The remaining seven were managed with surveillance of which one had a local recurrence at. Overall the local recurrence rate was 16/172 (9.3%), with a median time to local recurrence of 8.7 (95% CI: 3.2–19.9) months. Eighteen out of 174 (10.7%) patients died of penile cancer, while

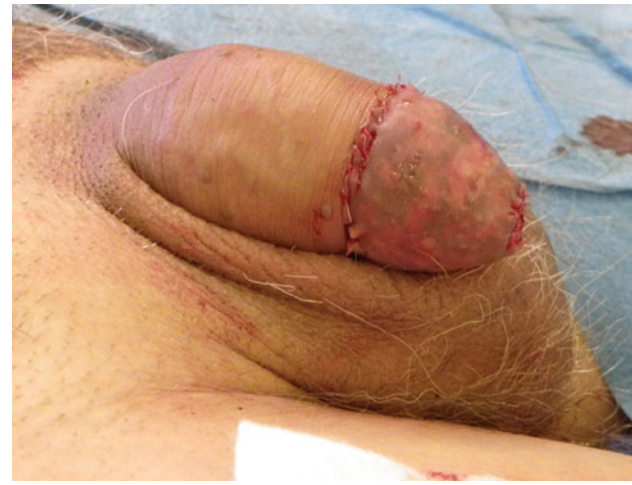


Fig. 7 Final appearance following glansectomy and split skin graft

Table 1 Glansectomy recurrence rates

Investigator	Procedure	Patients (n)	Local recurrence rate	Mean follow-up (mo)
Pietrzak et al. (2004)	Partial/total glansectomy	39	2.5%	16
Brown et al. (2005)	Partial/total glansectomy	5	0	12
Gulino et al. (2007)	Partial/total glansectomy	14	0	13
Smith et al. (2007b)	Partial/total glansectomy	72	4%	27
Palminteri et al. (2007)	Partial/total glansectomy	17	0	32
Morelli et al. (2009)	Partial/total glansectomy	15	0	36
O'Kane et al. (2011)	Total glansectomy	25	4%	28
Parnham et al. (2018)	Total glansectomy	177	9%	41

29 patients in total died during the follow-up period. Regrafting was required in 8.3% of patients. Only one patient required surgical intervention for meatal stenosis. The recurrence and mortality rate was higher than that compared to other studies, although this study included T3 disease as well as a higher percentage of T2 and G3 patients in the cohort (Table 1).

Lesions Extending into Corpus Cavernosa or More Proximal Spongiosum (pT2 or T3: Extending Beyond the Glans)

Partial Penectomy

Depending on patient factors (functional/stretched penile length), erectile function and obesity, as well as tumor factors (grade, stage, location, size), a partial penectomy can potentially render a man unable to penetrate during intercourse, nor able to void in the standing position. Thus during the procedure, assessment needs to be made of whether a perineal urethrostomy may serve the patient better.

A tourniquet may be applied. A circumferential incision is made proximal to the tumor. The incision is extended through corpus cavernosa and spongiosum. Biopsies of the distal remaining tissue must be sent for frozen section. As described earlier, a primary goal of penile-sparing surgery is complete oncological control. Frozen section improves the ability of the surgeon to avoid a positive margin which could lead to either early repeat resection or local recurrence. Although there are no published reports on frozen section in the context of penile SCC, it has an accuracy of 96% in SCC of the head/neck (Du et al. 2016). Ferreiro et al. reviewed 24,880 surgical

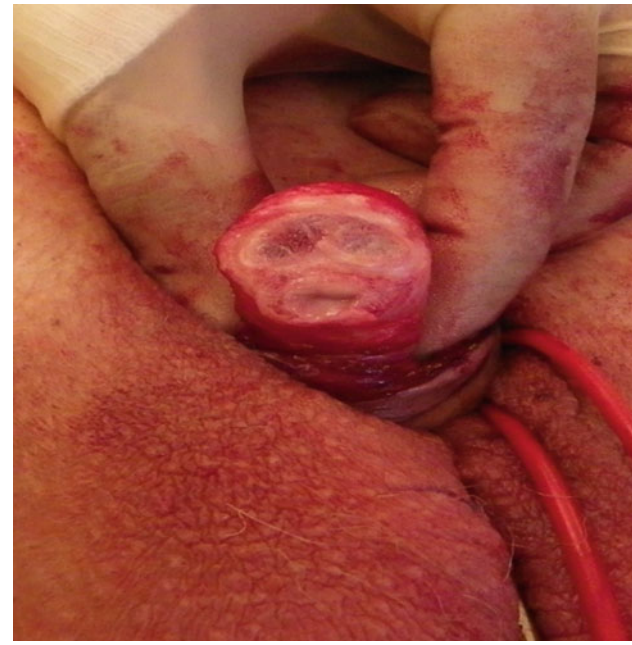


Fig. 8 Partial penectomy: corpora cavernosa and corpora spongiosum with urethra visible

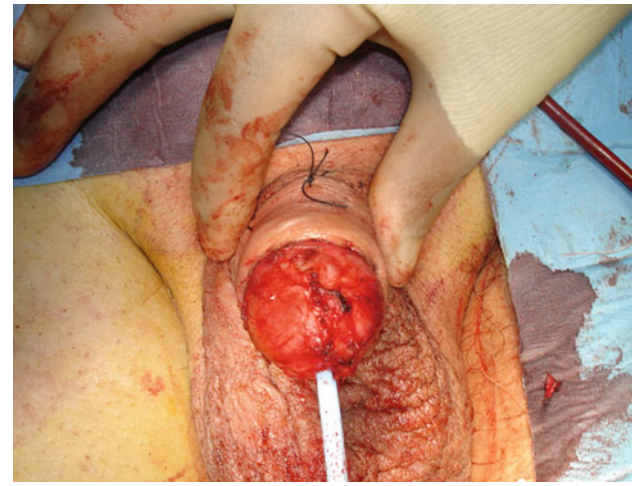


Fig. 9 Partial penectomy: corpora cavernosa closed in preparation for split skin graft

pathological cases at the Mayo Clinic – accuracy exceeding 97% was reported (Ferreiro et al. 1995). However, there is clearly a small but significant failure rate, and patients must be warned of a potential positive margin, despite negative frozen section report.

The corpus cavernosum should be oversewn at least 1 cm proximal to the urethra. Alternatively, a UCAPP procedure (urethral centralization after partial penectomy), as described by Shadev et al., can improve penile stump length and result in a normal appearing neo-glans (Sahdev et al. 2016). In this method, the corpora cavernosa are not oversewn – instead, they are left open and wrapped (ventrally) around the urethra. A small ventral incision of the corporal tunica may help facilitate this wrapping. A STSG is then applied (see "Glansectomy") (Figs. 8, 9, and 10).

As discussed previously, the local recurrence rates are higher for penile-sparing techniques (Table 2). It should be noted that in selected cases, a partial penectomy can be considered

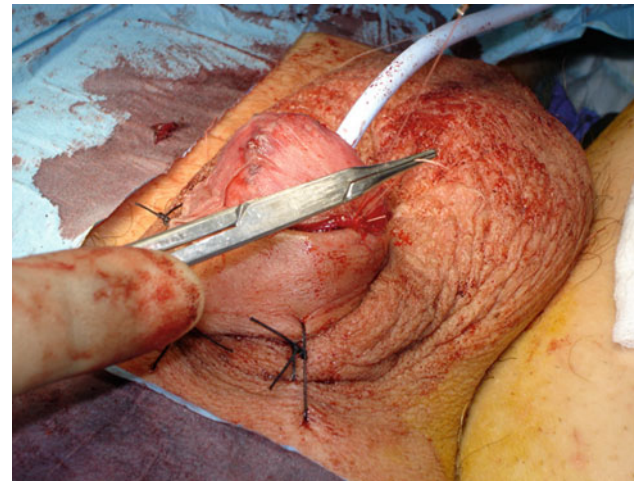


Fig. 10 Partial penectomy: split skin graft being sutured to neo-glans

Table 2 Partial penectomy recurrence rates

Investigator	Patients (n)	Local recurrence rate	Mean follow-up (mo)
Banon et al. (2000)	42	7.1%	67
Ficarra et al. (2002)	30	0	69
Rempelakos et al. (2004)	227	0	>120
Chen et al. (2004)	34	5.8%	37
Korets et al. (2007)	32	3.2%	34
Leijte et al. (2008)	214	5.1%	60.6
Ornellas et al. (2008)	522	4%	11
Veeratterapillay et al. (2015)	49	4%	61

functionally penile sparing, but unlike the other truly sparing techniques, PP tends to demonstrate superior local recurrence rates. A UK supra-regional center reported on 203 patients undergoing treatment for penile cancer from 2000 to 2008. Forty-nine patients underwent partial penectomy, 48 had TP; the local recurrence rate for these two surgeries was 4% (Veeratterapillay et al. 2015), while Korets et al. demonstrated no local recurrence of 32 patients over a mean follow-up of 34 months (Korets et al. 2007) (Table 2).

Conclusion

Changes in our understanding of the local disease process, in particular margins required and the lack of mortality related to local recurrence, have helped mold our current practice. A margin of 5 mm seems reasonable, and although this results in slightly higher local recurrence rates, the morbidity benefits of penile-sparing techniques is clear.

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Lymph Node Management in Penile Cancer

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Abstract

Lymph node metastases are frequently found in patients with penile cancer even in early stages. Since prognosis of patients with lymph node recurrence is extremely poor, sufficient initial lymph node management is the key for the survival of penile cancer patients. Invasive lymph node staging (dynamic sentinel node biopsy or modified inguinal lymph node dissection) is recommended in patients with nonpalpable lymph nodes with pT1G2 tumors or higher stages. In case of palpable inguinal lymph nodes, a radical inguinal lymph node dissection followed by adjuvant chemotherapy is indicated after histological verification of metastases. Patients with fixed inguinal or recurrent lymph node metastases should undergo a neoadjuvant chemotherapy followed by salvage lymph node dissection.

Introduction

Penile carcinoma is a rare tumor entity in Europe and North America with an incidence of 0.1–1.4% (Jemal et al. 2007; Hakenberg et al. 2015). Therefore there are is a paucity of data about lymph node management in patients with penile cancer. Most of the available data derives from single center retrospective series with low number of patients.

Since advanced metastatic penile carcinoma has an extremely poor prognosis every effort should be made to detect and treat this tumor type early in its progression prior to the development of extensive metastases (Hakenberg et al. 2006, 2015; Pizzocaro et al. 2008).

Due to the relevant complication rate of inguinal lymph node dissection, clear guideline recommendations are often ignored in practice resulting in suboptimal treatment outcomes. Various attempts have been made in recent years to reduce the morbidity of surgical lymph node dissection by either reducing the extent of lymphadenectomy or by selecting only patients suited for lymphadenectomy by clinical, pathological, or molecular parameters (Horenblas 2001a; Spiess et al. 2009; Naumann et al. 2005; Protzel et al. 2009).

Especially the extent of inguinal lymphadenectomy remains a matter of controversy. Lymph node metastases are the main known variable affecting patient survival in penile cancer. Since lymph node spread is often not detectable by clinical examination and noninvasive diagnostics, invasive lymph node staging with tissue sampling using either an image-guided biopsy sampling and/or sentinel lymph node biopsy should be recommended in all patients with relevant risk of lymph node spread. Since micrometastasis are frequently found in patients with invasive tumors (even in T1 tumors), recent guidelines recommend dynamic sentinel node biopsy or modified inguinal lymph node dissection in all patients with pT1 G2 tumors and higher (Hakenberg et al. 2015; Naumann et al. 2005). Sufficient intraoperative and postoperative management led to significant reduced complication rates within the last decade (Hakenberg et al. 2015; Protzel et al. 2009).

Lymphatic Spread in Penile Cancer

The lymphatic drainage of the penis leads into the lymph nodes of the inguinal groin. The inguinal lymph nodes of the penis are anatomically divided into the superficial and the deep group. The superficial nodes are found between the subcutaneous fascia and the fascia lata. The anatomically most relevant inguinal lymph node was described by *Rosenmüller* and *Cloquet* located at the medial

side of the femoral vein, marking the transition between inguinal and pelvic regions (Protzel et al. 2009). The deep nodes lie in the region of the fossa ovalis where the greater saphenous vein drains into the femoral vein through an opening in the fascia lata.

Further lymphatic drainage goes into the pelvic nodes around the iliac vessels and in the obturator fossa.

The superficial inguinal region is divided according to Daseler into five anatomical subgroups with the central zone being located at the confluence of greater saphenous and femoral vein. The four other zones were described as lateral superior, lateral inferior, medial superior, and medial inferior (Daseler et al. 1948).

In penile cancer, lymph node metastasis is most frequently found in the superior and medial region and in the central zone of Daseler (Protzel et al. 2009; Cabanas 1977; Horenblas et al. 2000).

Leijte et al. examined lymphatic drainage using SPECT-CT imaging in 50 clinically node-negative penile cancer patients. The first drainage nodes (sentinel nodes) were localized only in the superior and central Daseler zones of the inguinal region (Leijte et al. 2008a).

Clinical decisions for lymph node management in penile cancer are based on retrospective and prospective clinical studies showing that penile cancer like other squamous cell carcinomas has a clear tendency for locoregional growth with early and exclusively lymphatic spread according to the anatomical lymphatic drainage described above (Horenblas 2001b). Skip lesions has not been described. Hematogenous spread is only found late and in advanced cases.

Incidence of Lymph Node Metastases in Penile Cancer

Several studies have shown that in penile cancer, lymphatic spread is related to tumor grade, local disease stage, and the type of local tumor present. There is a strong association between the occurrence of lymph node metastasis and higher clinical grade of the primary tumor (0–29% in grade 1 vs. 33–50% in grade 3). Still the prognostic value of pathological grading remains under discussion since studies have shown a high interobserver variability even under specialized uro-pathologists. There is an ongoing discussion about the prognostic value of the local tumor stage. Some older studies have shown a strong increase in the rate of lymph node metastases with a higher local stage, with 50–100% node-positive cases in pT3/pT4 cases and 50–70% in pT2 disease (Protzel et al. 2009; Horenblas 2001b; Lont et al. 2007; Hegarty et al. 2006; Leijte and Horenblas 2009; Lopes et al. 1996a). Since the recent TNM classification has a new differentiation between T2 (corpus spongiosum) and T3 (corpus cavernosum), the prognostic value will be much better in further studies.

The Prognostic Significance of Inguinal Lymph Node Disease

The presence of lymph node metastasis in patients with penile cancer is significantly associated with an adverse prognosis. The extent of lymphatic spread as well as extranodal tumor growth and pelvic nodal involvement are very important prognostic factors (Lont et al. 2007).

Cancer-specific 3-year survival in inguinal node-negative and pN1 patients is almost 100% and is reduced to 73% in pN2 node-positive patients (Hegarty et al. 2006).

Prognostic Factors for Lymph Node Involvement

Histopathological Parameter

Since the standard histopathological parameters of the primary tumor (pT stage, grade, depth of invasion, and histological subtype) have shown contradictory results regarding the prognosis of lymph node spread – especially concerning pT stage and grade – other prognostic parameters available from the primary tumor tissue would be useful for the indication of lymph node dissection (Theodorescu et al. 1996; Slaton et al. 2001). Lymphovascular and vascular invasion in the

tumor were reported to be associated with lymph node metastases (Slaton et al. 2001; Ficarra et al. 2005). However, there have been contradictory results for lymphovascular invasion in other studies (Kroon et al. 2005a).

To improve the process of clinical decision concerning lymphadenectomy, a nomogram attempting to predict lymphatic disease in penile cancer has been developed by Ficarra et al. (Ficarra et al. 2006). This has to be critically discussed since according to this nomogram, the risk of metastases for intermediately differentiated and superficially spreading tumors is higher than that for poorly differentiated and vertically growing tumors. Unlike in prostate cancer, no large data driving such treatment decisions are available in penile cancer and therefore the very nature of the disease makes it difficult to devise reliable nomograms and predictive models.

Molecular Parameters

Like other tumor entities penile cancer is characterized by multiple genomic and metabolic changes. Recent studies have shown that some of them are associated with a higher risk of lymph node metastases (Protzel et al. 2007a, b, 2008; Kayes et al. 2007; Lont et al. 2006; Bezerra et al. 2001; Berdjis et al. 2005; Guimaraes et al. 2007). Especially defects and loss of expression of tumor suppressor genes play an important role in metastatic spread as well as epithelial mesenchymal transformation (EMT). Loss of heterozygocity and/or promoter hypermethylation of the tumor suppressor gene p16 is significantly associated with the occurrence of lymph node metastases. A reduced KAI1/CD82 expression has been reported to be predictive of lymph node involvement (Protzel et al. 2008). Several studies have implicated p53 status as a prognostic factor (better survival and less likelihood of node-positive disease with p53-negative tumors (Lopes et al. 2002; Martins et al. 2002). Human papilloma virus (HPV) DNA status has shown conflicting results in several studies (Lont et al. 2006; Bezerra et al. 2001). For Ki-67, a correlation with local tumor grade and stage has been found but conflicting results regarding node-positivity have been reported (Berdjis et al. 2005; Protzel et al. 2007b; Guimaraes et al. 2007).

In the future, a panel of tumor suppressor genes and EMT markers may be more reliable in predicting individual lymphatic spread.

Diagnosis of Lymph Node Disease

The dilemma is that lymph node disease in penile cancer is clinically diagnosed only in cases with a high tumor burden of lymphatic spread. Minimal lymphatic spread and micrometastatic disease evades clinical diagnosis but remains crucial in determining the prognosis in an individual case. Up to 25% of patients with nonpalpable lymph nodes harbor micrometastatic disease (Protzel et al. 2009).

Patients with palpable inguinal nodes also present uncertainties in that up to 30–50% of them will not have metastatic disease but have inflammatory lymph node swelling secondary to penile cancer. Other patients will have an inflammatory swelling of inguinal lymph nodes secondary to intercurrent inflammation of the lower limbs such as pedal fungal disease. This may be particularly true for patients with locally advanced penile cancer who often are in a state of general physical neglect.

Imaging studies are of no value in the diagnosis of inguinal lymph node metastases. Although metastatic lymph nodes can show typical radiological signs, common imaging techniques such as CT scan or conventional MRI are unable to detect micrometastases (Protzel et al. 2009; Singh et al. 2007). Scher et al. used ^{18}F-FDG PET/CT and detected 15 of 16 positive lymph nodes in 5 patients (sensitivity 80%, specificity 100%) (Scher et al. 2005). In a recent update of the study, PET/CT identified 18 of 21 histologically positive lymph nodes (sensitivity 75%), but the performance of this test is significantly better in the presence of palpable inguinal adenopathy (Scher et al. 2008). Much larger studies are required to assess such techniques properly.

The most widely studied technique is that of ultrasound-guided fine needle aspiration and

cytology. Saisorn et al. reported a sensitivity of 93% and specificity of 91% for palpable lymph nodes (Saisorn et al. 2006). However, in cases of nonpalpable lymph nodes, only 9 of 23 lymph node metastases (sensitivity 39%, specificity 100%) were detected by ultrasound-guided fine needle aspiration cytology in another study (Kroon et al. 2005b). Clearly, this technique is unreliable in this setting.

Management Strategies

Surveillance

Patients with low stage tumors and clinically unaffected inguinal nodes have in the past often undergone surveillance strategies, i.e., follow-up examinations with exploration of the inguinal region when palpable nodes develop during follow-up. Indeed, the current EAU guidelines recommend this approach in patients with superficial and well-differentiated tumors: pTis, pTa, pT1a G1 with superficial growth and without vascular invasion (Hakenberg et al. 2015).

Recent series have clearly demonstrated that survival in patients with pT2/pT3 penile cancer is better with immediate surgical lymph node staging (and subsequent lymphadenectomy if positive nodes are found). Thus, Lont et al. reported a 91% 3-year disease-specific survival in patients with pT2/pT3 disease managed with dynamic sentinel node staging compared to 79% in a historical series managed by surveillance (Lont et al. 2003). The same group reported for pT2/pT3 patients with nodal metastases a 35% disease-specific 3-year survival for those undergoing late lymphadenectomy after surveillance compared to 84% in patients who underwent early lymphadenectomy and were found to have nodal microscopic disease. Similarly, in the largest retrospective series reported so far (700 patients from 2 centers), Leijte et al. reported a markedly higher risk of recurrence in patients undergoing surveillance management (Leijte et al. 2008b). Clearly, early appropriate surgical staging and management of regional nodes is of vital importance in penile cancer.

Surgical Lymph Node Staging

The direct histological examination of inguinal lymph nodes remains the most reliable method to assess their involvement by metastases. Several approaches varying in extent of lymph node sampling exist.

Sentinel Node Biopsy

The idea of sentinel lymph node dissection in penile carcinoma was initially developed by Cabanas after a study of lymphangiograms and anatomic dissections (Cabanas 1977). The static detection of sentinel lymph node was unfortunately characterized by high false-negative rates.

The successful concept of radioguided detection of the marked first drainage node (sentinel node) after injection radioactive tracers in breast cancer and melanoma technique led to first studies concerning dynamic sentinel node biopsy (DSNB) in penile cancer (Allen et al. 2001; Statius Muller et al. 1999). Both groins can content more then one sentinel node. Technetium-99 m nanocolloid is injected around the penile tumor intradermally one day before or at the day of surgery. Patent blue dye can be injected intradermally additionally. The sentinel node is identified by a nuclear scanner and can be fused with a CT scan in single proton emission computed tomography. The sentinel lymph node is detected intraoperatively with a gamma ray detection probe. The lymph node gets preparated and removed. In case of positive histology, a radical inguinal lymph node dissection is performed.

The technique has been initially studied by the group from the Netherlands Cancer Institute. After a initial high rates of nondetected lymph node metastases (17–22%), false-negative rates were significantly reduced by modifications of the technique (4.8%) (Tanis et al. 2002; Kroon et al. 2004). The results have been revealed by several high volume centers, while results in smaller studies remain complicated. Therefore this technique is recommended for centers performing at least 20 procedures/year (Ficarra and Galfano 2007).

Modified Inguinal Lymphadenectomy

Catalona developed a modified approach of lymph node dissection in order to reduce the complication rates. The technique is based on shorter skin incision and limitation of the dissection (exclusion of the area lateral to the femoral artery and caudal to the fossa ovalis). The saphenous vein is preserved (Protzel et al. 2009; Catalona 1988).

The rate of skin flap necrosis, lymphoedema, and deep venous thrombosis was significantly reduced compared to a historical control groups of radical lymphadenectomy (skin necrosis 2.5% vs. 8.6% in radical lymphadenectomy, lymphoedema 3.4% vs. 22.4%, thrombosis 0% vs. 12%) (Bouchot et al. 2004; Lopes et al. 1996b; Wespes et al. 1986; Bevan-Thomas et al. 2002).

However, reduction of the dissection area increases the risk of false-negative cases. Therefore, a combination of modified lymph node detection and DSNB maybe discussed for high risk cases.

Radical Inguinal Lymphadenectomy

The dissection field of the classic radical inguinal lymphadenectomy reaches from the superior margin of the external ring to the anterior superior iliac spine, laterally from the anterior superior iliac spine extending 20 cm inferiorly, medially to a line drawn from the pubic tubercle 15 cm downwards. In former publications, the long saphenous vein was divided, but there is no clear need or data to do so, except in cases of direct tumor infiltration of the vessel. The femoral vessels can be covered by the sartorius muscle after dissection of the complete lymph nodes of the area (the superficial lymph nodes in all five anatomic groups described by Daseler and the deep inguinal nodes) (Protzel et al. 2009). Infiltrated parts of the cutis have to be dissected. Skin rotation flaps and myocutaneous flaps have been used for primary wound closure.

The radical lymphadenectomy is associated with a higher morbidity. Wound infection, skin necrosis, wound dehiscence, lymphoedema, and lymphocele are relevant and frequent complications (Bevan-Thomas et al. 2002; Ravi 1993). Careful skin handling and optimal thickness of skin flaps as well as a direct (low pressure, continuous) vacuum sealing after wound closure can help to reduce the rate of complications.

Video Endoscopic Lymphadenectomy and Robotic-Assisted Inguinal Lymphadenectomy

This recently described techniques are derived from laparoscopic/robotic surgery and have been evaluated several studies (Tobias-Machado et al. 2007, 2008; Sotelo et al. 2007; Gkegkes et al. 2019). It seems to carry a lower risk of skin complications but a relevant risk of lymphocele formation. An assessment of this technique for its oncological reliability remains to be done by ongoing studies.

Pelvic Lymphadenectomy

The pelvic lymph nodes are the second echelon of lymphatic drainage in penile cancer. Direct lymphatic drainage to pelvic lymph nodes skipping inguinal lymph nodes has not been detected for penile cancer thus far (Protzel et al. 2009; Cabanas 1977; Leijte et al. 2008a). Therefore inguinal lymph nodes are predicting the status of pelvic lymph nodes. In case of absence of inguinal node metastasis, pelvic lymphadenectomy has not to be performed. In patients with metastatic inguinal nodes, predictors for potential involvement of pelvic nodes are needed. The number of positive inguinal lymph nodes and extracapsular extent of metastatic disease in involved nodes have been shown to be of predictive value in determining the risk of occult pelvic lymph node metastases but there remains an ongoing discussion about the relevant number of positive inguinal nodes predicting this (Lont et al. 2007). Since the rate of positive pelvic nodes has been reported to be 15.2% in cases with <2 positive inguinal nodes and 18.6% for <3 inguinal nodes involved, pelvic lymphadenectomy is

recommended for 2 or more positive inguinal nodes by the EAU guidelines and for 3 and more positive lymph nodes by the NCCN guidelines (Zargar-Shoshtari et al. 2016). Pelvic lymph node dissection should be performed when extracapsular extent in inguinal nodes is seen. Lughezzani et al. showed a relevant higher risk of pelvic involvement for patients with inguinal lymph node metastatsis with a diameter of 30 mm or higher. In cases of very aggressive histological subtypes of penile cancer (grading G3/4 or sarcomatoid subtype) or in case of strong expression of p53 a pelvic lymph node dissection should be considered if any inguinal node is involved (Lughezzani et al. 2014).

There is no clear data for unilateral inguinal lymph node involvement whether pelvic lymphadenectomy should be done bilaterally or should be restricted to the ipsilateral side only (Zargar-Shoshtari et al. 2015). Pelvic lymphadenectomy may be necessary as simultaneous procedure in cases of positive pelvic lymph nodes on whole body PET-CT scan or as a secondary procedure. It can be performed extraperitoneally by a midline suprapubic incision or as a laparoscopic procedure.

Morbidity of Lymphadenectomy

Surgical morbidity is frequently found after radical inguinal lymphadenectomy. In former publications, wound infection, skin necrosis, wound dehiscence, and lymphocele have been reported in a high proportion of cases (Protzel et al. 2009; Bevan-Thomas et al. 2002). This rate was significantly reduced by modified approaches and the development of new techniques.

Modern intra- and postoperative management with improved knowledge of the potential complications as well as vacuum sealing of the wounds led to a reduction of morbidity. The modified inguinal lymphadenectomy showed a markedly decreased rate of complications (in recent series 6.8% early and 3.4% late complications). In a study by Bouchot et al., only 8/118 patients suffered any complications and these were only minor (Bouchot et al. 2004).

Nevertheless, inguinal lymphadenectomy still remains a procedure associated with local complications. The prophylactic application of antibiotics is recommended. Vacuum drains should be applicated, and the duration of drainage has to be adapted to the volume of drainage. Elastic stockings and/or pneumatic stockings should be used as well as postoperative anticoagulation. A review of management techniques for minimizing complications with lymphadenectomy was given by Spiess et al. (2009).

Reported complications rates for low invasive DSNB of around 14–15% compare favorably with those of modified and radical inguinal lymphadenectomy (Protzel et al. 2009; Perdona et al. 2005). Leijte et al. report a complication rate of only 5.7% (2007a). A prospective controlled comparison between DSNB and modified or radical inguinal lymphadenectomy has never been done.

Clinical Approach for Lymph Node Management

For clinical decision, patients are divided into three subgroups: patients with clinically normal inguinal nodes, patients with palpably enlarged nodes, and patients with enlarged and fixed nodes. In patients with enlarged and fixed nodes, metastatic disease has to be assumed, while patients with just enlarged nodes will harbor metastases in a relevant number of cases. The prognostic most difficult group is that with clinically unsuspicious nodes. Micrometastasis may be present in up to 25% of the patients.

Patients with Nonpalpable Inguinal Lymph Nodes

Lymph node dissection for all patients with nonpalpable lymph nodes would result in an overtreatment in over 75% of cases. Therefore, radical bilateral lymphadenectomy is not warranted in these patients.

The current EAU guidelines which were last updated in 2017 recommend an invasive lymph

node staging in all patients with pT1 G2 tumors or higher. Surveillance is only an option in patients with good compliance for follow-up considered at low risk based on pathological factors of tumor stage (pTis, pTa, and pT1 G1). Patients have to be informed about the risk of regional recurrence (Hakenberg et al. 2015).

Patients with pT1G2 tumors or higher invasive lymph node staging must be recommended since noninvasive lymph nodes staging (MRI, CT, and PET scan) are not able to detect micrometastasis and regional recurrence is associated with extremely poor prognosis. Options for invasive lymph node staging are modified inguinal lymphadenectomy or dynamic sentinel lymph node biopsy (DSNB). DSNB is only recommended for experienced centers due to the high number of false negative patients in smaller studies.

Patients with Palpable Lymph Nodes

In patients with penile cancer and enlarged palpable inguinal nodes, metastatic disease has to be assumed. The rate of positive nodes has been described with 50% or higher in these patients (Protzel et al. 2009; Hegarty et al. 2006). A course of antibiotic treatment in order to reduce lymph node swelling due to potential infection is not recommended any more as it has never been shown to safely clarify the nature of lymph node swelling in penile cancer (Horenblas 2001b).

Ultrasound-guided fine needle biopsy of the enlarged lymph nodes is an excellent, rapid, and easy option to clarify the histology in most of the cases. If the biopsy is negative, it needs to be repeated or surgical staging by excision biopsy has to be done. The approach of excision biopsy has to be discussed as a general option since a modified inguinal lymphadenectomy has to done in all cases and can be combined with fresh frozen section excision biopsy of the enlarged lymph nodes. In case of positive lymph nodes, the procedure should be extended to a radical lymph node dissection.

Dynamic sentinel lymph node biopsy is not reliable in this group of patients due to drainage blocking by metastatic lymph nodes (Hakenberg et al. 2015; Protzel et al. 2009; Kroon et al. 2004). Thus, in all patients with bilateral palpable enlarged lymph nodes, early lymphadenectomy should be performed on both sides (Hakenberg et al. 2015). In case of contralateral nonpalpable lymph nodes, a modified lymph node dissection should be done for the clinically unaffected side.

The role of radiochemotherapy for positive inguinal lymph nodes is currently being examined in a prospective randomized international study (International Penile Cancer Advanced – InPACT trial) run by the EORTC and aiming to definitely address the benefit if any of perioperative (neoadjuvant and adjuvant) systemic chemotherapy, radiotherapy, and pelvic lymphadenectomy.

Patients with Fixed Inguinal Lymph Nodes

The prognosis of patients with fixed metastatic lymph nodes has been improved in the last years due to new multimodal approaches. They should be managed by neoadjuvant chemotherapy followed by bilateral radical ileoinguinal lymphadenectomy in responders, i.e., deemed resectable with anticipated complete tumor removal (Hakenberg et al. 2015). In case of clinical response to chemotherapy followed by complete resection of residual lymph nodes, long-term survivors have been described (Bouchot et al. 2004). The prognosis of nonresponders is extremely poor, and large tumor resection procedures have to be avoided since there is no clinical benefit for survival, and the patients are often suffered from severe complications in their remaining life time. New options of smart drugs including check point inhibitors are investigated in ongoing clinical studies.

Conclusions

Sufficient lymph node management plays a key role for survival of patients with penile cancer since early detection and dissection of lymph node metastasis improves their prognosis. Efforts should be made to ensure that lymph node is performed according to current guidelines.

Surveillance strategies are only recommended in well-informed low-risk patients (<pT1 G2 tumors). In all other patients with clinically unaffected nodes, invasive lymph node staging is necessary. Dynamic sentinel node biopsy seems to be "low morbidity procedure" for lymph node staging but should only be routinely performed in specialized centers. A modified bilateral lymphadenectomy should be performed for all cases with pT1G2 or higher stages with clinically unaffected nodes in low volume centers. Patients with tumor positive inguinal nodes have to undergo radical inguinal lymphadenectomy on the positive side and invasive staging on the contralateral side. Pelvic inguinal lymphadenectomy should be performed if more than two inguinal nodes are metastatically involved. In patients with fixed and enlarged inguinal lymph nodes, neoadjuvant chemotherapy followed by salvage lymph node dissection in responders improves the prognosis. In those nonresponders, consideration of clinical trials, palliative radiotherapy, or palliative/supportive care is encouraged.

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Role of Neoadjuvant and Adjuvant Chemotherapy in Penile Cancer

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Contents

Abstract

The development of clinically or pathologically involved regional lymph nodes represents the most clinically impactful event in patients with penile squamous cell carcinoma (PSCC), and prognosis is dismal despite adequate treatment. Surgery, the mainstay of treatment, is insufficient as a stand-alone option in most cases, and multimodal approaches are recommended for these patients.

Additionally, huge uncertainties still characterize two important details of surgical extent: the need for pelvic extent and the role of contralateral lymphadenectomy.

Despite chemotherapy activity is frustratingly poor in PSCC, there are evidence in the literature supporting its use in the neoadjuvant or adjuvant setting in patients with extensite lymph node involvement. Conversely, very limited data are available regarding the use of perioperative radiotherapy on the inguinal lymph nodes. Therefore, clinical trials and multidisciplinary collaboration are needed in PSCC, along with multicenter collaborations aimed at identifying the optimal therapeutic pathways in this rare and complex tumor.

Keywords

Penile cancer · Squamous cell carcinoma · Neoadjuvant therapy · Adjuvant therapy

Conflict of Interest Statement

None of the authors have a relevant conflict of interest to disclose.

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Background for Perioperative Treatments in Penile Cancer

The development of clinically or pathologically involved regional lymph nodes represents the most clinically impactful event in patients with penile squamous cell carcinoma (PSCC, Fig. 1), and prognosis is dismal despite adequate treatment (Culkin and Beer 2003; Sonpavde et al. 2013; Necchi 2017). Surgery, the mainstay of treatment, is insufficient as a stand-alone option, and multimodal approaches are recommended for these patients. Additionally, huge uncertainties still characterize two important details of surgical extent: the need for pelvic extent and the role of contralateral lymphadenectomy.

Upon these surgical controversies, for patients with locally advanced disease, i.e., regional lymph node involvement or unresectable bulky primary tumors, clinical guidelines and trial designs recommend the administration induction chemotherapy, prior to radical surgery (Hakenberg et al. 2015; National Comprehensive Cancer Network). Additionally, outcomes are poor for patients who experience relapse after surgery or have extensive involvement of the locoregional lymph nodes (i.e., involvement of fixed inguinal lymph nodes or pelvic lymph nodes), and new therapeutic modalities are needed for such patients (Horenblas 2011; Trabulsi and Hoffman-Censits 2010).

To date, inguinal lymph node dissection, with or without the extension to pelvic lymph nodes, systemic treatments, and radiotherapy, has not demonstrated to improve survival; thus, curing advanced disease often requires a multimodal approach. Multiple neoadjuvant chemotherapies have shown moderate activity: the highest reported objective response rates (ORR) are approximately 50%, but relapse occurs in the majority of cases, and long-term remission is rare.

Importantly, the optimal timing of chemotherapy and radiotherapy administration with respect to lymph node dissection is still unclear, and the results of multiple small studies are conflicting (Necchi et al. 2017a). Usually, neoadjuvant therapy is the preferred treatment approach because tumor debulking can facilitate curative surgery and allow for assessment of the pathological response to chemotherapy. Pathological complete response (CR) is a surrogate for overall survival (OS) in these patients and is a reliable end point for phase 2 trials (Dickstein et al. 2016). Although the efficacy of adjuvant chemotherapy has only been evaluated in small studies that used obsolete chemotherapy regimens, that treatment approach

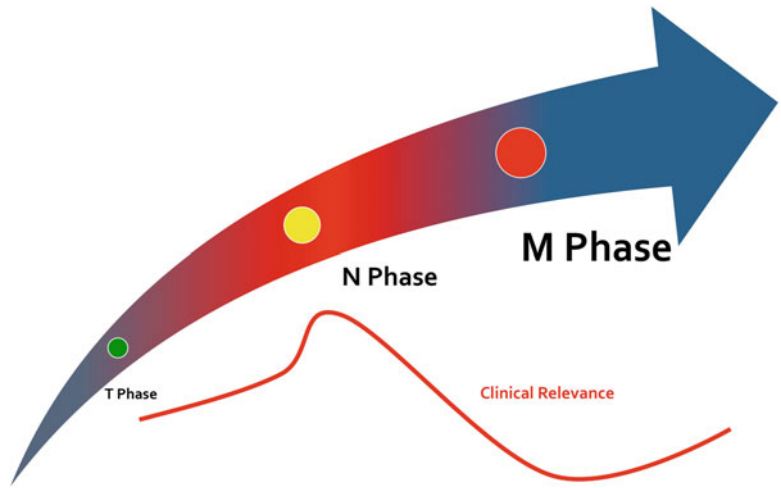

Fig. 1 Disease course of penile squamous cell carcinoma and prognostic relevance of disease extent in clinical practice. Legend: red line indicates the most impactful stage of disease in penile cancer, which is represented by the lymph node involvement. In fact, despite the development of distant metastases may be even more detrimental on patients' prognosis, such an occurrence is very rare, and for most of those men who are diagnosed or who develop advanced disease, we primarily refer to the occurrence of regional (i.e., inguinal or iliac) adenopathies

may benefit select high-risk patients, such as those with pathologically involved pelvic lymph nodes (Sharma et al. 2015). Many of the uncertainties regarding treatment for advanced PSCC described above may be clarified by the results of an ongoing prospective international study (i.e., the International Penile Advanced Cancer Trial, InPACT, NCT02305654). That study aims to evaluate the impact of neoadjuvant chemotherapy alone or in conjunction with radiotherapy in patients with lymph node-positive disease. However, until those results are published, information can only be obtained from retrospective analyses.

Results Obtained with the Use of Perioperative Chemotherapy

Neoadjuvant Chemotherapy

Presence of bulky or fixed inguinal lymphadenopathy uniformly signifies metastatic disease, and only a small portion of these patients will benefit from surgery as a monotherapy. Presurgical systemic therapy in these patients is an attractive treatment paradigm because it allows timely delivery of therapy to treat systemic disease, results in volume reduction of inguinal lymphadenopathy, and facilitates future surgical consolidation. Several retrospective series using various chemotherapeutic agents report an ORR that range 20–50%, including some clinical CR. As of today, the first option for neoadjuvant chemotherapy is represented by the combination of paclitaxel, cisplatin, and ifosfamide (TIP) or that with docetaxel, cisplatin, and 5-fluorouracil (TPF) (Pagliaro et al. 2010; Nicolai et al. 2016; Djajadiningrat et al. 2015; Nicholson et al. 2013). TIP chemotherapy yields Level 2 evidence in the guidelines (i.e., the highest available evidence) based on the results of an open-label, single-arm, phase 2 study that was conducted in 30 patients at the MD Anderson Cancer Center (Pagliaro et al. 2010). Conversely, TPF regimen is supported by several retrospective studies and some small prospective trials. Efficacy results are substantially overlapping between the two regimens, although the higher incidence of adverse events related to TPF administration claims further investigation in this patient category, usually represented by frail, unfit, elderly patients. Interestingly, no significant difference in any outcome was seen between TPF and PF chemotherapy or any other regimen in the largest published retrospective study on perioperative treatments in PSCC, although the major limitation of the retrospective nature of the data should be acknowledged (Necchi et al. 2017a). Most noteworthy, pathological complete responses (pCR) have been reported in about 15% of cases with the use of triple combination regimens, either TIP or TPF. It should be noted, however, that the role of pCR as a surrogate of improved OS, which was claimed in some studies, is still undetermined.

Lower ORR results were obtained in two prospective phase 2 studies that enrolled a mixed population of locally advanced and metastatic patients: the first with TPF chemotherapy in the UK CRUK/09/001 trial, showing an ORR of 38.5% in 26 patients, and the second with cisplatin and irinotecan doublet, sponsored by the European Organisation for the Research and Treatment of Cancer (EORTC), whereby 30.8% ORR in 26 patients was obtained (Theodore et al. 2008).

Additionally, small retrospective studies have examined various chemotherapy regimens in the perioperative and metastatic setting, including bleomycin, vincristine, methotrexate (BVM) combination and bleomycin, methotrexate, and cisplatin (BMP) triplet (Corral et al. 1998; Hakenberg et al. 2006; Dexeus et al. 1991; Haas et al. 1999; Pizzocaro and Piva1988). These regimens are not recommended nowadays in PSCC.

Adjuvant Chemotherapy

Very little is known about the outcomes of adjuvant chemotherapy after regional lymphadenectomy in patients with high-risk features like those with pelvic lymph node involvement, extranodal extension, bilateral disease, and large lymph node metastases. The current European Association of Urology (EAU) guidelines state that adjuvant chemotherapy with a triple-drug regimen is recommended whenever a curative treatment is aimed for (Hakenberg

et al. 2015). Although the few available results seem to suggest an improvement in survival, they are mainly biased by the use of obsolete chemotherapy (Pizzocaro and Piva 1988). Long-term disease-free survival occurred in 84% of 25 consecutive patients with lymph node extent from penile SCC treated with adjuvant BVM combination in the years 1979–1990. These findings suggested an improvement in outcomes compared to the 39% long-term survival obtained in a similar population of 38 consecutive patients who underwent radical lymph node dissection from 1960 to 1978.

More recently, based on the results obtained in the neoadjuvant setting, the National Comprehensive Cancer Network (NCCN) guidelines on penile cancer, version 1.2017, suggest to give four courses of TIP, adjuvantly, if it was not given preoperatively and the pathology shows high-risk features. Yet the results of the same chemotherapy when administered in the adjuvant setting have been presented in very few patients, and no definitive conclusion could be advocated. Substituting ifosfamide with 5FU, similarly to what has been reported in head and neck SCC, has proven to be also effective, although tolerability was a major concern in multiple retrospective studies. To our knowledge, the largest experience on a single chemotherapy regimen administered in the postoperative setting would support the use of TPF chemotherapy, based on the results of a single-institution experience from the National Cancer Institute of Milan, Italy (Nicolai et al. 2016). In this study, in spite of multiple inherent biases due to the retrospective nature of the data, survival estimates between pre- and postoperative TPF groups trended to significance in favor of the adjuvant group, and such findings seemed to be independent from clinical prognostic factors. Additional results from multiple institutions have been conducted in PSCC. In particular, the administration of adjuvant chemotherapy has proven to be independently associated with an improved OS in cases with the evidence of pelvic lymph node involvement (Sharma et al. 2015). In general, when looking at the available studies, the long-term survival of patients who have received multimodal therapy seems longer than that reported in patients who have received surgery without any chemotherapy. In the absence of prospective, randomized studies, if less than 10% of patients could achieve long-term survival according to many surgical case series, 10–30% were reported to be alive at long-term whenever modern chemotherapy was added to surgery.

Most noteworthy, according to the experience of adjuvant TPF from Milan investigators, the immunohistochemical expression of TP53 in lymph node metastases seemed to be associated with a shorter overall survival in TPF-treated patients (Necchi et al. 2016a). These findings represented a call for additional studies on the role of TP53 expression in PSCC. Indeed, improvements in the prognostic allocation of patients with locally advanced PSCC are awaited, possibly including the role of the molecular profiling of tumors to allow personalized medicine approaches (McDaniel et al. 2015; Ali et al. 2016; Necchi et al. 2016b).

Combining Radiotherapy with Perioperative Chemotherapy: Available Findings

Selected patients with inoperable, locally advanced PSCC may be considered appropriate for a concurrent chemoradiation approach, although high disease burden may lead to the initiation of systemic chemotherapy alone. However, no prospective studies have been conducted to investigate outcomes with concurrent chemoradiation for locoregionally advanced disease, and only anecdotal reports exist (Franks et al. 2011). According to a retrospective analysis of patients with PSCC receiving concurrent chemoradiotherapy for unresectable locoregionally advanced disease, no distinct effect of concomitant radiotherapy could be identified (Pond et al. 2014). Likewise, there was no statistically significant difference in any outcome between patients who received chemotherapy alone or in combination with chemoradiation. However, this analysis was also limited by the small sample size and the retrospective nature of the data. Experts in the field acknowledge the presence of an ongoing debate about the use of postoperative

radiotherapy in lymph node-positive patients. The data available in the literature indicate that men do not benefit from adjuvant inguinal radiotherapy in terms of decreased local recurrence or increased survival. The ongoing InPACT study is also evaluating the role of adjuvant radiotherapy in patients with locally advanced PSCC, and the results of that study are highly anticipated.

Neoadjuvant Therapy as the Foundation for New Drug Development in Penile SCC

Among the most suitable therapeutic targets in PSCC, epidermal growth-factor receptor (HER/EGFR) family genes did represent the objective of studies of first-generation anti-EGFR compounds, and a few case reports or small case series have been reported (Necchi et al. 2011, 2016c; Carthon et al. 2014). The use of a second-generation pan-HER tyrosine kinase inhibitor (TKI), like dacomitinib, proved the most promising results in this field, combined with surgery. The ORR in a phase 2 study that enrolled 28 patients was 32.1% (Necchi et al. 2017b). Unfortunately, no pCR were reported in this study, but the first-line/neoadjuvant platform demonstrated to be feasible and promising to test new drugs with the aim of replacing chemotherapy. Next studies will have to evaluate longer treatment duration, as well as the association of anti-HER compounds with chemotherapy or radiotherapy to improve the outcomes. A clinical trial of afatinib, another pan-HER TKI, is currently recruiting patients as second-line therapy in the USA (NCT02541903). Combined results from these studies may elucidate the role of HER-targeting throughout the treatment course of PSCC patients.

The next step in the development of new drugs in PSCC may be represented by the advent of immune checkpoint inhibitors. Early findings from retrospective studies suggested that the expression on programmed cell death ligand-1 (PD-L1) is frequent in this tumor and seems to have a negative prognostic impact (Udager et al. 2016; Ottenhof et al. 2017). A phase 2 trial with pembrolizumab, an anti-PD1 monoclonal antibody, is currently recruiting patients in the USA, and results are awaited (NCT02837042). Notably, mature results from the expansion cohort of the phase 1 trial of cabozantinib, nivolumab, and ipilimumab combination in urothelial and rare genitourinary cancers reported significant clinical responses obtained in a few patients enrolled with PSCC (Nadal et al. 2017).

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