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.

References

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data. Eur Urol. 2005;48:202–6.

Babjuk M, Bohle A, Burger M, Capoun O, Cohen D, Comperat EM, Hernandez V, Kaasinen E, Palou J, Roupret M, van Rhijn BWG, Shariat SF, Soukup V, Sylvester RJ, Zigeuner R. EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. 2017;71(3):447–461

Barentsz JO, Engelbrecht MRW, Witjes JAM, de la Rosette JJMCH, van der Graaf M. MR imaging of the male pelvis. European Radiology. 1999;9(9):1722–36.

Barentsz JO, Jager GJ, van Vierzen PB, Witjes JA, Strijk SP, Peters H, Karssemeijer N, Ruijs SH. Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. Radiology. 1996;201(1):185–93.

Bruins HM, Veskimae E, Hernandez V, Imamura M, Neuberger MM, Dahm P, Stewart F, Lam TB, N'Dow J, van der Heijden AG, Comperat E, Cowan NC, de Santis M, Gakis G, Lebret T, Ribal MJ, Sherif A, Witjes JA. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer : a systematic review. Eur Urol. 2014;66(6):1065–77.

Cambier S, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, Kirkelis WJ, Silva FC, Oosterlinck W, Prescott S, Kirkali Z, Powell PH, de Reijke TM, Turkeri L, Collette S, Oddens J. EORTC nomograms and risk groups for predicting recurrence, progression, and disease-specific and overall survival in non-muscle-invasive stage Ta-T1 urothelial bladder cancer patients treated with 1–3 years of maintenance bacillus Calmette-Guerin. Eur Urol. 2016;69(1):60-69

Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, Pruthi R, Quale DZ, Ritch CR, Seigne JD, Skinner EC, Smith ND, McKiernan JM. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol. 2016;196(4):1021–9.

Choi W, Porten S, Kim S, Willis D, Plimack ER, Hoffman-Censits J, Roth B, Cheng T, Tran M, Lee IL, Melquist J, Bondaruk J, Majewski T, Zhang S, Pretzsch S, Baggerly K, Siefker-Radtke A, Czerniak B, Dinney CP, McConkey DJ. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014a;25(2):152–65.

Choi W, Czerniak B, Ochoa A, Su X, Siefker-Radtke A, Dinney C, McConkey DJ. Intrinsic basal and luminal subtypes of muscle-invasive bladder cancer. Nat Rev Urol. 2014b;11:400–10.

Culp SH, Dickstein RJ, Grossman HB, Pretzsch SM, Porten S, Daneshmand S, Cai J, Goshen S, Siefker-Radtke A, Millikan RE, Czerniak B, Navai N, Wszolek MF, Kamat AM, Dinney CP. Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. J Urol. 2014;191(1):40–7.

Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, Reuter V. Cystectomy for bladder cancer: a contemporary series. J Urol. 2001;164(4):1111–6.

Eble JN, Sauter G, Epstein JI. World Health Organization classification of tumours: pathology and genetics of tumours of the urinary system and male genital organs. Lyon: IARC Press; 2004.

Fernandez-Gomez J, Madero R, Solsona E, Unda M, Martinez-Pineiro L, Gonzalez M, Portillo J, Ojea A, Pertusa C, Rodriguez-Molina J, Camacho JE, Rabadan M, Astobieta A, Montesinos M, Isorna S, Muntanola P, Gimeno A, Blas M, Martinez-Pineiro JA. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol. 2009;182:2195–203.

Groenendijk FH, de Jong J, Fransen van de Putte EE, Michaut M, Schlicker A, Peters D, Velds A, Nieuwland M, van den Heuvel MM, Kerkhoven RM, Wessels LF, Broeks A, van Rhijn BW, Bernards R, van der Heijden MS. ERBB2 mutations characterize a subgroup of muscle-invasive bladder cancers with excellent response to neoadjuvant chemotherapy. Eur Urol. 2016;69:384–8.

Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzan NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP, Raghavan D, Crawford ED. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349(9):859–66.

Hermans TJN, Fransen van de Putte EE, Horenblas S, Meijer RP, Boormans JL, Aben KKH, van der Heijden MS, de Wit R, Beerepoot LV, Verhoeven RH, van Rhijn BWG. Pathological downstaging and survival after induction chemotherapy and radical cystectomy for

clinically node-positive bladder cancer-results of a nationwide population-based study. Eur J Cancer. 2016;69:1–8.

Herr HW. Extent of surgery and pathology evaluation has an impact on bladder cancer outcomes after radical cystectomy. Urology. 2003;4395(2):105–8.

Herr HW, Donat SM. Quality control in transurethral resection of bladder tumours. BJU Int. 2008;102:1242–6.

Herr HW, Donat SM, Bajorin DF. Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. J Urol. 2001;165(3):811–4.

Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs-part B: prostate and bladder tumours. Eur Urol. 2016;70(1):106–19.

Joudi FN, Smith BJ, O'Donell MA, Konety BR. The impact of age on the response of patients with superficial bladder cancer to intravesical immunotherapy. J Urol. 2006;175(5):1634–40.

Kibel AS, Dehdashti F, Katz MD, Klim AP, Grubb RL, Humphrey PA, Siegel C, Cao D, Gao F, Siegel BA. Prospective study of fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. J Clin Oncol. 2009;27(26):4314–20.

Kirkali Z, Chang T, Manoharan M, Algaba F, Busch C, Cheng L, Kiemeney M, Montironi R, Murphy WM, Sesterhenn IA, Tachibana M, Weider J. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology. 2005;66(6 suppl 1):4–34.

Lotan Y, Gupta A, Shariat SF, Palapattu GS, Vazina A, Karakiewicz PI, Bastian PJ, Rogers CG, Amiel G, Perrotte P, Shoenberg MP, Lerner SP, Sagalowsky AI, Lymphovascular Invasion I. Independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. J Clin Oncol. 2005;23 (27):6533–9.

Lu YY, Chen JH, Liang JA, Wang HY, Lin CC, Lin WY, Kao CH. Clinical value of FDG PET or PET/CT in urinary bladder cancer: a systemic review and meta-analysis. Eur J Radiol. 2012;81(9):2411–6.

Malats N, Bustos A, Nascimento CM, Fernandez F, Rivas M, Puente D, Kogevinas M, Reals FX. P53 as a prognostic marker for bladder cancer: a meta-analysis and review. Lancet Oncol. 2005;6(9):678–86.

Margulis V, Lotan Y, Karakiewicz PI, Fradet Y, Ashfaq R, Capitanio U, Montorsi F, Bastian PJ, Nielsen MF, Muller SC, Rigaud J, Heukamp LC, Netto G, Lerner SP, Sagalowsky AI, Shariat SF. Multi-institutional validation of the predictive value of Ki-67 labeling index in patients with urinary bladder cancer. J Natl Cancer Inst. 2009;101(2):114–9.

Martin-Doyle W, Leow JJ, Orsola A, Chang SL, Bellmunt J. Improving selection criteria for early cystectomy in high-grade T1 bladder cancer: a meta-analysis of 15,215 patients. J Clin Oncol. 2015;33:643–50.

Mitra AP, Skinner EC, Miranda G, Daneshmand SA. Precystectomy decision model to predict pathological upstaging and oncological outcomes in clinical stage T2 bladder cancer. BJU Int. 2013;111 (2):240–8.

Mostofi FK. Histological typing of urinary bladder tumours. International histological classification of tumours, No 19. Geneva: World Health Organization; 1973.

Neuzillet Y, Soulie M, Larre S, Roupret M, Deforescu G, Murez T, Pignot G, Descazeaud A, Patard JJ, Bigot P, Salomon L, Colin P, Rigaud J, Bastide C, Durand X, Valeri A, Kleinclauss F, Bruyere F, Pfister C, Comite de Cancerologie de l'Association Francaise d'Urologie (CCAFU). Positive surgical margins and their locations in specimens are adverse prognosis features after radical cystectomy in non-metastatic carcinoma invading bladder muscle: results from a nationwide case-control study. BJU Int. 2013;111(8):1253–60.

Palou J, Rodriguez-Rubio F, Millan F, Algaba F, Rodriguez-Faba O, Huguet J, Villavicenco H. Recurrence at three months and high-grade recurrence as prognostic factor of progression in multivariate analysis of T1G2 bladder tumors. Urology. 2009;73:1313–7.

Palou J, Sylvester RJ, Faba OR, Parada R, Pena JA, Algaba F, Villavicencio H. Female gender and carcinoma in situ in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette. Eur Urol. 2012;62(1):118–52.

Powles T. Immunotherapy: the development of immunotherapy in urothelial bladder cancer. Nat Rev Clin Oncol. 2015;12(4):193–4.

Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullen A, Nilsson S, Malmstrom PU, Nordic Urothelial Cancer Group. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neo-adjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol. 2012;61(6):1229–38.

Roupret M, Seisen T, Comperat E, Larre S, Mazerolles C, Gobet F, Fetissof F, Fromont G, Safsaf A, d'Arcier BF, Celhay O, Validire P, Rozet F, Irani J, Soulie M, Pfister C, Comite de Cancerologie de l'Association Francaise d'Urologie. Prognostic Interest in Discriminating Muscularis Mucosa Invasion (T1a vs T1b) in Nonmuscle Invasive Bladder Carcinoma: French National Multicenter Study with Central Pathology Review. J Urol. 2013;189(6):2069–76.

Shariat SF, Ashfaq R, Sagalowsky AI, Lotan Y. Predictive value of cell cycle biomarkers in nonmuscle invasive bladder transitional cell carcinoma. J Urol. 2007;177 (2):481–7.

Shariat SF, Passoni N, Bagrodia A, Rachakonda V, Xylinas E, Robinson B, Kapus P, Sagalowsky AI, Lotan Y. Prospective evaluation of a preoperative biomarker panel for prediction of upstaging at radical cystectomy. BJU Int. 2014;113(1):70–6.

Sobin LH, Gospodarowicz M, Wittekind C. TNM classification of malignant tumors. UICC International Union Against Cancer. 8th ed. Oxford: Wiley-Blackwell; 2016.

Stein JP, LIeskovsky G, Gote R, Feng AC, Boyd S, Skinner E, Bochner B, Tangathurai D, Mikhail M, Raghaven D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666–75.

Svatek RS, Clinton TN, Wilson CA, Kamat AM, Grossman HB, Dinney CP, Shah JB. Intravesical tumor involvement of the trigone is associated with nodal metastasis in patients undergoing radical cystectomy. Urology. 2014;84(5):1147–51.

Sylvester RJ, van der Meijden APM, Oosterlink W, Witjes AJ, Bouffioux C, Denis L, Newling DWW, Kurth K. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC. Eur Urol. 2006;49(3):466–77.

Van Allen EM, Mouw KM, Kim P, Iyer G, Wagle N, Al-Ahmadie H, Zhu C, Ostrovnaya I, Kryukov GV, O'Connor KW, Sfakianos J, Garcia-Grossman I, Kim J, Guancial EA, Bambury R, Bahl S, Gupta N, Farlow D, Gu A, Signoretti S, Barletta JA, Reuter V, Boehm J, Lawrence M, Get G, Kantoff P, Bochner BH, Choueiri TK, Bajorin DF, Solit DB, Gabriel S, D'Andrea A, Garraway LA, Rosenberg JE. Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. Cancer Discovery. 2014;4:1140–53.

Van den Bosch S, Witjes JA. Long-term cancer-specific survival in patients with high-risk, non–muscle-invasive bladder cancer and tumour progression: a systematic review. Eur Urol. 2011;60:493–500.

Van Rhijn BWG, Burger M, Lotan Y, Solsona E, Stief CG, Sylvester RJ, Witjes JA, Zlotta AR. Recurrence and progression of disease in non–muscle-invasive bladder cancer: from epidemiology to treatment strategy. Eur Urol. 2009;56(3):430–42.

Van Rhijn BWG, van der Kwast TH, Alkhateeb SS, Fleshner NE, van Leenders GJLH, Bostrom PJ, van der Aa MNM, Kakiashvili DM, Bangma CH, Jewett MA, Zlotta ARA. New and highly prognostic system to discern T1 bladder cancer substage. Eur Urol. 2012;61(2):378–84.

Van Rhijn BWG, Catoo JW, Goebell PJ, Knuchel R, Shariat SF, van der Poel HG, Sanchez-Carbayo M, Thalmann GN, Schmitz-Drager BJ, Kiemeney LA. Molecular markers for urothelial bladder cancer prognosis: toward implementation in clinical practice. Urol Oncol. 2014;32(7):1078–87.

Witjes JA, Lebret T, Comperat EM, Cowan NC, de Santis M, Bruins HM, Hernandez V, Espinos EL, Dunn J, Rouanne M, Neuzillet Y, Veskimae E, van der Heijden AHG, Gakis G, Ribal MJ. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol. 2017;71(3):462–475