



Collaborative Review – Bladder Cancer

Recurrence and Progression of Disease in Non–Muscle-Invasive Bladder Cancer: From Epidemiology to Treatment Strategy

Bas W.G. van Rhijn^{a,*}, Maximilian Burger^b, Yair Lotan^c, Eduardo Solsona^d,
 Christian G. Stief^e, Richard J. Sylvester^f, J. Alfred Witjes^g, Alexandre R. Zlotta^a

^a Department of Surgical Oncology, Division of Urology, University of Toronto, UHN, Toronto, Ontario, Canada

^b Department of Urology, University of Regensburg, Regensburg, Germany

^c Department of Urology, The University of Texas, Southwestern Medical Centre, Dallas, Texas, USA

^d Department of Urology, Instituto Valenciano de Oncología, Valencia, Spain

^e Department of Urology, Ludwig Maximilians-Universität München, Munich, Germany

^f EORTC Headquarters, Brussels, Belgium

^g Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Article info

Article history:

Accepted June 17, 2009

Published online ahead of
 print on June 26, 2009

Keywords:

Bladder cancer
 Epidemiology
 Recurrence
 Progression
 Cystoscopy
 Stage
 Grade
 Treatment
 BCG
 Cystectomy

Abstract

Context: This review focuses on the prediction of recurrence and progression in non-muscle invasive bladder cancer (NMIBC) and the treatments advocated for this disease.

Objective: To review the current status of epidemiology, recurrence, and progression of NMIBC and the state-of-the art treatment for this disease.

Evidence acquisition: A literature search in English was performed using PubMed and the guidelines of the European Association of Urology and the American Urological Association. Relevant papers on epidemiology, recurrence, progression, and management of NMIBC were selected. Special attention was given to fluorescent cystoscopy, the new World Health Organisation 2004 classification system for grade, and the role of substaging of T1 NMIBC.

Evidence synthesis: In NMIBC, approximately 70% of patients present as pTa, 20% as pT1, and 10% with carcinoma in situ (CIS) lesions. Bladder cancer (BCa) is the fifth most frequent type of cancer in western society and the most expensive cancer per patient. Recurrence (in $\leq 80\%$ of patients) is the main problem for pTa NMIBC patients, whereas progression (in $\leq 45\%$ of patients) is the main threat in pT1 and CIS NMIBC. In a recent European Organisation for Research and Treatment of Cancer analysis, multiplicity, tumour size, and prior recurrence rate are the most important variables for recurrence. Tumour grade, stage, and CIS are the most important variables for progression. Treatment ranges from transurethral resection (TUR) followed by a single chemotherapy instillation in low-risk NMIBC to, sometimes, re-TUR and adjuvant intravesical therapy in intermediate- and high-risk patients to early cystectomy for treatment-refractory high-risk NMIBC.

Conclusions: NMIBC is a heterogeneous disease with varying therapies, follow-up strategies, and oncologic outcomes for an individual patient.

© 2009 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Division of Urology, UHN, University of Toronto, 610 University Avenue, 3-130, Toronto, ON M5G 2M9, Canada. Tel. +1 416 946 2909; Fax: +1 416 598 9997.
 E-mail address: basvanrhijn@hotmail.com (B.W.G. van Rhijn).

1. Introduction

The global incidence of urinary bladder cancer (BCa) was approximately 357 000 cases in 2002 [1]. The vast majority of these cancers are urothelial carcinomas, and it is a disease of the elderly population. The highest incidence rates are observed in North America and Western Europe [1,2], while the lowest incidence rates are found in the Asian countries (China, Japan, Korea) and central Africa [1,3]. Variation in registration of pTa (low-grade) tumours may partly be the cause of these differences [4]. Apart from age, the most important risk factors are smoking, occupational exposure, certain medical treatments, and genetic predisposition [4–11].

Table 1 shows the worldwide incidence, mortality, and prevalence of BCa for males and females and for more- and less-developed countries. Globally, BCa is the 7th most common cancer in men and the 17th in women [1]. In the United States, it is the 4th most common cancer in men and the 10th in women [2]. Most (75–85%) BCa incidences are non-muscle invasive at first diagnosis (pTa, pT1, carcinoma in situ [CIS]) [12]. In non-muscle-invasive bladder cancer (NMIBC), approximately 70% of patients present as pTa, 20% as pT1, and 10% as CIS lesions [13]. Generally, the prognosis of NMIBC is good, although 30–80% of cases will recur and 1–45% of cases will progress to muscle invasion within 5 yr [12–16]. Consequently, NMIBC is a chronic disease with varying oncologic outcomes requiring frequent follow-up and repeated treatments, making the cost per patient from diagnosis to death the highest of all cancers [17,18]. At any point in time, 2.7 million people in the world have a history of BCa [19].

2. Evidence acquisition

A literature search in English was performed using PubMed and the guidelines of the European Association of Urology (EAU) and the American Urological Association (AUA). Relevant papers on epidemiology, recurrence, progression, and management of NMIBC were selected. Next to clinical and pathologic variables for recurrence and progression, special attention has been paid to fluorescence cystoscopy (FC), the new World Health Organisation (WHO) 2004 classification system for grading, and the role of substaging

of T1 NMIBC. Treatment issues like transurethral resection (TUR), adjuvant intravesical instillations, and radical cystectomy for NMIBC are addressed in the last section of this paper.

3. Evidence synthesis

3.1. Prognostic factors for recurrence

3.1.1. Clinical and pathologic factors of recurrence

Clinical and pathologic factors for NMIBC recurrence have been studied extensively over the years [15,20–26]. Although studies vary in the number of patients included, duration of follow-up, variables analysed, and statistical analysis, the most important variables for prediction of recurrence in patients with NMIBC are multiplicity, prior recurrence rate, and tumour size [15,20–26]. Sylvester reviewed potential prognostic factors in 19 studies, of which most compared various intravesical chemotherapy drugs and regimens [26]. In an attempt to individualise prediction of recurrence, Sylvester et al [15] calculated the probability of recurrence using data from 2596 patients who participated in seven European Organisation for Research and Treatment of Cancer (EORTC) trials. The weighted score was based on six variables (Table 2). The risk calculator is available at the EORTC Web site at www.eortc.be/tools/bladdercalculator. The EAU subsequently adopted this system in its guidelines and, based on these scores, defined patients at low, intermediate, and high risk for recurrence (Table 3) [12,15]. Recently, Fernandez-Gomez et al [20] reported the data on prognostic factors from four Club Urológico Español de Tratamiento Oncológico (CUETO) trials, in which 1062 patients received 5–6 mo of bacillus Calmette-Guérin (BCG). Multiplicity, prior tumour, female gender, and CIS were significant predictors for recurrence in multivariate analysis [20]. A nomogram has been proposed to predict recurrence based on age, gender, cytology, and urinary nuclear matrix protein 22 (NMP22) in patients with a history of NMIBC (available at www.nomogram.org) [27,28]. Information on multiplicity, size, and prior histology was not available in the 2542 patients from 10 institutions [27]. Nevertheless, the nomogram provides complementary information to predict recurrence during

Table 1 – Worldwide incidence, mortality, and prevalence for bladder cancer in females and males in more and less developed regions [1]

Country/region	Incidence			Mortality			Prevalence	
	Cases	Crude rate	ASR(W)	Deaths	Crude rate	ASR(W)	1-yr	5-yr
Bladder, females								
World	82 699	2.7	2.5	36699	1.2	1.1	64 673	249 966
More developed regions	50 561	8.2	4.2	18 774	3.1	1.4	42 863	173 352
Less developed regions	32 060	1.3	1.6	17 894	0.7	0.9	21 810	76 614
Bladder, males								
World	273 858	8.8	10.1	108 310	3.5	4.0	224 742	860 299
More developed regions	174 681	30.1	19.5	52 133	9.0	5.6	156 692	622 755
Less developed regions	98 911	3.9	5.3	56 051	2.2	3.1	68 050	237 544

ASR(W) = age-standardised incidence rate (per 100 000).

Table 2 – Weighting used to calculate recurrence and progression scores [15]

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2–7	3	3
>8	6	3
Tumour diameter		
<3 cm	0	0
>3 cm	3	3
Prior recurrence rate		
Primary	0	0
<1 recurrence/yr	2	2
>1 recurrence/yr	4	2
Stage category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

CIS = carcinoma in situ; WHO = World Health Organisation.

follow-up compared to the models from the EORTC and CUETO [15,20].

3.1.2. Fluorescence cystoscopy

White light is the gold standard for visualisation of suspicious lesions during TUR. Despite complete removal of all lesions detected in white light cystoscopy (WLC), resections do not seem to be sufficiently radical in a significant fraction of cases, as residual tumour is found in up to 30–50% of cases [29,30]. Thus, methodologies to improve visualisation have been evaluated. One recent approach is FC, often referred to as *photodynamic diagnosis*, which is based on topical application of porphyrins acting as

fluorescing substances. The procedure is well tolerated [31–33]. Hexylaminolevulinat (Hexvix) has been approved for the diagnosis of BCa in 27 European Union countries [12,34].

The superior detection of malignant lesions by FC has been well established. Grossman and coworkers compared FC to white light in a large multicentre trial [31]. In 298 patients, FC detected at least one additional Ta in 29% of patients and at least one additional T1 lesion in 15% of patients, respectively. However, 37 of 40 additionally detected lesions were Ta. Mean detection rates for Ta and T1 lesions were 95% and 95% for FC, respectively, compared to 83% and 86% for white light, respectively ($p = 0.0001$). This increase in sensitivity has also been reported for flat lesions, which particularly defy visualisation in WLC. Fradet et al [32] evaluated the previously mentioned multicentre trial for detection of CIS. Of 113 CIS lesions, 92% and 68% were detected by FC as compared to white light, respectively. In the largest series to date, Hungerhuber et al [35] demonstrated a superior tumour-detection rate by FC in roughly 5000 biopsies, as 92% and 76% of tumours were detected by FC and white light, respectively. False-positive FC findings were discovered in 38% of biopsies [35], which may be attributed to inflammation or scarring as a result of previous TUR. Nevertheless, the additional sensitivity gained by FC is significant, as information for choosing further management options was obtained in 51% of cases as judged by the investigators [32]. Taken together, improved detection of CIS, low-stage/grade papillary lesions, as well as more multifocal NMIBCs have been detected in FC-TUR as compared to WLC-TUR [31–37]. Moreover, positive cytology and a negative WLC form an excellent indication for FC biopsies [38,39]. In patients with a negative WLC, malignancy was detected by FC in 63 of 77 (82%) patients with positive cytology as opposed to 43 of 271 (16%) patients with negative cytology [38].

Although detection of additional lesions can be achieved by FC, it is important to determine whether there is an oncologic and possible economic benefit. Two randomised trials have been published on this topic. Danilchenko et al [36] found that FC-TUR improved oncologic outcome

Table 3 – Probability of recurrence and progression according to total score [12,15]

	Probability of recurrence		Recurrence risk group
	at 1 yr % (95% CI)	at 5 yr % (95% CI)	
Recurrence score			
0	15 (10–19)	31 (24–37)	Low risk
1–4	24 (21–26)	46 (42–49)	Intermediate risk
5–9	38 (35–41)	62 (58–65)	Intermediate risk
10–17	61 (55–67)	78 (73–84)	High risk
	Probability of progression		Progression risk group
	at 1 yr % (95% CI)	at 5 yr % (95% CI)	
Progression score			
0	0.2 (0–0.7)	0.8 (0–1.7)	Low risk
2–6	1 (0.4–1.6)	6 (5–8)	Intermediate risk
7–13	5 (4–7)	17 (14–20)	High risk
14–23	17 (10–24)	45 (35–55)	High risk

CI = confidence interval.

significantly in 51 FC versus 51 WLC patients, as recurrence-free survival (RFS) rates after 60 mo were 41% versus 25%, respectively ($p = 0.02$) [36]. Secondary TUR was done in all cases but no adjuvant therapy was given, regardless of risk group. Thus, these data approximate the natural course of NMIBC. Denzinger et al [37] confirmed this finding in a larger set of 103 FC and 88 WLC in long-term follow-up, as 2- and 8-yr RFS rates were 88% versus 73% and 71% versus 45%, respectively ($p = 0.0003$). Again, all patients in this trial underwent secondary resection, but as opposed to the former study, adjuvant therapy was initiated in accordance with respective guidelines [12,16]. Taking into account the additional costs of FC, it was still cost effective, as the number of TURs per patient over a 7-yr period dropped from 2.0 (initial WLC-TUR patients) to 0.8 (initial FC-TUR patients) [40]. These German data are promising and require further economic evaluation.

FC has also been studied in high-risk T1 BCa. As opposed to CIS, no additional T1 lesions were found at FC-TUR. Denzinger et al [41] reported data on 46 pT1 G3 tumours following FC-TUR and WLC-TUR. RFS after 36 mo was 41% versus 27% in the FC and WLC groups, respectively ($p < 0.01$) [41]. Although recurrence rates seem to be advantageous in FC, progression rates were similar (14% vs 16%, respectively), which may be attributed to the aggressive tumour biology of early invasive BCa such that a more thorough TUR cannot prevent progression from occurring. Conversely, nine patients progressed in the WLC group as compared to four patients in the FC group in the study by Danilchenko et al [36]. It is anticipated that improved detection of CIS by FC would result in less progression. However, there are issues regarding statistical power. A meta-analysis when the North American study [31,32] has matured may give us more information on FC and progression. Although FC is far from being a standard procedure, its use is increasing, with approximately 750 units in Europe and 100 in the United States and Canada currently in use. In conclusion, FC has a higher sensitivity than WLC, especially for CIS, allowing a more thorough TUR. Decreased recurrence rates suggest that FC has an oncologic and economic benefit. However, whether FC can reduce progression is not yet clear.

3.2. Prognostic factors for progression

3.2.1. Clinical and pathologic prediction of progression

Fortunately, progression to muscle-invasive BCa is much less frequent than recurrence in NMIBC. Nevertheless, 5-yr probabilities range from $< 1\%$ to 45%, depending on the risk score (Tables 2 and 3) [15]. The most important variables for prediction of progression are CIS, grade 3, and stage T1 as opposed to size and multiplicity, which are stronger predictors of recurrence [15,25,26]. Studies addressing specific prognostic factors for high-risk patients will be discussed under management for high-risk NMIBC.

Sylvester et al [15] calculated the probability of progression using 2596 patients who participated in seven EORTC trials (Tables 2 and 3). The main limitation of the EORTC risk tables is that most patients were treated by

“old” intravesical chemotherapy regimens. Improvements in intravesical chemotherapy, use of a single chemotherapeutic instillation after TUR, re-TUR, and the increased use of (maintenance) BCG may reduce the predicted probabilities in these tables, especially for progression. Fernandez-Gomez et al [20] reported their data on prognostic factors in 1062 patients who received 5–6 mo of BCG. A recurrence at first cystoscopy, stage, grade, and prior tumour were prognostic factors in the multivariate analysis for progression. Concomitant CIS was only significant in univariate analysis [20]. Apart from possible differences in pathologic examinations, explanations for this observation may be that the patient population in the CUETO study included more high-risk patients than the EORTC study, which included all risk groups, and/or that BCG treatment given in the CUETO study was a more effective treatment for CIS [15,20].

A wide variety of molecular markers have been investigated for a better assessment of NMIBC prognosis [42–46]. Some of these have been shown to be associated with aggressive disease and hold promise to predict progression if used in combination [42–46]. Conversely, the FGFR3 mutation has been found to be a selective marker for favourable disease in several reports [45,47,48]. Still, the value of molecular markers over traditional histopathology is not clear. Nevertheless, these markers may offer a better understanding of the biology of tumours, and future research might lead to their use in clinical decision making.

3.2.2. Influence of the new grading system

A major drawback of the WHO 1973 [49] grading system was the high interobserver variation ($\leq 50\%$), calling into question its use for prediction of prognosis in individual cases [50–53]. The WHO 2004 classification system was initially proposed in 1998 by the WHO/International Society of Urological Pathology and was adopted as a three-tiered (papillary urothelial neoplasms of low malignant potential [PUNLMP], low-grade and high-grade BCa) grading system by the WHO [54,55]. The main reasons to propose a new system were the lack of clear definitions for the three WHO 1973 grades and the high percentage of NMIBC cases classified as G2 (the default diagnosis). In fact, a higher absolute number of patients with progression has been reported in most large series among those with a G2 lesion as compared to G3 NMIBC (WHO 1973) [21,45]. The new system introduced detailed histologic criteria to decrease observer variability, and, ideally, patients with PUNLMP lesions would have lower recurrence percentages and patients with low-grade BCa would have close to no progression to muscle invasion in follow-up. Consequently, a grade shift was put forward precluding a one-to-one translation between both grading systems: WHO 1973 G1 tumours become WHO 2004 PUNLMP or LG, WHO 1973 G2 tumours become WHO 2004 low-grade or high-grade tumours, and WHO 1973 G3 tumours are all WHO 2004 high-grade tumours (Fig. 1) [54–58]. Studies on observer variability have shown no benefit for the WHO 2004 grading system [57]. Recurrence in PUNLMP, which is considered benign, varied between 25% and 60% in

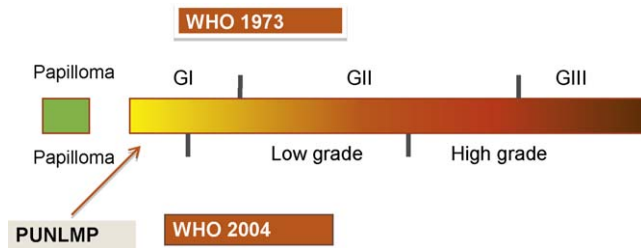


Fig. 1 – Comparison of the World Health Organisation (WHO) grading systems: 1973 versus 2004.
PUNLMP = papillary urothelial neoplasm of low malignant potential.

11 quoted studies [58], indicating that PUNLMP needs surveillance as low-risk NMIBC. Stage progression of low-grade BCa varied from 3.5% to 13%, assigning these patients to intermediate-risk NMIBC [58]. Progression in high-grade BCa (WHO 2004) and G3 (WHO 1973) was found more frequently in G3, as the high-grade BCa group is more heterogeneous [58–60]. However, one single pathologist did not review the cases for both classification systems in these studies. As the incidence of high-grade BCa among studies has been highly variable (ie, between 21% and 67% in five quoted studies [57]), comparison between high-grade BCa and G3 remains difficult. The main criticism of the new system is that it has been accepted in spite of a lack of clinical evidence and proper studies with long-term follow-up to assess its reproducibility and predictive value compared to the “old” WHO 1973 system [56,58,61]. In addition, evidence from large series we currently use, like the EORTC risk calculator, has been based on the 1973 system [15,20]. Therefore, the AUA and EAU guidelines advocate the use of both systems until the 2004 system has been properly validated [12,16]. However, the advantage of the new system over the WHO 1973 system will probably not be large, as interobserver variability remains high in both systems.

3.2.3. Substaging of T1 non-muscle-invasive bladder cancer

The prognosis of T1 NMIBC shows significant variability from patient to patient. One of the problems involves the reliability of staging pT1 tumours. Bol et al [52] asked three expert reviewers to reevaluate 130 Ta and T1 tumours. They found an 80% agreement among three reviewers, which increased to 88% after second review. Of the 63 T1 tumours that were originally classified as T1, 35 (56%) were downstaged to pTa and 8 (13%) were upstaged to muscle-invasive BCa by the reviewers [52]. Downstaged tumours showed less frequent progression, illustrating that pathologic variation has significant implications for patients. Apart from these observations, the “real” T1 cases are still characterised by a heterogeneous prognosis. Hence, there is a need for a reproducible, easy-to-use substaging system that provides prognostic information. Several reports have explored the utility of the muscularis mucosae and the vascular plexus beneath it, as shown in Fig. 2 [62]. Many of these have shown that substaging of T1 NMIBC (pT1a/pT1b/pT1c) is an important predictor for progression [63–67].

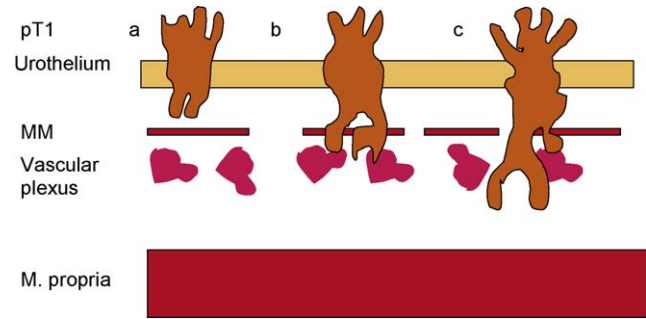


Fig. 2 – A substaging on the basis of depth of invasion into the lamina propria (pT1a, pT1b, pT1c) [62].
MM = muscularis mucosae; M. propria = muscularis propria (detrusor muscle).

Two studies addressed substaging in patients treated by BCG. One study [68] found no difference in progression for substage, whereas Orsola et al [67] found a significantly different progression-free survival (PFS) for T1a compared to T1b+c. The number of patients, however, was small ($n = 49$ [68] and $n = 59$ [67]) in both studies. Moreover, identification of the muscularis mucosae/vascular plexus was not possible in up to 35% of the cases [63–67], which led to the development of other ways to substage T1 NMIBC [69–71]. Cheng et al [70] found that depth of invasion measured by micrometer was possible in 100% of 83 TUR specimens. Outcomes stratified by depth of invasion showed a 5-yr PFS of 93% for those with <1.5-mm invasion compared to 67% for those with >1.5-mm subepithelial invasion. Van der Aa et al [71] defined microinvasive pT1 as a single spot of invasion only within one high-power field under the microscope, and pT1 cases not fulfilling these two criteria were assigned to the extensive invasive pT1 category. This system could be assessed in all 53 investigated cases, predicted progression, and proved reproducible in 81% of the tumours. Neither of these relatively new substaging systems has been compared to the pT1abc substaging system. Although data support routine pathologic assessment of substage, the optimal system still has to be determined. Consequently, substaging still has not been accepted in guidelines.

3.3. Treatment of non-muscle-invasive bladder cancer

3.3.1. Transurethral resection

The mainstay of patient treatment for NMIBC is TUR. The first TUR is essential for diagnosis and prognosis [72–75]. Complete macroscopic and microscopic removal of BCa is the goal of this procedure. Brausi et al [30] showed that recurrence at 3 mo for patients with multifocal tumours varied between 7% and 46% at the participating centres in seven EORTC phase 3 trials, suggesting differences in the quality of TUR. Grimm et al [29] routinely performed a re-TUR in a consecutive series of 83 patients. Residual tumour was found in 27% of pTa and 53% of pT1-cases, of which 81% were at the initial resection site. RFS at 5-yr follow-up was 63% in the re-TUR group versus 40% in the TUR-only group

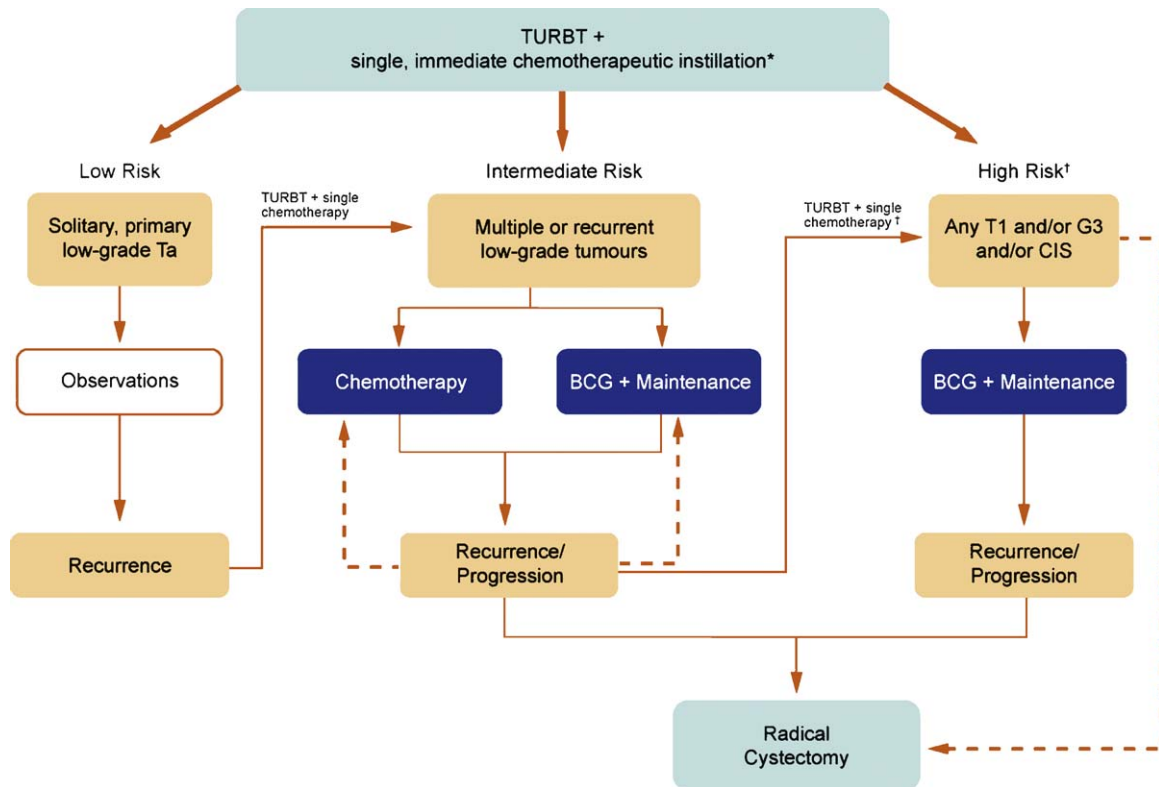


Fig. 3 – Algorithm for the treatment and management of primary non-muscle-invasive bladder cancer proposed by the International Bladder Cancer Group (reprinted with permission from Elsevier) [85]. For ease of use, these recommendations have been simplified and, therefore, will need to be customised for each individual patient. For example, a high-risk patient with a low-grade Ta recurrence on maintenance bacillus Calmette-Guérin would be a candidate for intravesical chemotherapy rather than cystectomy, as shown in the algorithm.

TURBT = transurethral resection of bladder tumour; CIS = carcinoma in situ; BCG = bacillus Calmette-Guérin.

* Except in those with a suspected bladder wall perforation.

† Efficacy of single, immediate chemotherapeutic instillation not studied in high-risk disease.

($p < 0.03$) [29]. In another study, a clinical staging error was found in 9–49% of cases and residual tumour in 26–83% of cases [76]. These data indicate the presence of major differences in the quality of TUR and the need for improved methods like FC.

3.3.2. Re-transurethral resection in high-risk non-muscle-invasive bladder cancer

A re-TUR is especially relevant in pT1 and high-grade NMIBC [73,75,77]. Upstaging to pT2 at second TUR occurred in 2–30%, radically changing the treatment strategy [73–75]. The highest percentage was reported by Herr et al [73]. A possible explanation is the subsequent difference in upstaging depending on the presence of deep muscle in the specimen reported by the pathologist. Upstaging to pT2 was found in 15% if deep muscle were present compared to 45% if muscle were absent in initial resection [73]. Furthermore, the prognosis of patients with an initial pT1 NMIBC highly depends on the pathology of the second TUR [78]. Of the patients with residual pT1, 75 of 92 patients (82%) progressed within 5 yr to muscle-invasive BCa compared to 49 of 260 patients (19%) who had pTa NMIBC or no malignancy at their second TUR [78]. Herr also reported that patients with high-risk NMIBC responded better to BCG after re-TUR, staging them more accurately compared to

patients who received BCG after one TUR [79]. Divrick et al [80] conducted a randomised clinical trial in 148 primary pT1 NMIBC patients, giving mitomycin C (MMC) to patients after the first or second TUR with the requirement of muscle in the specimen. At a mean follow-up of 32 mo, recurrence and progression rates were 26% and 4%, respectively, for the group that had a second TUR and 63% and 12%, respectively, for the group that had a single TUR before MMC [80]. This result supports the role of re-TUR in improving accurate staging and improving prognosis. In summary, a second resection should be performed when the first TUR was incomplete, muscle was reported as absent in the pathology report, and in T1 or high-grade NMIBC [12].

3.3.3. Intravesical treatment of non-muscle-invasive bladder cancer

3.3.3.1. A single chemotherapeutic instillation after transurethral resection. Several randomised clinical trials found a decrease in recurrence after a single instillation of a chemotherapeutic agent immediately (within 24 h) after TUR [81–84]. Epirubicin and MMC are the most commonly used drugs. A decrease of 39% in the odds of recurrence was found in the meta-analysis on this subject [82]. It is the treatment of choice for low-risk patients and recommended as the initial treatment after TUR for higher-risk categories (Fig. 3)

[82,85,86]. Approximately 8.5 patients need to be treated to prevent one recurrence [82,83]. Recently, Berrum et al [83] found that the recurrences prevented by a single instillation were mainly small and amendable to office-based fulguration. They concluded that the benefit of an immediate instillation after TUR may be limited [83]. Moreover, Gudjónsson et al [84] randomised patients to receive epirubicin 80 mg or no adjuvant treatment after TUR. As expected, recurrence was lower in the treatment arm 62% versus 77% (median follow-up: 3.9 yr) [84]. In subgroup analyses, the authors found that the treatment significantly reduced recurrences in patients with primary, solitary NMIBC, whereas it provided no clear advantage in patients with recurrent or multiple tumours, indicating that patients at intermediate or high risk of recurrence might not benefit to the same degree from an early instillation as the low-risk category [84]. Further studies are required to assess the value of an immediate instillation in intermediate- and high-risk patients who will receive additional instillations. Although of interest, a placebo-controlled study on recurrence in patients who had FC-TUR has not been reported yet.

3.3.3.2. Intravesical treatment: Induction and maintenance. Further intravesical treatment depends on the patient's prognosis (Fig. 3) [85]. The choice between further chemotherapy or BCG immunotherapy depends on the risk that needs to be reduced: recurrence or progression. Several meta-analyses have shown that adjuvant intravesical treatment (chemotherapy or BCG) reduces recurrence [86–90]. BCG is more effective but also more toxic [89]. The optimal schedule and duration of intravesical chemotherapy after an immediate instillation remain unknown [91,92]. Both intravesical chemotherapy and BCG are advocated as first-line treatment for intermediate-risk patients (Fig. 3) [86,90]. BCG but not intravesical chemotherapy additionally reduces the risk of progression in high-risk NMIBC patients [93–96]. A maintenance BCG schedule was found to be essential to prevent progression [86,93–96]. The benefit of maintenance BCG was shown by indirect comparisons (ie, the relative effect of BCG was greater in the presence than in the absence of maintenance [93]). However, a meta-analysis restricted to induction-only versus maintenance BCG treatment has not been done, and follow-up in the largest meta-analysis was short (2.5 yr) [93,97]. In the six trials directly comparing maintenance to induction BCG alone, progression was found in 30% (118/399) of the patients who received maintenance as compared to 33% (130/397) in the induction group [97]. Herr [97] concluded that despite the purported evidence from randomised trials and meta-analyses, liberal use of BCG, hoping it will forestall progression, does not seem to be the answer in high-risk NMIBC. In contrast, immunologic data support the use of maintenance BCG therapy [98]. It is of concern that despite the recommendations in the guidelines [12,16], Surveillance, Epidemiology, and End Results (SEER) data on 685 primary NMIBC patients indicated that intravesical therapy was only used in 31% of patients in US academic institutions [99]. In a subset of 350 high-risk patients, only

42% received intravesical therapy, suggesting significant undertreatment [99]. In summary, one instillation is indicated as the sole treatment prior to recurrence in low-risk patients. In intermediate-risk patients, additional intravesical chemotherapy or BCG is advocated. In high-risk patients, BCG is certainly the intravesical therapy of choice, although the positive effect of maintenance BCG on progression has been called into question [97].

3.3.3.3. Toxicity of bacillus Calmette-Guérin. Several possibilities for reducing BCG toxicity are available. CUETO has analysed dose reduction compared to standard doses. The results are promising, as recurrence and progression seem to be only marginally (not significantly) affected, whereas toxicity is significantly reduced [100–102]. In a multicentre EORTC trial on BCG maintenance, 20% stopped BCG because of local or systemic side-effects [103]. Interestingly, almost 70% of patients who stopped BCG because of side-effects did so during the first half year of treatment [103]. The side-effects were not predictive for BCa outcome [104]. Further maintenance was usually well tolerated [103]. In a randomised, double-blind, multicentre study with 115 patients, Colombel et al [105] showed that ofloxacin 200 mg once daily improved BCG compliance and significantly decreased the incidence of moderate to severe adverse events associated with BCG administration. One-year follow-up data show no difference in recurrence or progression [105]. The data on reducing toxicity are promising but need validation and longer follow-up.

3.3.3.4. New agents and methods of intravesical treatment. The efficacy of intravesical therapy is mainly restricted to reducing the short-term risk of recurrence [86,88,89]. Hence, chemotherapeutic alternatives and device-assisted therapies like thermo-chemotherapy and electromotive drug administration (EMDA) have been explored in an effort to improve treatment efficacy [86]. Au et al [106] found an improvement of MMC efficacy in patients with a high risk of recurrence in a randomised phase 3 trial in which one treatment arm had optimised MMC delivery consisting of decreasing urine output, alkalisation of the urine, and dose doubling to 40 mg and the control arm received standard 20 mg of MMC. Side-effects were more frequent in the optimised arm, but they did not cause treatment termination. At 5-yr follow-up, median time to recurrence was 12 versus 29 mo, and RFS was 26% versus 41%, both in favour of the optimised treatment arm [106]. Phase 2 (marker lesion response) studies have been conducted for two new intravesical chemotherapeutic agents: gemcitabine and apaziquone (EO9) [86,107,108]. Complete responses (CR; no malignancy at cytology and histology) were seen in 23–56% for gemcitabine [107] and in 67% for EO9 [108], making these drugs interesting for further research. Thermo-chemotherapy (Synergo) is currently used with MMC. It has been shown to be more effective than MMC alone despite an increased but acceptable local toxicity [86,109]. In addition, two studies reported very promising results in BCG failures (41% recurrence at 2 yr) and in patients with CIS (complete histologic and cytologic

response in 45 of 48 patients) [86,110]. Obviously, long-term follow-up is needed and awaited. EMDA is another device-assisted therapy that has shown promise as intravesical therapy. Di Stasi et al reported two studies on EMDA in high-risk patients [111,112]. They compared MMC only, EMDA-MMC, and BCG in 108 patients in the first study. They found a CR in 31%, 58%, and 64% of cases, respectively [111]. Median times to recurrence were 20, 35, and 26 mo, respectively [111]. Side-effects in EMDA patients were more than with MMC only but less than with BCG [111]. In the second study, maintenance BCG was compared to maintenance BCG/EMDA-MMC in 212 patients with T1 (after a second TUR) NMIBC [112]. The median follow-up was 88 mo, and significant differences in recurrence, progression, and disease-specific survival (DSS) were found, favouring the BCG/EMDA-MMC treatment [112]. Although the initial results of EMDA alone and in combination with BCG are interesting, confirmatory studies are needed. In summary, the new agents and methods provide promising results, but validation is required before they become standard first- or second-line treatments.

3.3.4. Cystectomy and conservative management for high-risk non-muscle-invasive bladder cancer

Many studies and reviews are available on early cystectomy for patients with NMIBC [113]. However, a randomised comparison of immediate cystectomy versus first-line conservative treatment is not available. In general, management of high-risk NMIBC consists of two TURs followed by BCG. Despite the high short-term response rate of BCG, 30–50% of patients will eventually relapse. The natural history (median follow-up: 15 yr) of 86 patients with high-risk NMIBC showed a DSS of 63%, and 27% were alive with an intact bladder [114]. Progression was found in 53% of cases [114]. Raj et al [115] compared a historical cohort of 307 patients to a contemporary cohort of 589 patients, with both groups undergoing initial treatment with BCG. DSS at 5 yr was better in the contemporary cohort: 48% versus 31% [115]. The authors attribute this improvement to the use of cystectomy for BCG failures, which was not performed in the historical cohort but was performed in 65 of 129 patients in the contemporary cohort [115]. If we analyse the patient populations from the two large studies on prognostic factors in NMIBC, the percentage of CIS and G3 was low in both studies (ie, 4% and 10% [15] and 7.5% and 25% [20], respectively). In the CUETO study, intermediate- and high-risk patients were included, and a separate analysis in the high-risk patients only was not reported [20]. In the EORTC study, 194 patients had T1G3 NMIBC. The presence of CIS conferred a poor prognosis, with 1- and 5-yr progression probabilities of 29% and 74%, respectively [15]. This indicates that high-risk patients compose a relatively small but dangerous group in the NMIBC spectrum.

The goal in these high-risk patients is to identify prognostic factors for the patients who will benefit from immediate radical surgery. The following adverse prognostic factors are important in high-risk NMIBC, and some have been discussed above: restaging second TUR, demon-

strating persistent pT1 disease [78], absence of deep muscle in a pT1 TUR specimen [73], CIS next to pT1 NMIBC [15], (sub)-stage (pT1b/c) [67], grade (G3) [15], micropapillary BCa [116], lympho-vascular invasion [117,118], and a solid tumour pattern [118]. Masood et al [119] reported their prognostic factors in 21 pT1G3 patients treated with early cystectomy. Multiplicity and CIS were associated with upstaging to muscle-invasive BCa, whereas absence of these variables was associated with pT0 at cystectomy [119]. Denzinger et al [120] found that the combination of CIS, size, and multiplicity was predictive for cancer-related death in a cohort of 132 T1G3 patients treated with BCG [120]. Solsona et al [121] evaluated 191 high-risk NMIBC patients treated with intravesical therapy (BCG in 75 cases). The presence of tumour at 3 mo and the presence of T1, CIS, G3, or prostate mucosa involvement were the significant variables for progression in a multivariate analysis. The authors advocate early cystectomy in these cases [121]. Another group found BCG to be less effective in T1+ CIS high-risk patients compared to BCG in primary CIS or Ta+ CIS, with progression rates of 49% versus 20% and 18% at a median follow-up of 3.5 yr, respectively [122]. Nevertheless, TUR and adjuvant BCG with the possibility of deferred cystectomy seems a reasonable approach for the majority of high-risk patients as long as there is close surveillance and cystectomy as soon as progression occurs [123–125]. In contrast, Stein et al [126] already found positive nodes in 14 of 208 (7%) of pT1 cystectomies, and RFS at 10 yr postcystectomy was 75% in these patients. Patard et al [124] reported similar DSS percentages for patients treated with BCG and cystectomy. In a report from the Bladder Cancer Research Consortium, with a median follow-up of 34 mo, 30 of 162 (19%) patients with clinical T1G3 disease who underwent cystectomy died from BCa [127]. Although 50% were upstaged at cystectomy, 17% already had nodal involvement [127]. Indeed, several studies suggest a narrow time window for cystectomy for high-risk or T1G3 NMIBC when BCG fails [115,127–132]. For example, Denzinger et al [132] offered early cystectomy to 105 patients with pT1G3 disease with two or three additional risk factors (size >3 cm, multifocality, and CIS). Fifty-four (51%) patients opted for early cystectomy, while 51 (49%) had deferred cystectomy [132]. Early cystectomy was associated with a significantly better 10-yr cancer-specific survival rate compared to deferred cystectomy—78% versus 51% ($p < 0.01$) in this nonrandomised comparison [132]. However, the results of the group successfully managed with BCG are not reported, making a comparison with other series (eg, the study by Thalmann et al [125]) difficult. In conclusion, based on retrospective findings and the inherent biases, BCG induction followed by maintenance is recommended in high-risk NMIBC after a second TUR [12,16]. Cystectomy is recommended in BCG failures (ie, persistence of high-risk disease at 6 mo) and an option in patients with a higher risk for progression based on adverse prognostic factors. A second course of BCG, intravesical chemotherapy, or device-assisted chemotherapy may be an option in select patients or patients who refuse cystectomy [12,16].

3.4. Follow-up strategy

The most common approach (AUA guidelines) to follow patients with NMIBC after TUR consists of urinalysis, cystoscopy, and cytology every 3 mo for 2 yr, every 6 mo until 5 yr, and annually thereafter [16]. The EAU advocates a more tailored follow-up scheme [12]. The follow-up scheme above with annual imaging of the upper tract (computed tomography scanning, intravenous urography) is recommended in NMIBC at high risk for progression, including follow-up of patients with CIS [12,133]. Upper-tract surveillance is not recommended for patients at low and intermediate risk for progression [12]. In addition, the EAU advocates a lower cystoscopy frequency in low- and intermediate-risk NMIBC based on several reports, suggesting that the recurrence seldom progresses to a higher grade and/or stage (ie, <15% of cases [134]) and the safety of watchful waiting in small recurrent papillary lesions, indicating that immediate treatment is not necessary [135,136]. The result of the cystoscopy at 3 mo after TUR is essential, as it is a strong prognostic factor for subsequent recurrence and progression [15,21,137–140]. An algorithm for follow-up and treatment of NMIBC based on risk grouping has been proposed by the International Bladder Cancer Group after review of the current EAU, AUA, First International Consultation on Bladder Tumours, and National Comprehensive Cancer Network guidelines (Fig. 3) [85]. Cytology is still routinely used in many urology practices for all NMIBC patients. However, the data do not support its use in the follow-up of low- and intermediate-risk patients based on a low overall sensitivity [12]. Although many urine-based tumour markers have been developed, their role in surveillance has not been sufficiently validated, and their use has not been recommended in the guidelines [12,16,141].

4. Conclusions

NMIBC is a frequent and heterogeneous disease with varying oncologic outcomes. FC is a valuable add-on to WLC, as FC allows a more complete TUR, resulting in lower recurrence rates. It is not clear yet whether FC also results in lower progression rates. Multiplicity, tumour size, and prior recurrence rate are the most important variables for recurrence. Grade, stage, and CIS are the most important variables for progression. The new WHO 2004 classification system for grade precludes a one-on-one translation to the WHO 1973 system. Although the new system is widely used, proper studies on observer variation and its predictive value are still lacking. Substaging of T1 NMIBC has significant prognostic value, but the optimal system has to be determined. Treatment in low-risk NMIBC consists of TUR followed by a single chemotherapy instillation, which seems most effective in single, small, and primary lesions. Adjuvant intravesical therapy is indicated in intermediate-risk patients. Controversy in the management of high-risk NMIBC by BCG or cystectomy continues.

Author contributions: Bas W.G. van Rhijn had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: van Rhijn.

Acquisition of data: van Rhijn, Burger.

Analysis and interpretation of data: van Rhijn, Burger, Lotan, Solsona, Stief, Sylvester, Witjes, Zlotta.

Drafting of the manuscript: van Rhijn.

Critical revision of the manuscript for important intellectual content: van Rhijn, Burger, Lotan, Solsona, Stief, Sylvester, Witjes, Zlotta.

Statistical analysis: van Rhijn.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Burger, Lotan, Solsona, Stief, Sylvester, Witjes, Zlotta.

Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgement statement: The authors acknowledge Cathy Pierce for her excellent job managing this international review.

References

- [1] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5, version 1.0. International Agency for Research on Cancer Web site. <http://www-dep.iarc.fr>.
- [2] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
- [3] Colombel M, Soloway M, Akaza H, et al. Epidemiology, staging, grading, and risk stratification of bladder cancer. *Eur Urol Suppl* 2008;7:618–26.
- [4] Wu X, Ros MM, Gu J, Kiemeny L. Epidemiology and genetic susceptibility to bladder cancer. *BJU Int* 2008;102:1207–15.
- [5] Zeegers MP, Tan FE, Dorant E, van den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. *Cancer* 2000;89:630–9.
- [6] Murta-Nascimento C, Schmitz-Dräger BJ, Zeegers MP, et al. Epidemiology of urinary bladder cancer: from tumor development to patient's death. *World J Urol* 2007;25:285–95.
- [7] Kiemeny LA, Thorlacius S, Sulem P, et al. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nat Genet* 2008;40:1307–12.
- [8] Aben KK, Witjes JA, Schoenberg MP, Hulsbergen-van de Kaa C, Verbeek AL, Kiemeny LA. Familial aggregation of urothelial cell carcinoma. *Int J Cancer* 2002;98:274–8.
- [9] Kaldor JM, Day NE, Kittelmann B, et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case-control study. *Int J Cancer* 1995;63:1–6.
- [10] Nieder AM, Porter MP, Soloway MS. Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study. *J Urol* 2008;180:2005–9.
- [11] García-Closas M, Malats N, Silverman D, et al. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet* 2005;366:649–59.

- [12] Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. *Eur Urol* 2008;54:303–14.
- [13] Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. *Urology* 2005;66 (Suppl 6A):4–34.
- [14] Kiemeny LA, Witjes JA, Verbeek AL, Heijbroek RP, Debruyne FM. The clinical epidemiology of superficial bladder cancer. Dutch South-East Cooperative Urological Group. *Br J Cancer* 1993;67: 806–12.
- [15] Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. 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 trials. *Eur Urol* 2006;49:466–77.
- [16] Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007;178:2314–30.
- [17] Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer. *Pharmacoeconomics* 2003;21: 1315–30.
- [18] Riley GF, Potosky AL, Lubitz JD, Kessler LG. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. *Med Care* 1995;33:828–41.
- [19] Ploeg M, Aben KK, Kiemeny LA. The present and future burden of urinary bladder cancer in the world. *World J Urol* 2009;27: 289–93.
- [20] Fernandez-Gomez J, Solsona E, Unda M, et al. Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin: multivariate analysis of data from four randomized CUETO trials. *Eur Urol* 2008;53:992–1002.
- [21] Kurth KH, Denis L, Bouffloux C, et al. Factors affecting recurrence and progression in superficial bladder tumours. *Eur J Cancer* 1995;31A:1840–6.
- [22] Kurth K-H, Sylvester RJ. Prognostic factors in non-muscle-invasive bladder tumors: I. Clinical prognostic factors: a review of the experience of the EORTC Genito-Urinary group II: biologic prognostic markers. *Eur Urol Suppl* 2007;6:789–99.
- [23] Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, Vicente-Rodriguez J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. *J Urol* 2000;164:680–4.
- [24] Zieger K, Wolf H, Olsen PR, Hojgaard K. Long-term follow-up of non-invasive bladder tumours (stage Ta): recurrence and progression. *BJU Int* 2000;85:824–8.
- [25] Millán-Rodríguez F, Chéchile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodríguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. *J Urol* 2000;163: 73–8.
- [26] Sylvester RJ. Natural history, recurrence and progression in superficial bladder cancer. *TSW Urology* 2006;1(Suppl 2):15–23.
- [27] Shariat SF, Zippe C, Lüdecke G, et al. Nomograms including nuclear matrix protein 22 for prediction of disease recurrence and progression in patients with Ta, T1 or CIS transitional cell carcinoma of the bladder. *J Urol* 2005;173:1518–25.
- [28] Shariat SF, Margulis V, Lotan Y, Montorsi F, Karakiewicz PI. Nomograms for bladder cancer. *Eur Urol* 2008;54:41–53.
- [29] Grimm M-O, Steinhoff Ch, Simon X, Spiegelhalder P, Ackermann R, Vögeli TA. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* 2003;170:433–7.
- [30] Brausi M, Collette L, Kurth K, et al. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. *Eur Urol* 2002;41:523–31.
- [31] Grossman HB, Gomella L, Fradet Y, et al. A phase III, multicenter comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. *J Urol* 2007;178:62–7.
- [32] Fradet Y, Grossman HB, Gomella L, et al. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol* 2007;178:68–73.
- [33] Lee CSD, Yoon CY, Witjes JA. The past, present, and future of cystoscopy: the fusion of cystoscopy and novel imaging technology. *BJU Int* 2008;102:1228–33.
- [34] Schmidbauer J, Witjes F, Schmeller N, Donat R, Susani M, Marberger M. Hexvix PCB301/01 Study Group. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol* 2004;171:135–8.
- [35] Hungerhuber E, Stepp H, Kriegmair M, et al. Seven years' experience with 5-aminolevulinic acid in detection of transitional cell carcinoma of the bladder. *Urology* 2007;69:260–4.
- [36] Daniltschenko DI, Riedl CR, Sachs MD, et al. Long-term benefit of 5-aminolevulinic acid fluorescence assisted transurethral resection of superficial bladder cancer: 5-year results of a prospective randomized study. *J Urol* 2005;174:2129–33.
- [37] Denzinger S, Burger M, Walter B, et al. Clinically relevant risk of reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid induced fluorescence diagnosis: 8-years results of prospective randomized study. *Urology* 2007;69: 675–9.
- [38] Karl A, Tritschler S, Stanislaus P, et al. Positive urine cytology but negative white-light cystoscopy: an indication for fluorescence cystoscopy? *BJU Int* 2009;103:484–7.
- [39] Ray ER, Chatterton K, Khan MS, Thomas K, Chandra A, O'Brien TS. Hexylaminolaevulinate 'blue light' fluorescence cystoscopy in the investigation of clinically unconfirmed positive urine cytology. *BJU Int* 2009;103:1363–7.
- [40] Burger M, Zaak D, Stief CG, et al. Photodynamic diagnostics and noninvasive bladder cancer: is it cost-effective in long-term application? A Germany-based cost analysis. *Eur Urol* 2007;52: 142–7.
- [41] Denzinger S, Wieland WF, Otto W, Filbeck T, Knuechel R, Burger M. Does photodynamic transurethral resection of bladder tumour improve the outcome of initial T1 high-grade bladder cancer? A long-term follow-up of a randomized study. *BJU Int* 2008;101: 566–9.
- [42] Stein JP, Grossfeld GD, Ginsberg DA, et al. Prognostic markers in bladder cancer: a contemporary review of the literature. *J Urol* 1998;160:645–59.
- [43] Karam JA, Shariat SF, Hsieh JT, Knowles MA. Genomics: a preview of genomic medicine. *BJU Int* 2008;102:1221–7.
- [44] Knowles MA. Molecular subtypes of bladder cancer: Jekyll and Hyde or chalk and cheese. *Carcinogenesis* 2006;27:361–73.
- [45] van Rhijn BW, Vis AN, van der Kwast TH, et al. Molecular grading of urothelial cell carcinoma with fibroblast growth factor receptor 3 and MIB-1 is superior to pathologic grade for the prediction of clinical outcome. *J Clin Oncol* 2003;21:1912–21.
- [46] Spruck III CH, Ohneseit PF, Gonzalez-Zulueta M, et al. Two molecular pathways to transitional cell carcinoma of the bladder. *Cancer Res* 1994;54:784–8.
- [47] Burger M, van der Aa MNM, van Oers JMM, et al. Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by *FGFR3* mutation status: a prospective study. *Eur Urol* 2008;54:835–44.
- [48] Hernández S, López-Knowles E, Lloreta J, et al. Prospective study of *FGFR3* mutations as a prognostic factor in nonmuscle invasive urothelial bladder carcinomas. *J Clin Oncol* 2006;24:3664–71.

- [49] Mostofi FK, Sobin LH, Torloni H. Histological typing of urinary bladder tumours. In: *International Histological Classification of Tumours*. No. 10. Geneva, Switzerland: World Health Organization; 1973. p. 21–31.
- [50] Ooms EC, Anderson WA, Alons CL, Boon ME, Veldhuizen RW. Analysis of the performance of pathologists in the grading of bladder tumors. *Hum Pathol* 1983;14:140–3.
- [51] Tosoni I, Wagner U, Sauter G, et al. Clinical significance of inter-observer differences in the staging and grading of superficial bladder cancer. *BJU Int* 2000;85:48–53.
- [52] Bol MG, Baak JP, Buhr-Wildhagen S, et al. Reproducibility and prognostic variability of grade and lamina propria invasion in stages Ta, T1 urothelial carcinoma of the bladder. *J Urol* 2003;169:1291–4.
- [53] Witjes JA, Moonen PM, van der Heijden AG. Review pathology in a diagnostic bladder cancer trial: effect of patient risk category. *Urology* 2006;67:751–5.
- [54] Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Am J Surg Pathol* 1998;22:1435–48.
- [55] Eble J, Sauter G, Epstein J, Sesterhenn I. *Pathology and genetics of tumours of the urinary system and male genital organs*. Lyon, France: IARC Press; 2004.
- [56] Lopez-Beltran A, Montironi R. Non-invasive urothelial neoplasms: according to the most recent WHO classification. *Eur Urol* 2004;46:170–6.
- [57] MacLennan GT, Kirkali Z, Cheng L. Histologic grading of noninvasive papillary urothelial neoplasms. *Eur Urol* 2007;51:889–98.
- [58] Hofmann T, Knüchel-Clarke R, Hartmann A, et al. Clinical implications of the 2004 WHO histological classification on non-invasive tumours of the urinary bladder. *EAU-EBU Update Series* 2006;4:83–95.
- [59] Samarasinghe H, Makarov DV, Epstein JI. Comparison of WHO/ISUP and WHO classification of noninvasive papillary urothelial neoplasms for risk of progression. *Urology* 2002;60:315–9.
- [60] Yin H, Leong AS. Histologic grading of noninvasive papillary urothelial tumors: validation of the 1998 WHO/ISUP system by immunophenotyping and follow-up. *Am J Clin Pathol* 2004;121:679–87.
- [61] Harnden P. A critical appraisal of the classification of urothelial tumours: time for a review of the evidence and a radical change? *BJU Int* 2006;99:723–5.
- [62] Younes M, Sussman J, True LD. The usefulness of the level of the muscularis mucosae in the staging of invasive transitional cell carcinoma of the urinary bladder. *Cancer* 1990;66:543–8.
- [63] Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. The importance of the depth of invasion in stage T1 bladder carcinoma: a prospective cohort study. *J Urol* 1997;157:800–3.
- [64] Smits G, Schaafsma E, Kiemeny L, Caris C, Debruyne F, Witjes JA. Microstaging of pT1 transitional cell carcinoma of the bladder: identification of subgroups with distinct risks of progression. *Urology* 1998;52:1009–13.
- [65] Hasui Y, Osada Y, Kitada S, Nishi S. Significance of invasion to the muscularis mucosae on the progression of superficial bladder cancer. *Urology* 1994;43:782–6.
- [66] Angulo JC, Lopez JI, Grignon DJ, Sanchez-Chapado M. Muscularis mucosa differentiates two populations with different prognosis in stage T1 bladder cancer. *Urology* 1995;45:47–53.
- [67] Orsola A, Trias I, Raventós CX, et al. Initial high-grade T1 urothelial cell carcinoma: feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. *Eur Urol* 2005;48:231–8.
- [68] Kondylis FI, Demirci S, Ladaga L, Kolm P, Schellhammer PF. Outcomes after intravesical bacillus Calmette–Guerin are not affected by substaging of high grade T1 transitional cell carcinoma. *J Urol* 2000;163:1120–3.
- [69] Cheng L, Weaver AL, Neumann RM, Scherer BG, Bostwick DG. Substaging of T1 bladder carcinoma based on the depth of invasion as measured by micrometer: A new proposal. *Cancer* 1999;86:1035–43.
- [70] Cheng L, Neumann RM, Weaver AL, Spotts BE, Bostwick DG. Predicting cancer progression in patient with T1 bladder carcinoma. *J Clin Oncol* 1999;17:3182–7.
- [71] van der Aa MN, van Leenders GJ, Steyerberg EW, et al. A new system for substaging pT1 papillary bladder cancer: a prognostic evaluation. *Hum Pathol* 2005;36:981–6.
- [72] Sedelaar JPM, Witjes JA. Technique of TUR of bladder tumours: value of repeat TUR and random biopsies. *EAU-EBU Update Series* 2007;5:139–44.
- [73] Herr HW, Donat SM. Quality control in transurethral resection of bladder tumours. *BJU Int* 2008;102:1242–6.
- [74] Zlotta AR. When and how to treat superficial and muscle-invasive bladder cancer. *Eur Urol* 2007;52:1554–7.
- [75] Jakse G, Algaba F, Malmström P-U, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? *Eur Urol* 2004;45:539–46.
- [76] Miladi M, Peyromaure M, Zerbib M, Saïghi D, Debré B. The value of a second transurethral resection in evaluating patients with bladder tumours. *Eur Urol* 2003;43:241–5.
- [77] Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? *J Urol* 2001;165:808–10.
- [78] Herr HW, Donat SM, Dalbagni G. Can restaging transurethral resection of T1 bladder cancer select patients for immediate cystectomy? *J Urol* 2007;177:75–9.
- [79] Herr HW. Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to bacillus Calmette–Guerin therapy. *J Urol* 2005;174:2134–7.
- [80] Divrik RT, Yildirim Ü, Zorlu F, Özen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *J Urol* 2006;175:1641–4.
- [81] Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. *J Urol* 1999;161:1120–3.
- [82] Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a metaanalysis of published results of randomized clinical trials. *J Urol* 2004;171:2186–90.
- [83] Berrum-Svennung I, Granfors T, Jahnson S, Boman H, Holmäng S. A single instillation of epirubicin after transurethral resection of bladder tumors prevents only small recurrences. *J Urol* 2008;179:101–5.
- [84] Gudjónsson S, Adell L, Merdasa F, et al. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomised multicentre study. *Eur Urol* 2009;55:773–80.
- [85] Lamm D, Colombel M, Persad R, et al. Clinical practice recommendations for the management of non-muscle invasive bladder cancer. *Eur Urol Suppl* 2008;7:651–66.
- [86] Witjes JA, Hendricksen K. Intravesical pharmacotherapy for non-muscle-invasive bladder cancer: a critical analysis of currently

- available drugs, treatment schedules, and long-term results. *Eur Urol* 2008;53:45–52.
- [87] Herr HW, Schwalb DM, Zhang ZF, et al. Intravesical bacillus Calmette-Guérin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. *J Clin Oncol* 1995;13:1404–8.
- [88] Pawinski A, Sylvester R, Kurth KH, et al. A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of TaT1 bladder cancer. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Part on Superficial Bladder Cancer. *J Urol* 1996;156:1934–41.
- [89] Böhle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol* 2003;169:90–5.
- [90] Malmström P-U, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. *Eur Urol* 2009;56:247–56.
- [91] Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non-muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. *Eur Urol* 2008;53:709–19.
- [92] Hendricksen K, Witjes WPJ, Idema JG, et al. Comparison of three schedules of intravesical epirubicin in patients with non-muscle-invasive bladder cancer. *Eur Urol* 2008;53:984–91.
- [93] Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2002;168:1964–70.
- [94] Böhle A, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology* 2004;63:682–7.
- [95] Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus Calmette-Guérin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2005;174:86–91.
- [96] Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol* 2000;163:1124–9.
- [97] Herr HW. Is maintenance bacillus Calmette-Guérin really necessary? *Eur Urol* 2008;54:971–3.
- [98] Zlotta AR, Drowart A, Van Vooren JP, et al. Evolution and clinical significance of the T cell proliferative and cytokine response directed against the fibronectin binding antigen 85 complex of bacillus Calmette-Guerin during intravesical treatment of superficial bladder cancer. *J Urol* 1997;157:492–8.
- [99] Huang GJ, Hamilton AS, Lo M, Stein JP, Penson DF. Predictors of intravesical therapy for nonmuscle invasive bladder cancer: results from the surveillance, epidemiology and end results program 2003 patterns of care project. *J Urol* 2008;180:520–4.
- [100] Martinez-Pineiro JA, Flores N, Isorna S, et al. Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guérin with a reduced dose of 27 mg in superficial bladder cancer. *BJU Int* 2002;89:671–80.
- [101] Martinez-Pineiro JA, Martinez-Pineiro L, Solsona E, et al. Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. *J Urol* 2005;174:1242–7.
- [102] Ojea A, Nogueira JL, Solsona E, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. *Eur Urol* 2007;52:1398–406.
- [103] van der Meijden APM, Sylvester RJ, Oosterlinck W, Hoeltl W, Bono AV, for the EORTC Genito-Urinary Tract Cancer Group. Maintenance bacillus Calmette-Guerin for Ta, T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group phase III trial. *Eur Urol* 2003;44:429–34.
- [104] Sylvester RJ, van der Meijden APM, Oosterlinck W, Hoeltl W, Bono AV, for the EORTC Genito-Urinary Tract Cancer Group. The side effects of bacillus Calmette-Guerin in the treatment of Ta T1 bladder cancer do not predict its efficacy: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group phase III trial. *Eur Urol* 2003;44:423–8.
- [105] Colombel M, Saint F, Chopin D, Malavaud B, Nicolas L, Rischmann P. The effect of ofloxacin on bacillus Calmette-Guérin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol* 2006;176:935–9.
- [106] Au JL, Baladament RA, Wientjes MG, et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. *J Natl Cancer Inst* 2001;93:597–604.
- [107] Hendricksen K, Witjes JA. Intravesical gemcitabine: an update of clinical results. *Curr Opin Urol* 2006;16:361–6.
- [108] van der Heijden AG, Moonen PM, Cornel EB, et al. Phase II marker lesion study with intravesical instillation of apaziquone for superficial bladder cancer: toxicity and marker response. *J Urol* 2006;176:1349–53.
- [109] Colombo R, Da Pozzo LF, Salonia A, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *J Clin Oncol* 2003;21:4270–6.
- [110] van der Heijden AG, Kiemeneij LA, Gofrit ON, et al. Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder. *Eur Urol* 2004;46:65–72.
- [111] Di Stasi SM, Giannantoni A, Stephen RL, et al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. *J Urol* 2003;170:777–82.
- [112] Di Stasi SM, Giannantoni A, Giurioli A, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol* 2006;7:43–51.
- [113] Stein JP, Penson DF. Invasive T1 bladder cancer: indications and rationale for radical cystectomy. *BJU Int* 2008;102:270–5.
- [114] Cookson MS, Herr HW, Zhang ZF, Soloway S, Sogani PC, Fair WR. The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J Urol* 1997;158:62–7.
- [115] Raj GV, Herr H, Serio AM, et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol* 2007;177:1283–6.

- [116] Kamat AM, Gee JR, Dinney CP, et al. The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. *J Urol* 2006;175:881–5.
- [117] Kunju LP, You L, Zhang Y, Daignault S, Montie JE, Lee CT. Lymphovascular invasion of urothelial cancer in matched transurethral bladder tumor resection and radical cystectomy specimens. *J Urol* 2008;180:1928–32.
- [118] Andius P, Johansson SL, Holmäng S. Prognostic factors in stage T1 bladder cancer: tumor pattern (solid or papillary) and vascular invasion more important than depth of invasion. *Urology* 2007;70:758–62.
- [119] Masood S, Sriprasad S, Palmer JH, Mufti GR. T1G3 bladder cancer—indications for early cystectomy. *Int Urol Nephrol* 2004;36:41–4.
- [120] Denzinger S, Otto W, Fritsche HM, et al. Bladder sparing approach for initial T1G3 bladder cancer: do multifocality, size of tumor or concomitant carcinoma in situ matter? A long-term analysis of 132 patients. *Int J Urol* 2007;14:995–9.
- [121] Solsona E, Iborra I, Dumont R, Rubio-Briones J, Casanova J, Almenar S. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. *J Urol* 2000;164:685–9.
- [122] Griffiths TR, Charlton M, Neal DE, Powell PH. Treatment of carcinoma in situ with intravesical bacillus Calmette-Guerin without maintenance. *J Urol* 2002;167:2408–12.
- [123] Davis JW, Sheth SI, Doviak MJ, Schellhammer PF. Superficial bladder carcinoma treated with bacillus Calmette-Guerin: progression-free and disease specific survival with minimum 10-year followup. *J Urol* 2002;167:494–500.
- [124] Patard J-J, Rodriguez A, Leray E, Rioux-Leclercq N, Guillé F, Lobel B. Intravesical bacillus Calmette-Guerin treatment improves patient survival in T1G3 bladder tumours. *Eur Urol* 2002;41:635–42.
- [125] Thalmann GN, Markwalder R, Shahin O, Burkhard FC, Hochreiter WW, Studer UE. Primary T1G3 bladder cancer: organ preserving approach or immediate cystectomy? *J Urol* 2004;172:70–5.
- [126] Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666–75.
- [127] Gupta A, Lotan Y, Bastian PJ, et al. Outcomes of patients with clinical T1 grade 3 urothelial cell bladder carcinoma treated with radical cystectomy. *Urology* 2008;71:302–7.
- [128] Schrier BPh, Hollander MP, van Rhijn BWG, Kiemeny LALM, Witjes JA. Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumors and implications for therapy. *Eur Urol* 2004;45:292–6.
- [129] Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol* 2001;166:1296–9.
- [130] Solsona E, Iborra I, Rubio J, Casanova J, Almenar S. The optimum timing of radical cystectomy for patients with recurrent high-risk superficial bladder tumour. *BJU Int* 2004;94:1258–62.
- [131] Stöckle M, Alken P, Engelmann U, Jacobi GH, Riedmiller H, Hohenfellner R. Radical cystectomy – often too late? *Eur Urol* 1987;13:361–7.
- [132] Denzinger S, Fritsche H-M, Otto W, Blana A, Wieland W-F, Burger M. Early versus deferred cystectomy for initial high-risk pT1G3 urothelial carcinoma of the bladder: do risk factors define feasibility of bladder-sparing approach? *Eur Urol* 2008;53:146–52.
- [133] van der Meijden APM, Sylvester R, Oosterlinck W, et al. EAU guidelines on the diagnosis and treatment of urothelial carcinoma in situ. *Eur Urol* 2005;48:363–71.
- [134] Borhan A, Reeder JE, O'Connell MJ, et al. Grade progression and regression in recurrent urothelial cancer. *J Urol* 2003;169:2106–9.
- [135] Soloway M, Bruck DS, Kim SS. Expectant management of small recurrent, non-invasive papillary bladder tumours. *J Urol* 2003;170:438–41.
- [136] Gofrit ON, Pode D, Lazar A, Katz R, Shapiro A. Watchful waiting policy in recurrent Ta G1 bladder tumors. *Eur Urol* 2006;49:303–7.
- [137] Holmang S, Johansson SL. Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. *J Urol* 2002;167:1634–7.
- [138] Öge O, Erdem E, Atsü N, Ahin A, Özen H. Proposal for changes in cystoscopic follow-up of patients with low-grade pTa bladder tumor. *Eur Urol* 2000;37:271–4.
- [139] Mariappan P, Smith G. A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on a 25-year prospective database. *J Urol* 2005;173:1108–11.
- [140] Mariappan P, Smith G, Lamb AD, Grigor KM, Tolley DA. Pattern of recurrence changes in noninvasive bladder tumors observed during 2 decades. *J Urol* 2007;177:867–75.
- [141] van Rhijn BWG, van der Poel HG, van der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. *Eur Urol* 2005;47:736–48.