



## Review – Bladder Cancer

# EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder

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### Abstract

**Context and objective:** To present the updated version of 2008 European Association of Urology (EAU) guidelines on non-muscle-invasive bladder cancer.

**Evidence acquisition:** A systematic review of the recent literature on the diagnosis and treatment of non-muscle-invasive bladder cancer was performed. The guidelines were updated and the level of evidence and grade of recommendation were assigned.

**Evidence synthesis:** The diagnosis of bladder cancer depends on cystoscopy and histologic evaluation of the resected tissue. A complete and correct transurethral resection (TUR) is essential for the prognosis of the patient. When the initial resection is incomplete or when a high-grade or T1 tumour is detected, a second TUR within 2–6 wk should be performed.

The short- and long-term risks of both recurrence and progression may be estimated for individual patients using the scoring system and risk tables. The stratification of patients to low, intermediate, and high-risk groups—separately for recurrence and progression—represents the cornerstone for indication of adjuvant treatment. In patients at low risk of tumour recurrence and progression, one immediate instillation of chemotherapy is strongly recommended. In those at an intermediate or high risk of recurrence and an intermediate risk of progression, one immediate instillation of chemotherapy should be followed by further instillations of chemotherapy or a minimum of 1 yr of bacillus Calmette-Guerin (BCG). In patients at high risk of tumour progression, after an immediate instillation of chemotherapy, intravesical BCG for at least 1 yr is indicated. Immediate cystectomy may be offered to the highest risk patients and in patients with BCG failure. The long version of the guidelines is available on [www.uroweb.org](http://www.uroweb.org).

**Conclusions:** These EAU guidelines present the updated information about the diagnosis and treatment of non-muscle-invasive bladder cancer and offer the recent findings for the routine clinical application.

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## 1. Background

The first European Association of Urology (EAU) guidelines on bladder cancer were published in 2002 [1]. Since then, the long version of the guidelines has been updated continuously, with the most recent version available on [www.uroweb.org](http://www.uroweb.org). This overview represents an updated version of 2008 EAU guidelines on non-muscle-invasive bladder cancer.

## 2. Epidemiology

Bladder carcinoma is the most common malignancy of the urinary tract. In Europe, the highest incidence (ASR = age standardized rate) is reported from the western (23.6 in males and 5.4 in females) and southern parts (27.1 in males and 4.1 in females), followed by northern Europe (16.9 in males and 4.9 in females). The lowest incidence can be observed in eastern European countries (14.7 in males and 2.2 in females, respectively) [2].

Approximately 75–85% of patients with bladder cancer present with the disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1).

## 3. Classification

The 2002 tumour, node, metastasis (TNM) classification approved by the Union International Contre le Cancer (UICC) has been widely accepted and is used in these guidelines (Table 1) [3].

The new classification for grading of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) and published by the WHO in 2004 (Table 2) [4]. It differentiates between papillary urothelial neoplasms of low malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas.

The PUNLMP are lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. They have a negligible risk for progression, but still have a tendency to recur. The intermediate grade (grade 2), which was the subject of controversy in the 1973 WHO classification, has been eliminated.

Until the 2004 WHO classification has been validated by more clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications (Table 2).

Despite well-defined criteria, there is important interobserver variability in classifying dysplasia and

**Table 1 – 2002 TNM classification of urinary bladder cancer**

<b>T – Primary tumour</b>	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: ‘flat tumour’
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
<b>N – Lymph nodes</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
<b>M – Distant metastasis</b>	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

**Table 2 – WHO grading in 1973 and in 2004**

<b>1973 WHO grading</b>	
Urothelial papilloma	
Grade 1:	well differentiated
Grade 2	moderately differentiated
Grade 3:	poorly differentiated
<b>2004 WHO grading</b>	
Urothelial papilloma	
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	
Low-grade papillary urothelial carcinoma	
High-grade papillary urothelial carcinoma	
WHO = World Health Organization.	

carcinoma in situ (CIS, Tis), stage T1 versus Ta tumours and grading of the tumours [5]. As a consequence, we recommend that the urologist reviews histologic findings with the pathologist.

#### 4. Risk factors

The urologist should be aware of the types of occupational exposures that may be related to urothelial carcinogens [6]. Aromatic amines were the first to be recognized. At-risk groups include workers in the following industries: printing, iron, and aluminium processing, industrial painting, gas and tar manufacturing (level of evidence: 3).

Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer and leads to its higher mortality [7] (level of evidence: 3).

#### 5. Diagnosis

Haematuria is the most common finding in non-muscle-invasive bladder tumours. Bladder irritation, dysuria, or urgency may be symptoms of CIS.

##### 5.1. Imaging

Using intravenous urography (IVU) large tumours may be seen as filling defects in the bladder. It is also utilized to detect filling defects in the upper urinary tract or hydronephrosis, which may indicate the presence of a ureteral tumour. The necessity to perform routine IVU is now questioned because of the low incidence of significant findings [8,9] (level of evidence: 3). The incidence of simultaneous upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone [8]. The risk of

tumour recurrence in the upper urinary tract during follow-up increases in multiple and high-risk tumours [9].

In many centres, CT urography is used as an alternative to conventional IVU.

Transabdominal ultrasound (US) permits characterization of renal masses, detection of hydronephrosis, and visualization of intraluminal filling defects in the bladder. Combined with plain abdominal film, it can be as accurate as IVU in the diagnosis of the cause of haematuria (level of evidence: 3).

##### 5.2. Urinary cytology

Examination of a voided urine or bladder washing specimen for exfoliated cancer cells has high sensitivity in high-grade tumours but low sensitivity in low-grade tumours (level of evidence: 2a) [10]. It is thus useful when a high-grade malignancy or CIS is present; however, a negative result cannot exclude the presence of a low-grade cancer.

Positive urinary cytology may indicate urothelial tumour anywhere in the urinary tract. Cytological interpretation is user dependent [11]. The evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations. In experienced hands however the specificity exceeds 90% [10] (level of evidence: 2a). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable, as cytolysis may be often present.

##### 5.3. Urine molecular tests

Several tests based on detection of soluble or cell-associated markers in urine are available [10]. Most of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower (level of evidence: 2a). It remains unclear whether these tests offer additional information which is useful for detection and management of non-muscle-invasive bladder tumours [10]. Moreover, the additional costs of some of these tests should be considered.

##### 5.4. Cystoscopy

The diagnosis of bladder cancer ultimately depends on cystoscopic examination and histologic evaluation of the resected tissue.

In general, cystoscopy is initially performed in the office, using flexible instruments. If a bladder tumour has been visualized in earlier imaging studies, a diagnostic cystoscopy can be omitted.

A careful description of the finding is necessary. It should include the site, size, number, and appearance (papillary or solid) of the tumours as well as a description of mucosal abnormalities.

#### 5.5. Transurethral resection (TUR)

The goal of the TUR in TaT1 bladder tumours is to make the correct diagnosis and remove all visible lesions.

Small tumours (less than 1 cm) can be resected en bloc, the specimen should contain a part of the underlying bladder wall. Some experts believe that a deep resection is not necessary in small, apparently low-grade lesions with a previous history of TaG1 tumour.

Larger tumours should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. The specimens from different fractions must be referred to the pathologist in separate containers. Cauterization has to be avoided as much as possible during the resection to prevent tissue destruction.

The pathologic report should specify the grade of the lesion, and the depth of tumour invasion into the bladder wall and give information on whether the lamina propria and muscle are present in the specimen [12].

A complete and correct TUR is essential for the prognosis of the patient [13].

#### 5.6. Bladder and prostatic urethra biopsies

Bladder tumours are often multifocal. Moreover, TaT1 tumours can be accompanied by CIS or dysplasia. These lesions may present themselves as velvet-like, reddish areas indistinguishable from inflammation or may be not visible at all.

The biopsies from normal-looking mucosa in patients with TaT1 tumours, so-called random biopsies (R-biopsies) or selected site mucosal biopsies, are not routinely recommended. The likelihood of detecting CIS in low-risk tumours is extremely low (less than 2%), and the choice of adjuvant intravesical therapy is not influenced by the biopsy result [14] (level of evidence: 2a). Cold cup biopsies from normal-looking mucosa should be performed when cytology is positive or when exophytic tumour is of nonpapillary appearance. When abnormal areas of urothelium are seen, it is advised to take "cold cup" biopsies or biopsies with a resection loop. Material obtained by random or directed biopsies must be sent for pathologic assessment in separate containers.

The involvement of the prostatic urethra and ducts in male patients with TaT1 bladder tumours has been reported. Although the exact risk is not known, it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours [15,16] (level of evidence: 3). In these cases and when cytology is positive with no evidence of tumour in the bladder or when abnormalities of prostatic urethra are visible, biopsies of the prostatic urethra should be considered.

#### 5.7. Fluorescence cystoscopy

The use of white light may lead to missing lesions that are present but not visible.

Fluorescence cystoscopy is performed using violet light after intravesical instillation of a photosensitizer or its precursor, usually 5-aminolevulinic acid (5-ALA) or hexylaminolevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumour, particularly CIS [17] (level of evidence: 2a). False positivity, however, can be induced by inflammation and recent TUR or intravesical instillation.

The benefit of fluorescence-guided TUR for recurrence-free survival was shown in several small randomised clinical trials [18], but its definitive value in improving the outcome of patients for progression rates or survival remains to be proven. The additional costs of the equipment should be considered.

#### 5.8. Second resection

The significant risk of residual tumour after the initial TUR of TaT1 lesions has been demonstrated [13,19] (level of evidence: 1). Moreover, the tumour may be understaged by the initial resection.

A second TUR should be considered if there is a suspicion that the initial resection was incomplete, eg when multiple or large tumours are present or when the pathologist reported no muscle tissue in the specimen. Furthermore, it should be performed when a high-grade non-muscle-invasive tumour or a T1 tumour was detected at the initial TUR.

It has been demonstrated that a second TUR can increase recurrence-free and progression-free survival [20] (level of evidence: 2a). Most authors recommend resection 2–6 wk after the initial TUR. The procedure should include a resection of the primary tumour site. The summary of recommendations for diagnosis of non-muscle-invasive bladder cancer is presented in Table 3.

**Table 3 – Recommendations for diagnosis of non-muscle-invasive bladder tumours**

- Renal and bladder ultrasonography, intravenous urography (IVU) or CT-urography in selected cases (tumours located in the trigone) (grade of recommendation: B).
- Cystoscopy with description of the tumour (site, size, number, and appearance) and mucosal abnormalities.
- Urine cytology.
- Transurethral resection (TUR) in one piece for small tumours (less than 1 cm). The specimen should contain a part of the underlying bladder wall (grade of recommendation: B).
- TUR in fractions (including muscle tissue) for larger tumours (grade of recommendation: B).
- Biopsies of abnormal-looking urothelium, biopsies from normal-looking mucosa when cytology is positive or when exophytic tumour is of nonpapillary appearance (grade of recommendation: C).
- Biopsy of the prostatic urethra in the case of bladder neck tumour, when bladder CIS is present or suspected, in the case of positive cytology without evidence of tumour in the bladder or when abnormalities of prostatic urethra are visible. If it was not performed during the initial procedure it can be completed at the time of the second resection. The biopsy is taken using resection loop from the precolicular area (grade of recommendation: C).
- If equipment is available, fluorescence-guided biopsy when bladder CIS is suspected (eg positive cytology, recurrent tumour with previous history of a high grade lesion) (grade of recommendation: C).
- A second TUR 2–6 wk after the initial resection when it was incomplete or when a high-grade or T1 tumour was detected (grade of recommendation: B).
- The pathological report should specify the grade, the depth of tumour invasion, and whether the lamina propria and muscle are present in the specimen (grade of recommendation: C).

## 6. Predicting recurrence and progression

The classic way to categorize patients with TaT1 tumours is to divide them into risk groups based on prognostic factors derived from multivariate analyses. In order to separately predict the short-term and long-term risks of both recurrence and progression in individual patients, a scoring system and risk tables have been developed [21]. The basis was the European Organization for Research and Treatment of Cancer (EORTC) database, which provided individual patient data for 2596 patients diagnosed with TaT1 tumours randomized in seven trials, which did not contain a second TUR and maintenance bacillus Calmette-Guerin (BCG) therapy. The scoring system is based on the six most significant clinical and pathological factors:

- Number of tumours
- Tumour size
- Prior recurrence rate
- T category
- Presence of concomitant CIS
- Tumour grade.

Table 4 illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 5 shows the total scores stratified, as in the original article [21], into four categories reflecting various probabilities of recurrence and progression at 1 and 5 yr. With combining two of the four categories distinctly in recurrence and progression, the EAU working group suggests to use, as shown in the rightmost column in Table 5, a 3-tier system defining low, intermediate, and high-risk groups for recurrence and progression.

## 7. Adjuvant intravesical chemotherapy

### 7.1. One, immediate, post-operative intravesical instillation

TaT1 tumours recur frequently and progress to muscle-invasive disease in a limited number of cases. It is therefore necessary to consider adjuvant therapy in all patients.

In meta-analysis of seven randomized trials, one immediate instillation of chemotherapy after TUR

**Table 4 – Weighting used to calculate recurrence and progression scores (CIS = carcinoma in situ)**

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2 to 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
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

**Table 5 – Probability of recurrence and progression according to total score (electronic calculators for Tables 4 and 5 are available at <http://www.eortc.be/tools/bladdercalculator/>)**

Recurrence score	Probability of recurrence at 1 yr		Probability of recurrence at 5 yr		Recurrence risk group
	%	(95% CI)	%	(95% CI)	
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
Progression score	Probability of progression at 1 yr		Probability of progression at 5 yr		Progression risk group
	%	(95% CI)	%	(95% CI)	
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

decreased the percent of patients with recurrence by 12% and the odds of recurrence by 39%. The benefit was confirmed in single and multiple tumours [22] (level of evidence: 1a).

The difference of 12% means that 8.5 patients must be treated to prevent one recurrence.

The effect can be explained by the destruction of circulating tumour cells or as an ablative effect of residual tumour cells at the resection site.

The timing of the instillation is crucial. In all studies, the instillation was administered within 24 h. One study reported that if the first instillation was not given the same day as TUR, there was a twofold increase in the relative risk of recurrence [23] (level of evidence: 2a).

Mitomycin C (MMC), epirubicin, and doxorubicin have all shown a comparable beneficial effect [22] (level of evidence: 1b).

Severe complications are very rare. They have been reported when extravasation of the drug occurred [24]. Thus, an immediate instillation should be omitted in case of overt or suspected intra- or extraperitoneal perforation, which is most likely to appear in extensive TUR procedures. Clear instructions should be given to the nursing staff for controlling the free flow of the bladder catheter at the end of the instillation.

### 7.2. Additional intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on the patient's prognosis. In patients with a low risk of recurrence (Table 5), a single immediate instillation may be considered to be sufficient treatment [22] (level of evidence: 1a). For other patients, however, it remains an incomplete treat-

ment as the likelihood of recurrence and/or progression is considerable.

The effect of the immediate instillation of chemotherapy occurs during the first and second year [25] (level of evidence: 1b).

The choice between further chemotherapy or BCG immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. A meta-analysis comparing intravesical chemotherapy to TUR alone demonstrated that chemotherapy prevents recurrence but not progression [26] (level of evidence: 1a). The efficacy of intravesical chemotherapy in reducing the risk of tumour recurrence was confirmed by two other meta-analyses in primary [27] and recurrent tumours [28].

It is still controversial how long and how frequently intravesical chemotherapy instillations have to be given. From a systematic review of the literature of randomised clinical trials, comparing different schedules of intravesical chemotherapy instillations, one could only conclude that the ideal duration and intensity of the schedule remains undefined because of conflicting data [29].

### 7.3. Optimizing intravesical chemotherapy

It was demonstrated that adapting the urinary pH, decreasing the urinary excretion, and buffering the intravesical solution reduce the recurrence rate [30] (level of evidence: 1b).

Concentration was more important than the duration of the treatment [31] (level of evidence: 1b). In view of these data, it seems advisable to dissolve the drug in a buffered solution at optimal pH and to ask the patient not to drink the morning before instillation.

## 8. Adjuvant intravesical BCG immunotherapy

Four meta-analyses confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy in preventing recurrences of TaT1 tumours [32–35] (Level of evidence: 1a).

Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [36,37] (level of evidence: 1a). A reduction of 27% in the odds of progression with BCG treatment was noted ( $p = 0.0001$ ). The size of the reduction is similar in patients with TaT1 tumours and in those with CIS [36].

Another two meta-analyses, however, suggested a possible bias in favour of BCG by the inclusion of patients previously treated with intravesical chemotherapy [38,39].

### 8.1. The optimal BCG schedule and dose

For optimal efficacy, the BCG must be given in a maintenance schedule [35–37] (level of evidence: 1a). In the EORTC meta-analysis, only patients receiving maintenance BCG benefited. In the four trials where no maintenance was given, no reduction in progression was observed. In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the odds of progression was observed ( $p = 0.00004$ ). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective [36]. In a meta-analysis, it was concluded that at least 1 yr of maintenance BCG was required to show the superiority of BCG over MMC in preventing recurrence or progression [35,37].

Induction BCG instillations are classically given according to the empirical 6-wk induction schedule, and many different maintenance schedules have been used with up to 30 instillations given over 3 yr [40]. The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown. Based on the extent of intravesical immune response, it is suggested that 3 consecutive weekly instillations give a maximum response [41].

To reduce toxicity, one-third and one-quarter dose of BCG were proposed. Comparing one-third dose to full-dose no overall difference in efficacy was found. However, there was a suggestion that a full dose of BCG may be more effective in multifocal disease [42] (level of evidence: 1b). Although fewer patients reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar. Further reduction to one-sixth dose was followed by a decrease of efficacy with equal toxicity [43].

### 8.2. BCG toxicity

Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis have compromised the use of BCG. However, with increased experience in applying BCG, the side-effects now appear to be less prominent. Serious side-effects are encountered in fewer than 5% of patients [44] (level of evidence: 1b). Major complications can appear after systemic absorption of the drug. BCG thus should not be administered during the first 2 wk after TUR, in patients with haematuria and after traumatic catheterization.

### 8.3. Indications for BCG

Although BCG is a very effective treatment, consensus exists that not all patients with non-muscle-invasive bladder cancer should be treated with BCG due to the risk of toxicity. BCG may be considered to be overtreatment for tumours at low risk of recurrence and progression (Table 5). In patients with tumours at high risk of progression, after an immediate instillation of chemotherapy, BCG including a maintenance schedule is indicated.

Although patients at intermediate risk of progression were included in the meta-analyses [35,37], a separate confirmation of the superiority of BCG in these patients is not available. BCG can be offered in this group if chemotherapy is badly tolerated or if the patient continues to recur in spite of repeated chemotherapy instillations. BCG should then be given for at least 1 yr. Recommendations for intravesical therapy are summarized in Table 6.

## 9. Treatment of failures of intravesical therapy

Patients with non-muscle-invasive recurrences after intravesical chemotherapy can profit from BCG instillations [38].

Treatment with BCG is considered to have failed in following situations:

- If muscle-invasive tumour is detected.
- If high-grade non-muscle-invasive tumour is present at both 3 and 6 mo [45]. In patients with tumour presence at 3 mo an additional BCG course provokes complete response in more than 50% of cases [45,46].
- Any worsening of the disease under BCG treatment, such as a higher number of recurrences, higher T or grade, appearance of CIS, in spite of initial response (level of evidence: 3).

**Table 6 – Recommendations for adjuvant therapy**

- The type of intravesical therapy is based on the risk groups as designed in Table 5.
- In patients at low risk of tumour recurrence and progression, one immediate instillation of chemotherapy is strongly recommended as the complete adjuvant treatment (grade of recommendation: A).
- In patients at an intermediate or high risk of recurrence and an intermediate risk of progression, one immediate instillation of chemotherapy should be followed by further instillations of chemotherapy or a minimum of 1 yr of bacillus Calmette-Guerin (grade of recommendation: A).
- If chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug during instillation by reducing fluid intake. The optimal schedule and the duration of the chemotherapy instillations remain unclear, but it should probably be given for 6–12 mo (grade of recommendation: B).
- In patients at high risk of tumour progression, after an immediate instillation of chemotherapy, intravesical BCG for at least 1 yr is indicated (grade of recommendation: A).
- Immediate cystectomy may be offered to patients at highest risk of tumour progression. In patients with BCG failure, cystectomy is recommended (grade of recommendation: C).

**Table 7 – Recommendations for follow-up cystoscopy**

- Patients with tumours at low risk of recurrence and progression should have a cystoscopy at 3 mo. If negative, the following cystoscopy is advised at 9 mo and consequently yearly for 5 yr (grade of recommendation: C).
- Patients with tumours at high risk of progression should have a cystoscopy and urinary cytology at 3 mo. If negative, the following cystoscopies and cytologies should be repeated every 3 mo for a period of 2 yr, every 4 mo in the third year, every 6 mo thereafter until 5 yr, and yearly thereafter. A yearly exploration of the upper tract is recommended (grade of recommendation: C).
- Patients with intermediate risk of recurrence and/or progression should have an in-between follow-up scheme using cystoscopy and cytology, adapted according to individual factors (grade of recommendation: C).

Patients with a later recurrence after completion of BCG therapy can be treated according to the risk classification (Tables 4 and 5).

Changing from BCG to intravesical chemotherapy or device-assisted chemotherapy instillations can yield responses in selected cases with BCG failure. Experience however is limited and these strategies are considered experimental. Because of the high risk of development of muscle-invasive tumour in these patients [45,47] (level of evidence 3) immediate cystectomy is strongly advocated.

## 10. Cystectomy

Many experts consider it is reasonable to propose immediate cystectomy to those patients who are at high risk of progression. According to the risk tables of the EORTC (Tables 4 and 5) these are:

- Multiple recurrent high-grade tumours
- High-grade T1 tumours
- High-grade tumours with concomitant CIS.

Cystectomy is advocated in patients with BCG failure. Delaying cystectomy in these patients may lead to decreased disease specific survival [48].

## 11. Follow-up

Because of the risk of recurrence and progression, patients need to be followed. However, the fre-

quency and duration of cystoscopies and upper urinary tract investigations should reflect the degree of risk [21]:

- The prompt detection of muscle-invasive and high-grade non-muscle-invasive recurrences is critical, where a delay in diagnosis and therapy threatens a patient's life.
- Tumour recurrence in the low-risk group is nearly always low stage and low grade. Small, non-invasive (Ta), low-grade papillary recurrences do not present an immediate danger to the patient and their early detection is not essential for successful therapy [49] (level of evidence: 2b).
- The result of the first cystoscopy after TUR at 3 mo is a very important prognostic factor for recurrence and for progression [21,47,50] (level of evidence: 1a). The first cystoscopy should thus always be performed 3 mo after TUR.
- The risk of upper urinary tract recurrence increases in patients with multiple and high-risk tumours [9] (level of evidence: 3).

Recommendations for the follow-up schedule are presented in Table 7.

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### Editorial Comment on: EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder

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It is a difficult and time-consuming task to review the literature and provide a comprehensive set of guidelines to be considered and hopefully embraced by our colleagues. It is thus with a great deal of respect that I congratulate this European Association of Urology (EAU) group for a job well done! I would like to expand on the few comments I have been allotted by the editors. I have been given a word limit as have the authors of the manuscript (we await the long version) [1]. Below I list a few thoughts and personal biases (some of which are data driven and some of which are derived from mistakes and information gained over the years from others).

- (1) It is imperative for urologists to emphasize the causal effect of cigarettes to the patients and their families, to teach more people about the relationship between tobacco and BC (bladder cancer). Maybe a few of the patients' children will quit.
- (2) We must teach the next generation of urologists the critical role of the transurethral resection of the bladder tumor (TUR BT). Too often, those doing the instruction in our teaching centers are only a year or two senior to the "surgeon." Instruction should always be complete and thorough. It can be easy or difficult, as is any surgery, but it all starts with an accurate diagnosis. Thus, the critical role of the second TUR BT in all T1s and multifocal HG Ta.
- (3) It is a great guideline to review all biopsies with the pathologist, but this is often impractical. I suggest that we mandate tumor conferences so we review key cases and periodically look at what we resect. Should we be doing more cold cup biopsies to provide nicer material? How can we minimize cautery artifact? The tumor conference with the uropathologist at our facility has been applauded and is now standing room only.
- (4) Fractionating a TUR BT is not a bad idea, but in my experience, it is not always practical or necessary. Again, work with your pathologist as a diagnostic team.
- (5) It is critical to understand—as so well illustrated in these guidelines—the importance of risk stratification. We must not overtreat the patients who harbor low-grade nonthreatening bladder tumors. For example, we should avoid extensive and frequent TUR BTs, yet aggressively manage those with life-threatening high-grade cancers. We cannot be perfect with our crystal ball, but our data sets are far better than they were in the past, and the tools at our disposal far greater. We have safer major surgery with orthotopic reconstruction, and so forth.
- (6) If a high-grade tumor is present after a 3-month trial of "bladder preservation" with an initial TUR BT, followed by a second TUR BT, then followed with Bacillus Calmette-Guérin treatment, seriously consider whether to delay a cystectomy for an additional 3 mo. I have been convinced that the weight of evidence and experience favors an earlier cystectomy. We have no cure for metastatic bladder cancer, with few exceptions.

As I write these comments, my heart is deeply saddened by the tragic death of one of our brightest

and most gifted experts in the field of urologic oncology and more specifically urothelial cancer—John Stein. John and I have discussed and, yes, argued over many of these issues on panels, conferences, and across the table over meals. I, and so many others, will miss these opportunities to learn from him. It is our duty to remember what he has taught us and carry on his work.

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