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European Association of Urology

Guidelines

EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2013

Marko Babjuk [a,*], *Maximilian Burger* [b], *Richard Zigeuner* [c], *Shahrokh F. Shariat* [d], *Bas W.G. van Rhijn* [e], *Eva Compérat* [f], *Richard J. Sylvester* [g], *Eero Kaasinen* [h], *Andreas Böhle* [i], *Joan Palou Redorta* [j], *Morgan Rouprêt* [k,l]

[a] *Department of Urology, Hospital Motol, Second Faculty of Medicine, Charles University, Prague, Czech Republic;* [b] *Department of Urology and Paediatric Urology, Julius-Maximilians-University Medical Centre, Würzburg, Germany;* [c] *Department of Urology, Medical University of Graz, Graz, Austria;* [d] *Department of Urology, Medical University of Vienna, Vienna General Hospital, Vienna, Austria;* [e] *Department of Surgical Oncology (Urology), Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [f] *Department of Pathology, Hôpital de la Pitié-Salpêtrière, UPMC, Paris, France;* [g] *Department of Biostatistics, EORTC Headquarters, Brussels, Belgium;* [h] *Department of Surgery, Hyvinkää Hospital, Hyvinkää, Finland;* [i] *Department of Urology, HELIOS Agnes-Karll-Krankenhaus, Bad Schwartau, Germany;* [j] *Department of Urology, Fundació Puigvert, Universitat Autónoma de Barcelona, Spain;* [k] *AP-HP, Hôpital de la Pitié-Salpêtrière, Service d'Urologie, Paris, F-75013, France;* [l] *UPMC Université de Paris 06, GRC5, ONCOTYPE-Uro, Institut Universitaire de Cancérologie, F-75005, Paris, France*

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Abstract

Context: The first European Association of Urology (EAU) guidelines on bladder cancer were published in 2002 [1]. Since then, the guidelines have been continuously updated.
Objective: To present the 2013 EAU guidelines on non–muscle-invasive bladder cancer (NMIBC).
Evidence acquisition: Literature published between 2010 and 2012 on the diagnosis and treatment of NMIBC was systematically reviewed. Previous guidelines were updated, and the levels of evidence and grades of recommendation were assigned.
Evidence synthesis: Tumours staged as Ta, T1, or carcinoma *in situ* (CIS) are grouped as NMIBC. Diagnosis depends on cystoscopy and histologic evaluation of the tissue obtained by transurethral resection (TUR) in papillary tumours or by multiple bladder biopsies in CIS. In papillary lesions, a complete TUR is essential for the patient's prognosis. Where the initial resection is incomplete, where there is no muscle in the specimen, or where a high-grade or T1 tumour is detected, a second TUR should be performed within 2–6 wk. The risks of both recurrence and progression may be estimated for individual patients using the EORTC scoring system and risk tables. The stratification of patients into low-, intermediate-, and high-risk groups is pivotal to recommending adjuvant treatment. For patients with a low-risk tumour, one immediate instillation of chemotherapy is recommended. Patients with an intermediate-risk tumour should receive one immediate instillation of chemotherapy followed by 1 yr of full-dose bacillus Calmette-Guérin (BCG) intravesical immunotherapy or by further instillations of chemotherapy for a maximum of 1 yr. In patients with high-risk tumours, full-dose intravesical BCG for 1–3 yr is indicated. In patients at highest risk of tumour progression, immediate radical cystectomy should be considered. Cystectomy is recommended in BCG-refractory tumours. The long version of the guidelines is available from the EAU Web site: http://www.uroweb.org/guidelines/.
Conclusions: These abridged EAU guidelines present updated information on the diagnosis and treatment of NMIBC for incorporation into clinical practice.
Patient summary: The EAU Panel on Non-muscle Invasive Bladder Cancer released an updated version of their guidelines. Current clinical studies support patient selection into different risk groups; low, intermediate and high risk. These risk groups indicate the likelihood of the development of a new (recurrent) cancer after initial treatment (endoscopic resection) or progression to more aggressive (muscle-invasive) bladder cancer and are most important for the decision to provide chemo- or immunotherapy (bladder installations). Surgical removal of the bladder (radical cystectomy) should only be considered in patients who have failed chemo- or immunotherapy, or who are in the highest risk group for progression.
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* Corresponding author. Department of Urology, Hospital Motol, Second Faculty of Medicine, Charles University, V Úvalu 84, Prague 5, 15006, Czech Republic. Tel. +420 224434801; Fax: +420 224434821.
E-mail address: marek.babjuk@lfmotol.cuni.cz (M. Babjuk).

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1. Introduction

The first European Association of Urology (EAU) guidelines on bladder cancer were published in 2002 [1]. Since then, the guidelines have been continuously updated, and the most recent version is available from the EAU Web site (http://www.uroweb.org/guidelines/). An overview of the updated 2013 EAU guidelines on non–muscle-invasive bladder cancer (NMIBC) (Ta, T1, and carcinoma *in situ* [CIS]) is provided in this paper. The information presented is limited to urothelial carcinoma, if not specified otherwise. The aim is to provide practical guidance on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

2. Evidence acquisition

A systematic literature search was performed by the panel members. For identification of original and review articles published between 2010 and 2012, Medline, Web of Science, and Embase databases were used. Focus of the searches was identification of all level 1 scientific data (ie, randomised controlled trials [RCTs], systematic reviews, and meta-analyses of RCTs).

Panel members selected records with the highest level of evidence (LE) according to a modified classification system from the Oxford Centre for Evidence-based Medicine Levels of Evidence [2]. Recommendations were graded to provide transparency regarding the underlying LE for each recommendation given.

3. Epidemiology

Bladder cancer (BCa) is the most common malignancy of the urinary tract and the 7th most common cancer in men and the 17th in women. In the European Union, the age-standardised incidence rate is 27 per 100 000 in men and six per 100 000 in women [3].

Incidence varies between regions and countries; in Europe, the highest age-standardised incidence rate has been reported in Spain (41.5 in men and 4.8 in women [per 100 000 inhabitants]) and the lowest in Finland (18.1 in men and 4.3 in women) [3].

In the European Union, age-standardised mortality rate per 100 000 is 8 in men and 3 in women [3]. In 2008, BCa was the eighth most common cause of cancer-specific mortality in Europe [3].

The incidence of BCa has decreased in some registries possibly reflecting the decreased impact of causative agents [4]. The mortality of BCa has also decreased, possibly reflecting an increased standard of care [5].

Approximately 75% of patients with BCa present with a NMIBC that is either confined to the mucosa (stage Ta, CIS) or to the submucosa (stage T1).

4. Risk factors

Genetic predisposition has a significant influence on BCa, especially via its impact on susceptibility to other risk factors [6]. Tobacco smoking is the most important risk factor for BCa, accounting for approximately 50% of cases [6,7] (LE: 3).

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons is the second most important risk factor for BCa, accounting for about 10% of all cases. Such occupational exposure occurs mainly in the paint processing, dye, metal and petroleum product industries [6,8] (LE: 3).

The exposure to ionising radiation is connected with an increased risk of BCa (LE: 3). Schistosomiasis is a cause of BCa, particularly squamous cell carcinoma [6] (LE: 3).

5. Classification

5.1. *TNM classification and definition of non–muscle-invasive bladder cancer*

The Tumour, Node, Metastasis (TNM) classification system approved by the Union International Contre le Cancer (UICC), which was updated in 2009, is used in these guidelines (Table 1) [9]. Papillary tumours confined to the mucosa and those which have invaded the lamina propria are classified as stage Ta and stage T1, respectively. Ta and T1 tumours can be removed by transurethral resection (TUR), and therefore they are grouped under the heading of NMIBC for therapeutic purposes. Also included under this heading are flat, high-grade [HG] tumours that are confined to the mucosa, and classified as CIS (Tis). However, the term NMIBC is a suboptimal description. Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.

5.2. *Grading*

The new classification for grading noninvasive urothelial bladder carcinomas proposed by the World Health Organisation (WHO) and the International Society of Urological Pathology was published in 2004 (Table 2) [10]. It provides some changes compared with the original 1973 classification. Among papillary lesions the classification defines papillary urothelial neoplasms of low malignant potential (PUNLMP), and low-grade (LG) and HG urothelial carcinomas. PUNLMP are lesions that do not have cytologic features of malignancy but show normal urothelial cells in a papillary configuration. They have a negligible risk for progression but have a tendency to recur. The intermediate grade (grade 2), which was the subject of controversy in the 1973 WHO classification, was removed from the 2004 version (Table 2).

The published comparisons, however, have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification [11,12].

The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. Attempts to demonstrate better prognostic value of one of them, however, have yielded controversial results [11,13–16]. Most of the clinical trials published to date on Ta, T1 bladder tumours have been performed using the 1973 WHO classification, and

Table 1 – 2009 TNM classification of urinary bladder cancer

T: Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Noninvasive 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
N: Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)
M: Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

therefore, the following guidelines are based on this version. Until the WHO 2004 system is validated by more prospective trials and incorporated into prognostic models, both classifications should be used.

5.3. *Variability among pathologists*

Despite well-defined criteria, there is significant variability among pathologists for the diagnosis of CIS, in the classification of stage T1 versus Ta tumours, and tumour grading in both the 1973 and 2004 classifications. The general conformity in staging and grading is between 50% and 60% [11,16–18] (LE: 2a).

Table 2 – World Health Organisation grading in 1973 and in 2004

1973 WHO grading	
Urothelial papilloma	
Grade 1: (G1)	Well differentiated
Grade 2: (G2)	Moderately differentiated
Grade 3: (G3)	Poorly differentiated
2004 WHO grading	
Flat lesions	
Hyperplasia (flat lesion without atypia or papillary)	
Reactive atypia (flat lesion with atypia)	
Atypia of unknown significance	
Urothelial dysplasia	
Urothelial carcinoma *in situ*	
Papillary lesions	
Urothelial papilloma (which is a completely benign lesion)	
Papillary urothelial neoplasm of low malignant potential	
Low-grade papillary urothelial carcinoma	
High-grade papillary urothelial carcinoma	

WHO = World Health Organisation.

5.4. *Specific characteristics of carcinoma in situ and its clinical classification*

CIS is a flat HG noninvasive urothelial carcinoma. It can occur in the whole urothelium (ie, the bladder, in the upper urinary tract, and in the prostatic ducts and urethra).

Bladder CIS is classified into one of four different clinical types [19]:

- Primary: Isolated CIS with no previous or concurrent papillary tumours and no previous CIS
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder
- Recurrent: Repeat occurrence of isolated CIS after initial successful response to intravesical treatment.

6. Diagnosis

6.1. *Symptoms*

Patient history should be taken and recorded for all important information with any possible connection to BCa. Haematuria is the most common finding in NMIBC. Lower urinary tract symptoms may reveal a CIS.

6.2. *Imaging*

Intravenous urography (IVU) is used to detect filling defects in the calyces, renal pelvis and ureters, and hydronephrosis, which can indicate the presence of a ureteral tumour. Large exophytic tumours may be seen as filling defects in the bladder. The necessity to perform routine IVU once a bladder tumour has been detected is questioned because of the low incidence of significant findings [20,21] (LE: 2a). The incidence of upper urinary tract tumours (UTUCs) is low (1.8%) but increases to 7.5% in tumours located in the trigone [21] (LE: 2b). The risk of tumour recurrence as a UTUC during follow-up increases in multiple and high-risk tumours [22] (LE: 2b).

Computed tomography (CT) urography is used as an alternative to conventional IVU. Especially in muscle-invasive tumours of the bladder and UTUCs, CT urography gives more information than IVU.

Transabdominal ultrasound (US) permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder. It can be as accurate as IVU for the diagnosis of upper urinary tract obstruction [20] (LE: 3). US is therefore a useful tool for the detection of obstruction in patients with haematuria; however, it cannot exclude the presence of upper tract tumours.

CIS cannot be diagnosed with imaging methods.

6.3. *Urinary cytology*

Examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG/G3

tumours but low sensitivity in LG/G1 tumours. The sensitivity of cytology for CIS detection is 28–100% [23] (LE: 2b). Cytology is thus useful when a HG/G3 malignancy or CIS is present. It is often negative, however, in the presence of LG/G1 cancer. Positive voided urinary cytology can indicate a urothelial tumour anywhere in the urinary tract; however, negative cytology does not exclude the presence of a tumour.

Cytologic interpretation is user dependent [24]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations. In experienced hands, however, the specificity exceeds 90% [25] (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.

6.4. Urine molecular tests

Driven by the low sensitivity of urine cytology, extensive laboratory research has developed numerous urinary tests for BCa detection [25–27]. The tests have usually higher sensitivity but lower specificity than urinary cytology (LE:3). Benign conditions and bacillus Calmette-Guérin (BCG) influence many urinary marker tests [25–27] (LE: 3).

6.5. Practical application of urinary cytology and markers

The following applications of urinary cytology or molecular tests must be considered:

- Screening of the population at risk of BCa. The application of haematuria dipstick, NMP22, or UroVysion in BCa screening in high-risk populations has been reported [28,29]. However, routine application of screening is currently not recommended.
- Exploration of patients after haematuria or other symptoms suggestive of BCa (primary detection). None of the tests can replace cystoscopy. However, urinary cytology or markers can be used as an adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, sensitivity for HG/G3 tumours and specificity are particularly important. Urinary cytology is highly specific, but urinary markers lack this high specificity and are not recommended for primary detection.
- Facilitating surveillance of NMIBC [30–32]. (1) Follow-up of high-risk NMIBC: High-risk tumours should be detected early in follow-up. Therefore, the best surveillance strategy for these patients includes frequent cystoscopy and cytology. (2) Follow-up in low/intermediate-risk NMIBC: To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large and numerous. According to current knowledge, no urinary marker can replace cystoscopy during follow-up or help to lower cystoscopic frequency routinely. One prospective randomised study confirmed that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [33] (LE: 1b).

6.6. Cystoscopy

The diagnosis of papillary BCa depends on cystoscopic examination of the bladder and histologic evaluation of the resected tissue. CIS is diagnosed by a combination of cystoscopy, urine cytology, and histologic evaluation of multiple bladder biopsies. Cystoscopy is initially performed in the office. The use of a flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance, especially in men [34].

Careful inspection of the whole urothelial lining in the bladder should be performed. A description should include the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended.

If a bladder tumour has been visualised in earlier imaging studies, diagnostic cystoscopy can be omitted because the patient will undergo TUR.

6.7. Transurethral resection

The goal of the TUR in Ta, T1 BCa is to make the correct diagnosis and remove all visible lesions. TUR should be performed systematically as follows:

- Bimanual palpation under anaesthesia.
- Insertion of the resectoscope, in men under visual guidance, with inspection of the whole urethra.
- Inspection of the whole urothelial lining of the bladder.
- Cold-cup bladder biopsies and biopsy from prostatic urethra if indicated (see section 6.9).
- Resection of the tumour. The strategy of resection depends on the size of the lesion. Small tumours (<1 cm) can be resected en bloc, which includes the entire tumour and part of the underlying bladder wall. Larger tumours should be resected separately in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. This approach provides good information about the vertical and horizontal extent of the tumour and helps to improve resection completeness [35] (LE: 3). Deep resection is not necessary in small, apparently LG/G1 lesions with a previous history of Ta (LG/G1) tumour. Cauterisation should be avoided as much as possible during TUR to prevent tissue destruction.
- In patients with palpable lesions before TUR, bimanual palpation should be repeated after resection.
- The protocol is formulated, which must describe all steps of the procedure, as well as the extent and completeness of resection.
- An order form for pathologic evaluation is prepared.

The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers.

Complete and correct TUR is essential to achieve a good prognosis [36]. Absence of detrusor muscle in the specimen

is associated with a significantly higher risk of residual disease and early recurrence [37] (LE: 2b).

Training in the methods of TUR should be included in teaching programmes because it can improve results [38].

6.8. Office-based fulguration

In patients with a history of small LG/G1 Ta tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option [39] (LE: 3).

6.9. Bladder and prostatic urethra biopsies

CIS can present as a velvet-like reddish area that is indistinguishable from inflammation, or it might not be visible at all.

When abnormal areas of urothelium are seen, it is advised to take cold-cup biopsies or biopsies with a resection loop.

Biopsies from normal-looking mucosa, so-called random (mapping) biopsies, are not routinely recommended because the likelihood of detecting CIS, especially in low-risk tumours, is extremely low (<2%) [40] (LE: 2a). They should be performed, however, in patients with positive urinary cytology and the absence of visible bladder tumour, in addition to upper tract diagnostics. It is recommended to take biopsies from the trigone, bladder dome, and from the right, left, anterior, and posterior bladder walls.

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. The incidence of CIS in prostatic urethra was 11.7% in one report (LE: 2b) [41]. The risk of prostatic urethra or duct involvement is higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours [42] (LE: 3). Thus, when bladder CIS is suspected, cytology is positive with no evidence of bladder tumour, or abnormalities of prostatic urethra are visible, prostatic urethral biopsies are recommended [41]. The biopsy is taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock positions) using a resection loop. In primary NMIBC when stromal invasion is not suspected, a cold-cup biopsy with forceps can be performed [43].

6.10. Photodynamic diagnosis (fluorescence cystoscopy)

Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). Fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly for CIS [44,45] (LE: 2a). PDD had lower specificity than white light endoscopy [45]. False positivity can be induced by inflammation or recent TUR, and during the first 3 mo after BCG instillation [46,47] (LE: 3).

Prospective randomised studies evaluating the impact of ALA fluorescence-guided TUR on disease recurrence rate have shown controversial results [44,45,48,49]. A large multicentre prospective randomised trial that compared HAL fluorescence-guided TUR with standard TUR reported an absolute reduction of no more than 9% in the recurrence rate within 9 mo in the HAL arm. Median time to recurrence improved from 9.4 mo in the white light arm to 16.4 mo in the HAL arm [50] (LE: 1b).

The value of fluorescence cystoscopy for improvement of the outcome in relation to progression rate or survival remains to be demonstrated.

PDD is recommended in patients who are suspected of harbouring a HG/G3 tumour (eg, for biopsy guidance in patients with positive cytology, or with a history of HG/G3 tumour).

6.11. Second resection

The significant risk of residual tumour after initial TUR of Ta, T1 lesions has been demonstrated [36,51] (LE: 2a). The tumour is often understaged by initial resection. It has been demonstrated that a second TUR can increase the recurrence-free survival [52] (LE: 2a).

A second TUR of the bladder is recommended in the following situations:

- After incomplete initial TUR
- If there was no muscle in the specimen after initial resection, with exception of Ta, LG/G1 tumours and primary CIS
- In all T1 tumours
- In all HG/G3 tumours, except primary CIS.

The second resection should be performed 2–6 wk after initial TUR, and it should include resection of the primary tumour site.

6.12. Pathologic report

The pathologic report should specify [53] the following:

- Location of the evaluated sample (mapping)
- Grade of each tumour
- Depth of tumour invasion
- CIS
- Detrusor muscle in the specimen
- Lymphovascular invasion
- Aberrant histology.

Close cooperation between urologists and pathologists is recommended.

Table 3 summarises the recommendations for the diagnosis of NMIBC.

7. Predicting recurrence and progression

7.1. Prognosis of Ta, T1 tumours

Patients with Ta, T1 tumours can be divided into risk groups based on prognostic factors. To predict separately the short- and long-term risks of both recurrence and progression in individual patients, a scoring system and risk tables were

Table 3 – Recommendations for the diagnosis of non–muscle-invasive bladder cancer

Initial diagnosis	GR
Patient history should be taken and recorded regarding all important information with possible connection to bladder cancer including risk factors and history of suspect symptoms.	A
Renal and bladder US may be used during initial work-up in patients with haematuria.	C
At the time of initial diagnosis of bladder cancer, CT urography or IVU should be performed only in selected cases (eg, tumours located in the trigone).	B
Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or by any other noninvasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Voided urine cytology is advocated to predict HG/G3 tumour before TUR.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C
TUR of the bladder	
TUR should be performed systematically in individual steps: bimanual palpation under anaesthesia; insertion of the resectoscope, under visual control with inspection of the whole urethra; inspection of the whole urothelial lining of the bladder; biopsy from prostatic urethra (if indicated); cold-cup bladder biopsies (if indicated); resection of the tumour; bimanual palpation after resection; protocol formulation; formulation of order form for pathologic evaluation.	C
Perform resection in one piece for small papillary tumours (<1 cm), including part from the underlying bladder wall.	B
Perform resection in fractions (including muscle tissue) for tumours >1 cm in diameter.	B
Biopsies should be taken from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior, and posterior bladder walls) are recommended only when cytology is positive or when exophytic tumour has a nonpapillary appearance.	C
Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Biopsy of the prostatic urethra should be taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock position) using a resection loop. In primary non–muscle-invasive tumours when stromal invasion is not suspected, the cold-cup biopsy with forceps can be used.	C
If equipment is available, fluorescence-guided (PDD) biopsy should be performed instead of random biopsies when bladder CIS or HG/G3 tumour is suspected (eg, positive cytology, recurrent tumour with previous history of a HG/G3 lesion).	B
The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers and labelled separately.	C
TUR protocol must describe all steps of the procedure, as well as the extent and completeness of resection.	C
A second TUR is recommended in the following situations:	A
- After incomplete initial TUR	
- If there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS	
- In all T1 tumours	
- In all G3 tumours, except primary CIS	
A second TUR should be performed 2–6 wk after initial resection.	C
Classification and pathologic report	
Depth of tumour invasion is classified according to the TNM system.	A
For histologic classification, 1973 and 2004 WHO grading systems are used. Until the WHO 2004 system is validated by more prospective trials and incorporated into prognostic models, both classifications should be used.	A
Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.	A
The pathologic report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathologic report should specify the presence of LVI or aberrant histology.	C

CIS = carcinoma *in situ*; CT = computed tomography; GR = grade of recommendation; HG = high-grade; IVU = intravenous urography; LVI = lymphovascular invasion; NMIBC = non–muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TUR = transurethral resection; US = ultrasonography; WHO = World Health Organisation.

developed by the EORTC [54]. The EORTC database provided individual data for 2596 patients who did not have a second TUR or receive maintenance BCG therapy. The EORTC scoring system is based on the six most significant clinical and pathologic factors:

- Number of tumours
- Tumour size
- Prior recurrence rate
- T category
- Presence of concurrent CIS
- Tumour grade (WHO 1973).

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression was developed by the Club Urológico Español de Tratamiento Oncológico (CUETO). Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression probabilities, it is lower only in high-risk patients [55]. The lower risks in the CUETO tables may be attributable to using BCG, which is a more effective instillation therapy.

Further prognostic factors have been described in selected patient populations. Female sex and CIS in the prostatic urethra are important prognostic factors in T1, G3 patients treated with TUR and an induction course of BCG [41] (LE: 2b). Recurrence at 3 mo was the most important predictor of progression in T1, G2 tumours treated with TUR [56] (LE: 2b).

7.2. *Prognosis of carcinoma in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [57]. There are no reliable prognostic factors that can be used to predict the course of CIS. Some studies have reported a worse prognosis

Table 4 – Risk group stratification

Risk group	Definition
Low-risk tumours	Primary, solitary, Ta, LG/G1, <3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following:
	• T1 tumour
	• HG/G3 tumour
	• CIS
	• Multiple and recurrent and large (>3 cm) Ta, G1, G2 tumours (all conditions must be presented in this point)

CIS = carcinoma *in situ*; LG = low grade, HG = high.grade.

Table 5 – Recommendations for stratification of NMIBC

Recommendation	GR
Stratify patients into three risk groups according to Table 4.	B
Use EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TUR.	B

GR = grade of recommendation; EORTC = European Organisation for Research and Treatment of Cancer; TUR = transurethral resection.

in patients with concurrent CIS and T1 tumours compared with primary CIS, extended CIS, and those who do not respond to BCG treatment [57,58] (LE: 3).

7.3. *Recommendation for patients' stratification in risk groups*

The guidelines panel recommends stratification of patients into three risk groups that will facilitate treatment recommendations. Their definition, which takes into account the EORTC risk tables probabilities of recurrence and especially progression, can be found in Table 4. The recommendation is similar to that provided by the International Bladder Cancer Group [59].

For individual prediction of the risk of tumour recurrence and progression at different intervals after TUR, the application of EORTC risk tables and calculator is recommended (electronic calculator is available at http://www.eortc.be/tools/bladdercalculator/).

Recommendations for NMIBC patients' stratification can be found in Table 5.

8. Adjuvant intravesical chemotherapy

Ta, T1 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.

8.1. *One immediate postoperative intravesical instillation*

Early single instillation has been shown to function by the destruction of circulating tumour cells resulting from TUR, and by an ablative effect on residual tumour cells at the resection site and on small overlooked tumours [60,61] (LE: 3).

In a meta-analysis of 1476 patients, one immediate instillation of chemotherapy after TUR significantly reduced recurrence rate by 11.7% compared with TUR alone [62] (LE: 1a). A similar efficacy was reported in two more recent studies [63,64], with subgroup analyses suggesting that immediate instillation is the most effective in tumour types with the lowest tendency towards recurrence, that is, in single primary or small tumours. Mitomycin C (MMC), epirubicin, and doxorubicin have all shown a beneficial effect, with no efficacy comparisons made between the drugs [62] (LE: 1a).

There is evidence that immediate instillation might have an impact on recurrence even when further adjuvant instillations are given [65,66] (LE: 2a). In contrast, a sufficient number of delayed repeat chemotherapy instillations can also reduce recurrence stemming from tumour implantation [60,65,66]. Nevertheless, it is likely that immediate instillation is more effective in preventing recurrence than any of the individual instillations that follow the immediate instillation [60,67] (LE: 3).

Prevention of tumour cell implantation should be initiated within the first hours after cell seeding [68] (LE: 3). In all single instillation studies, the instillation was administered within 24 h. To maximise the efficacy of immediate instillation, flexible practices should be devised that allow the instillation to be given as early as possible.

Immediate instillation of postoperative chemotherapy should be omitted in any case of intra- or extraperitoneal perforation, which is most likely to appear in extensive TUR procedures and in situations with bleeding that require bladder irrigation. Clear instructions should be given to the nursing staff to control the free flow of the bladder catheter at the end of the instillation. Severe complications have been reported in patients with drug extravasation [69].

8.2. *Additional intravesical chemotherapy instillations*

The need for further adjuvant intravesical therapy depends on prognosis. In patients with tumours at low risk (Table 4), a single immediate instillation reduces the risk of recurrence and is considered as the standard and sufficient treatment [62] (LE: 1a). For other patients, however, a single immediate instillation remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression.

A meta-analysis of 3703 patients from 11 RCTs showed a highly significant 44% reduction in the odds of recurrence (corresponding to an absolute difference of 13–14%) at 1 yr in favour of chemotherapy instillations over TUR alone but no effect on tumour progression [70].

It is still controversial for how long and how frequently chemotherapy instillations should be given [71]. The available evidence does not support any treatment >1 yr (LE: 3).

8.3. *Optimising intravesical chemotherapy*

Some promising data have been presented about enhancing the efficacy of MMC using microwave-induced hyperthermia

(Synergo) or electromotive drug administration in patients with high-risk tumours. The current evidence, however, is limited [72,73] (LE: 2b). Both treatment modalities are considered experimental.

Adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution during chemotherapy instillation reduces the recurrence rate [74] (LE: 1b). Concentration is more important than treatment duration [75] (LE: 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 on the morning before instillation.

9. Adjuvant intravesical bacillus Calmette-Guérin immunotherapy

9.1. *Bacillus Calmette-Guérin efficacy*

Five meta-analyses have confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy for the prevention of tumour recurrence [76–80] (LE: 1a). Three recent RCTs on patients with intermediate- and high-risk tumours compared BCG with a combination of epirubicin and interferon [81], MMC [82], or epirubicin alone [83]. All of these studies have confirmed the superiority of BCG for the prevention of tumour recurrence (LE: 1a). It has been shown that the effect was long lasting [82,83], and it was also observed in a separate analysis of patients with intermediate-risk tumours [82,83].

One meta-analysis [76] evaluated the individual data from 2820 patients enrolled in nine RCTs that compared MMC versus BCG. In the trials with BCG maintenance, a 32% reduction in the risk of recurrence for BCG compared with MMC was found, whereas there was a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance.

Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [84,85] (LE: 1a). A recent RCT with long-term observation demonstrated significantly fewer distant metastases and better overall survival and disease-specific survival in patients treated with BCG compared with epirubicin [83] (LE: 1b). In contrast, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [76].

The conflicting results in the progression outcomes of the studies can be explained by different patient characteristics, duration of follow-up, methodology, and statistical power. Most studies were, however, able to show a reduction in the risk of progression in high- and intermediate-risk tumours if BCG was applied including a maintenance schedule.

9.2. *The optimal schedule of BCG instillations*

Induction BCG instillations are classically given according to the empirical 6-weekly schedule. For optimal efficacy, BCG must be given on a maintenance schedule [76,80,84,85] (LE: 1a). In the EORTC Genito-Urinary (GU) group meta-analysis, only patients who received maintenance BCG benefited. The most effective BCG maintenance schedule, however, cannot be determined [85]. In their meta-analysis, Böhle et al. concluded that at least 1 yr of maintenance BCG is required to obtain superiority of BCG over MMC for the prevention of recurrence or progression [80,84] (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations remain unknown. However, in an RCT of 1355 patients, the EORTC recently showed that when BCG is given at full dose, 3 yr of maintenance reduces the recurrence rate as compared with 1 yr in high-risk but not in intermediate-risk patients. There were no differences in progression or overall survival [86] (LE: 1b).

9.3. *Bacillus Calmette-Guérin toxicity*

BCG intravesical treatment is associated with more side effects compared with intravesical chemotherapy [87] (LE: 1a). Serious side effects are encountered in <5% of patients and can be treated effectively [88] (LE: 1b). It has been shown that the maintenance schedule is not associated with an increased risk of side effects compared with the induction course [88].

Major complications can appear after systemic absorption of the drug. Thus contraindications of BCG intravesical instillation should be respected.

BCG should not be administered when the following absolute contraindications exist:

- During the first 2 wk after TUR
- In patients with macroscopic haematuria
- After traumatic catheterisation
- In patients with symptomatic urinary tract infection.

The presence of leukocyturia or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [89] (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (immunosuppression, human immunodeficiency virus infection) [90] (LE: 3).

The management of side effects after BCG should reflect their type and grade [91].

9.4. *Optimal dose of bacillus Calmette-Guérin and bacillus Calmette-Guérin strain*

To reduce BCG toxicity, instillation of a reduced dose was proposed. Comparing a one-third dose to full-dose BCG, CUETO found no overall difference in efficacy. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [92,93] (LE: 1b). Although fewer patients have reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar. In another trial, a further reduction to one-sixth dose resulted in a decrease in efficacy with equal toxicity [94] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full-dose BCG; however, the former

was associated with a higher recurrence rate, especially when it was given only for 1 yr [86] (LE: 1b).

No robust evidence assessing a difference in clinical efficacy between various BCG strains has been reported so far.

9.5. Indications for bacillus Calmette-Guérin

There is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends on the patient's risk (Table 4):

- BCG does not alter the natural course of low-risk tumours, and it could be considered as overtreatment for this category.
- In patients with high-risk tumours, for whom radical cystectomy is not carried out, 1–3 yr of full-dose maintenance BCG is indicated. The additional beneficial effect of the second and third years of maintenance on recurrence in high-risk tumours should be weighed against its added costs and inconveniences.
- In intermediate-risk tumours, full-dose BCG with 1 yr of maintenance is more effective than chemotherapy for prevention of recurrence; however, it has more side effects than chemotherapy. For this reason both BCG with maintenance and intravesical chemotherapy remain an option. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.

10. Specific aspects of treatment of carcinoma *in situ*

CIS cannot be resolved by TUR alone. Histologic diagnosis of CIS must be followed by further treatment, either intravesical instillations or radical cystectomy (LE: 2). No consensus exists about whether conservative therapy (intravesical BCG instillations) or aggressive therapy (cystectomy) should be performed. Tumour-specific survival rates after early cystectomy for CIS are excellent, but up to 40–50% of patients may be overtreated [57] (LE: 3).

10.1. Intravesical treatment of bladder carcinoma in situ

A meta-analysis of clinical trials that has compared intravesical BCG with intravesical chemotherapy has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [95] (LE: 1a).

In an EORTC-GU group meta-analysis, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared with intravesical chemotherapy or different immunotherapy [85] (LE: 1b).

In summary, compared with chemotherapy, BCG treatment of CIS increases the complete response rate and the overall percentage of patients who remain disease free, and it reduces the risk of tumour progression (LE: 1a).

10.2. Treatment of extravesical carcinoma in situ

Patients with CIS are at high risk of extravesical involvement in the upper urinary tract and in the prostatic urethra. Patients with extravesical involvement had worse survival than those with bladder CIS alone [96] (LE: 3).

Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. TUR of the prostate can improve the contact of BCG with the prostatic urethra [97] (LE: 3).

In patients with prostatic duct involvement, radical cystectomy should be considered [97] (LE: 3).

Treatment of CIS that involves the upper urinary tract is discussed in the guidelines on urothelial carcinomas of the upper urinary tract.

Table 6 – Recommendations for adjuvant therapy in Ta, T1 tumours and for treatment of CIS

Recommendation	GR
The type of intravesical therapy should be based on the risk groups shown in Tables 4 and 9.	A
One immediate chemotherapy instillation is recommended in tumours presumed to be at low or intermediate risk.	–
In patients with low-risk tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with intermediate-risk tumours, one immediate instillation of chemotherapy should be followed by 1 yr of full-dose BCG treatment or by further instillation of chemotherapy for a maximum of 1 yr.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1–3 yr is indicated.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG is an option.	C
In patients at highest risk of tumour progression (Table 9), immediate radical cystectomy should be considered.	C
In BCG-refractory tumours, radical cystectomy is indicated.	B
Intravesical chemotherapy	
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation (after extensive TUR or bleeding requiring bladder irrigation).	C
The optimal schedule of further intravesical chemotherapy instillations and its duration is not defined; it should not exceed 1 yr.	C
If intravesical 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.	B
The length of individual instillation should be 1–2 h.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are during the first 2 wk after TUR; in patients with macroscopic haematuria; after traumatic catheterization; and in patients with symptomatic urinary tract infection.	C
The management of side effects after BCG intravesical instillation should reflect their type and grade.	C

BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; GR = grade of recommendation; TUR = transurethral resection.

Table 6 summarises the recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS.

11. Treatment of failures of intravesical therapy

11.1. Failure of intravesical chemotherapy

Patients with recurrence of NMIBC after a chemotherapy regimen can profit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation [76] (LE: 1a).

11.2. Recurrence and failure after intravesical bacillus Calmette-Guérin immunotherapy

Categories of unsuccessful treatment with intravesical BCG are summarised in Table 7.

Patients with BCG failure are unlikely to respond to further BCG therapy; therefore, radical cystectomy is the preferred option.

Several bladder preservation strategies are available [98]. Changing from BCG to these options can yield responses in selected cases with BCG failure [99–101] (LE: 3). However, experience is limited, and treatments other than radical cystectomy must be considered oncologically inferior at the present time [102] (LE: 3).

The results of various studies suggest that repeat BCG therapy is appropriate for non–high-grade and even for some HG/G3 recurrent tumours [103] (LE: 3). Treatment recommendations are provided in Table 8.

12. Radical cystectomy for non–muscle-invasive bladder cancer

If radical cystectomy is indicated before pathologically confirmed progression into muscle-invasive tumour, immediate (directly following NMIBC diagnosis) and early (after BCG failure) radical cystectomy can be distinguished.

Table 7 – Categories of unsuccessful treatment with intravesical BCG

BCG failure
Whenever a muscle-invasive tumour is detected during follow-up.
BCG-refractory tumour:
1. If HG/G3, non–muscle-invasive papillary tumour is present at 3 mo [102]. Further conservative treatment with BCG is connected with increased risk of progression [103] (LE: 3).
2. If CIS (without concurrent papillary tumour) is present at both 3 mo and 6 mo. In patients with CIS present at 3 mo, an additional BCG course can achieve a complete response in >50% of cases [57] (LE: 3).
3. If HG/G3 tumour appears during BCG therapy.*
HG/G3 recurrence after BCG. Recurrence of HG/G3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response (LE: 3).*
BCG intolerance
Severe side effects that prevent further BCG instillation before completing induction [91].

BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; LE = level of evidence; WHO = World Health Organisation.
* Patients with LG recurrence during or after BCG treatment are not considered as BCG failure.

Table 8 – Treatment recommendations for BCG failure and recurrences after BCG

Category	Treatment recommendation	GR
BCG-refractory tumour	1. Radical cystectomy 2. Bladder-preserving strategies in patients not suitable for cystectomy	B
HG/G3 recurrence after BCG	1. Radical cystectomy 2. Repeat BCG course 3. Bladder-preserving strategies	C
Non–HG/G3 recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

BCG = bacillus Calmette-Guérin; GR = grade of recommendation.

The potential benefit of radical cystectomy must be weighed against the risk and impact on quality of life. It is reasonable to propose immediate radical cystectomy to those patients with NMIBC who are at highest risk of progression. These are patients with the following characteristics [41,54,55] (LE: 3):

- Multiple and/or large (>3 cm) T1, (HG/G3) tumours
- T1, (HG/G3) tumours with concurrent CIS
- Recurrent T1, (HG/G3) tumours
- T1, G3 and CIS in prostatic urethra
- Micropapillary variant of urothelial carcinoma.

In these cases, discussing immediate radical cystectomy and conservative treatment with BCG instillation is recommended.

Radical cystectomy is strongly recommended in patients with BCG-refractory tumours, as mentioned earlier. Delay of radical cystectomy might lead to decreased disease-specific survival [104] (LE: 3).

Table 9 summarises the treatment principles for NMIBC.

13. Follow-up of patients with non–muscle-invasive bladder cancer

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed up; however, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk. Using risk tables, we are able to predict the short- and long-term risks of recurrence and progression in individual patients, and can adapt the follow-up schedule accordingly [54,55]. When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 NMIBC recurrence is crucial because a delay in diagnosis and therapy can be life threatening.
- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small non-invasive (Ta), LG/G1 papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy [105] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a

Table 9 – Summary of treatment recommendations in Ta, T1 tumours according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, LG/G1, <3 cm, no CIS	One immediate instillation of chemotherapy
Intermediate-risk tumours	All cases between categories of low and high risk	One immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 yr or 1 yr of full-dose BCG
High-risk tumours	Any of the following:	Intravesical full-dose BCG instillations for 1–3 yr or cystectomy (in highest risk tumours)
	• T1 tumours	
	• HG/G3 tumours	
	• CIS	
	• Multiple and recurrent and large (>3 cm) Ta, G1, G2 tumours (all these conditions must be presented)	
Subgroup of highest risk tumours	T1, HG/G3 associated with concurrent bladder CIS, multiple and/or large T1, HG/G3 and/or recurrent T1, HG/G3, T1, HG/G3 with CIS in prostatic urethra, micropapillary variant of urothelial carcinoma	Radical cystectomy should be considered
	BCG failure	Radical cystectomy is recommended

BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*.

Table 10 – Recommendations for follow-up of non–muscle-invasive bladder cancer in patients after TUR

Recommendation	GR
The follow-up is based on regular cystoscopy.	A
Patients with low-risk tumours should undergo cystoscopy at 3 mo. If negative, subsequent cystoscopy is advised 9 mo later, and then yearly for 5 yr.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 mo. If negative, subsequent cystoscopy and cytology should be repeated every 3 mo for a period of 2 yr, and every 6 mo thereafter until 5 yr, and then yearly.	C
Patients with intermediate-risk tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available), and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

CT = computed tomography; GR = grade of recommendation; IVU = intravenous urography; PDD = photodynamic diagnosis; R-biopsies = random biopsies.

safe option [39] (LE: 3). Some authors have even defended temporary surveillance in selected cases [105] (LE: 3).

- The first cystoscopy after TUR at 3 mo is an important prognostic indicator [54,56,106,107] (LE: 1a). The first cystoscopy should thus always be performed 3 mo after TUR.
- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low [106] (LE: 3). Discontinuation of cystoscopy or its replacement with less invasive methods can be considered [107].
- In tumours originally at intermediate or high risk, recurrences after a 10-yr tumour-free interval are not unusual [108] (LE: 3). Therefore, lifelong follow-up is recommended [107].
- The risk of upper urinary tract recurrence increases in patients with multiple and high-risk tumours [22] (LE: 3).
- Knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [33] (LE: 1b).

Recommendations for the follow-up schedule of NMIBC are presented in Table 10.

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Study concept and design: Babjuk, Böhle, Burger, Compérat, Kaasinen, Redorta, van Rhijn, Rouprêt, Shariat, Sylvester, Zigeuner.
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Analysis and interpretation of data: Babjuk, Böhle, Burger, Compérat, Kaasinen, Redorta, van Rhijn, Rouprêt, Shariat, Sylvester, Zigeuner.
Drafting of the manuscript: Babjuk.
Critical revision of the manuscript for important intellectual content: Babjuk, Böhle, Burger, Compérat, Kaasinen, Redorta, van Rhijn, Rouprêt, Shariat, Sylvester, Zigeuner.
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