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Guidelines

EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016

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Abstract

Context: The European Association of Urology (EAU) panel on Non–muscle-invasive Bladder Cancer (NMIBC) released an updated version of the guidelines on Non–muscle-invasive Bladder Cancer.

Objective: To present the 2016 EAU guidelines on NMIBC.

Evidence acquisition: A broad and comprehensive scoping exercise covering all areas of the NMIBC guidelines published between April 1, 2014, and May 31, 2015, was performed. Databases covered by the search included Medline, Embase, and the Cochrane Libraries. Previous guidelines were updated, and levels of evidence and grades of recommendation were assigned.

Evidence synthesis: Tumours staged as TaT1 or carcinoma *in situ* (CIS) are grouped as NMIBC. Diagnosis depends on cystoscopy and histologic evaluation of the tissue obtained by transurethral resection of the bladder (TURB) in papillary tumours or by multiple bladder biopsies in CIS. In papillary lesions, a complete TURB is essential for the patient's prognosis. If the initial resection is incomplete, there is no muscle in the specimen, or a high-grade or T1 tumour is detected, a second TURB should be performed within 2–6 wk. The risks of both recurrence and progression may be estimated for individual patients using the European Organisation for Research and Treatment of Cancer (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 and intermediate-risk patients at a lower risk of recurrence, one immediate instillation of chemotherapy is recommended. Patients with an intermediate-risk tumour should receive 1 yr of full-dose bacillus Calmette–Guérin

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(BCG) intravesical immunotherapy or 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 (RC) should be considered. RC is recommended in BCG-refractory tumours. The long version of the guidelines is available at the EAU Web site (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 European Association of Urology has released updated guidelines on Non-muscle-invasive Bladder Cancer (NMIBC). Stratification of patients into low-, intermediate-, and high-risk groups is essential for decisions about adjuvant intravesical instillations. Risk tables can be used to estimate risks of recurrence and progression. Radical cystectomy should be considered only in case of failure of instillations or in NMIBC with the highest risk of progression.

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1. Introduction

This overview represents the updated European Association of Urology (EAU) guidelines for Non-muscle-invasive Bladder Cancer (NMIBC): TaT1 and carcinoma *in situ* (CIS). The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical guidance on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

Clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather they help to focus decisions, also taking personal values and preferences/individual circumstances of patients into account.

2. Evidence acquisition

A broad and comprehensive scoping exercise covering all areas of the NMIBC guidelines was performed. The search was limited to studies representing high levels of evidence (LE) only published in the English language. The search was restricted to articles published during the period from April 1, 2014, to May 31, 2015. Databases covered by the search included Medline, Embase, and the Cochrane Libraries. A total of 1040 unique records were identified, retrieved, and screened for relevance. A detailed search strategy is available online at <https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications>.

Recommendations in this text are assessed according to their LE, and are given a grade of recommendation according to a classification system modified from the 2009 Oxford Centre for Evidence-Based Medicine Levels of Evidence. Additional methodology information can be found online at the EAU Web site: <http://uroweb.org/guidelines/>.

3. Epidemiology

Bladder cancer (BCa) is the seventh most commonly diagnosed cancer in the male population worldwide. It drops to 11th when both genders are considered [1]. The worldwide age-standardised incidence rate (per 100 000 person-years)

is 9.0 for men and 2.2 for women [1]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [1]. In Europe, the highest age-standardised incidence rate was reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [1,2].

Worldwide, the BCa age-standardised mortality rate (per 100 000 person-years) was 3.2 for men versus 0.9 for women in 2012 [1]. The incidence and mortality of BCa has decreased in some registries, possibly reflecting the decreased impact of causative agents [3].

Approximately 75% of patients with BCa present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) [2].

4. Risk factors

Tobacco smoking is the most important risk factor for BCa, accounting for approximately 50% of cases [2,4] (LE: 3). Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons accounts for about 10% of cases. This type of exposure occurs mainly in industrial plants processing paint, dye, metal, and petroleum products [2,5]. Genetic predisposition has an influence on susceptibility to other risk factors [2,6].

The chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, and exposure to arsenic in drinking water increases risk [2,7] (LE: 3). Exposure to ionising radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [2] (LE: 3). Schistosomiasis, based on recurrent infection with a parasitic trematode, is also a cause of BCa [2] (LE: 3).

5. Classification

5.1. Definition of non-muscle-invasive bladder cancer

Papillary tumours confined to the mucosa or invading the lamina propria are classified as stage Ta or T1, respectively, according to the TNM classification system. Flat high-grade (HG) tumours confined to the mucosa are classified as CIS (Tis). These tumours are grouped under the heading of NMIBC for therapeutic purposes. However, molecular biology techniques and clinical experience have demonstrated the

highly malignant potential of CIS and T1 lesions. Consequently, the terms *NMIBC* and *superficial BCa* are suboptimal descriptions.

5.2. TNM classification and definition of non-muscle-invasive bladder cancer

The 2002 TNM classification approved by the Union Internationale Contre le Cancer was updated in 2009 (7th edition) (Table 1) [8].

5.3. Grading

In 2004, the World Health Organisation (WHO) and the International Society of Urological Pathology published a new histologic classification of urothelial carcinomas that provides a different patient stratification compared with the older 1973 WHO classification (Table 2). A new update of the WHO grading classification was published recently, but the following guidelines are still based on the 1973 and 2004 WHO classifications [9,10].

5.4. Carcinoma in situ and its clinical classification

CIS is a flat HG/G3 noninvasive urothelial carcinoma. It can be missed at cystoscopy if it is not biopsied. CIS is often multifocal and can occur in the bladder but also in the upper urinary tract, prostatic ducts, and prostatic urethra [11].

Table 1 – 2009 TNM classification of urinary bladder cancer [8]

T: Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : "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 common iliac lymph node(s)
M: Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
* The WHO 2016 recommends pT1 substaging as clinically relevant without specific details on extent of invasion.	

Table 2 – 1973 and 2004/2016 World Health Organisation grading classifications

1973 WHO grading system	
<i>Urothelial papilloma</i>	
Grade 1: Well differentiated	
Grade 2: Moderately differentiated	
Grade 3: Poorly differentiated	
2004/2016 WHO grading system [papillary lesions]	
<i>Urothelial papilloma (completely benign lesion)</i>	
PUNLMP	
LG papillary urothelial carcinoma	
HG papillary urothelial carcinoma	
Flat lesions (2004 WHO grading system)	
Urothelial proliferation of uncertain malignant potential (arcinia hyperplasia)	
Reactive atypia (flat lesion with atypia)	
Atypia of unknown significance	
Urothelial dysplasia	
Urothelial CIS (always HG)	
CIS = carcinoma <i>in situ</i> ; HG = high grade; LG = low grade; PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organisation.	

Classification of CIS into clinical type is as follows:

- 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

5.5. Inter- and intraobserver variability in staging and grading

Pathologists vary significantly in their diagnosis of CIS, and agreement is achieved in 70–78% of cases [12] (LE: 2a). There is also interobserver variability 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% [12–15] (LE: 2a). The published comparisons have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification [13,16].

5.6. Further promising pathology parameters

Lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours [17] (LE: 3). Some variants of urothelial carcinoma (micropapillary, plasmocytoid, nested, sarcomatoid, microcystic, squamous, and adeno variants of urothelial carcinoma) have a poor prognosis [18] (LE: 3). Table 3 lists recommendations for BCa classification.

6. Diagnosis

6.1. Patient history, signs, and symptoms

A comprehensive patient history is mandatory. Haematuria is the most common finding in NMIBC. CIS might be

Table 3 – Recommendations for non-muscle-invasive bladder cancer classification

Recommendation	GR
For classification of the depth of tumour invasion (staging), use the 2009 TNM system.	A
For histologic classification, use the 1973 and 2004/2016 WHO grading systems.	A
Do not use the term <i>superficial bladder cancer</i> .	A
Whenever you use the terminology NMIBC in individual cases, mention the tumour stage and grade.	A
GR = grade of recommendation; NMIBC = non-muscle-invasive bladder cancer; WHO = World Health Organisation.	

suspected in patients with storage lower urinary tract symptoms.

6.2. Physical examination

Physical examination does not reveal NMIBC.

6.3. Imaging

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract that can be seen as filling defects or indicated by hydronephrosis. Intravenous urography (IVU) can be an alternative if CT is not available [19] (LE: 3), but particularly in muscle-invasive tumours of the bladder and in upper tract urothelial carcinomas (UTUCs), CT urography offers more information than IVU.

The necessity to perform a CT urography or IVU once a bladder tumour has been detected is questionable due to the low incidence of significant findings obtained [20] (LE: 2a). The incidence of UTUCs is low (1.8%) but increases to 7.5% in tumours located in the trigone [20] (LE: 2b). The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [21] (LE: 3).

Transabdominal ultrasound (US) permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder (LE: 3). Consequently, US is a useful tool in patients with haematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

The diagnosis of CIS cannot be made with imaging methods (LE: 4).

6.4. Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG tumours (84%) but low sensitivity in low-grade (LG) tumours (16%) [22]. The sensitivity for CIS detection is 28–100% [23] (LE: 2b). Cytology is useful, particularly as an adjunct to cystoscopy, if HG/CIS malignancy is present. Positive voided urinary cytology can indicate a urothelial tumour anywhere in the urinary tract; negative cytology, however, does not exclude the presence of a tumour.

Cytologic interpretation is user dependent [24]. Evaluation can be hampered by low cellular yield, urinary tract

Table 4 – Recommendations for the primary assessment of non-muscle-invasive bladder cancer

Recommendation	GR
Patient history should be taken.	A
Renal and bladder US may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of NMIBC, CT urography (or IVU) should be performed in selected cases (eg, tumours located in the trigone, multiple or high-risk tumours).	B
Cystoscopy is recommended in all patients with symptoms suggestive of BCa. 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 as an adjunct to cystoscopy to detect HG tumour.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C
BCa = bladder cancer; CT = computed tomography; GR = grade of recommendation; HG = high grade; IVU = intravenous urography; NMIBC = non-muscle-invasive bladder cancer; US = ultrasound.	

infections, stones, or intravesical instillations, but in experienced hands specificity exceeds 90% [25] (LE: 2b).

Urine collection should be performed with respect to the recommendations provided in Table 4. One cytospin slide from the sample is usually sufficient. In patients with suspect cytology it is reasonable to repeat the investigation (LE: 3).

6.5. Urine molecular tests

Driven by the low sensitivity of urine cytology, numerous urinary tests were developed [25–27]. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines.

6.6. Cystoscopy

The diagnosis of papillary BCa depends on cystoscopic examination 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. A flexible instrument with intraurethral anaesthetic lubricant instillation results in better compliance compared with a rigid instrument, especially in men [28]. Table 4 lists recommendations for the primary assessment of BCa.

6.7. Transurethral resection of bladder cancer

6.7.1. Strategy of the procedure

The goal of transurethral resection of the bladder (TURB) in TaT1 BCa is to make the correct diagnosis and completely remove all visible lesions. TURB should be performed systematically in individual steps (Table 5). The strategy of resection depends on the size of the lesion. Separate resection of larger tumours provides good information about the extent of the tumour and helps improve completeness of resection [29,30] (LE: 3).

Table 5 – Recommendations for transurethral resection of the bladder and/or biopsies and pathology report

Recommendation	GR
In patients suspected of harbouring BCa, TURB followed by pathology investigation of the obtained specimen(s) is recommended as a diagnostic procedure and initial treatment step.	A
Perform TURB systematically in individual steps:	C
<ul style="list-style-type: none"> • 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 • Surgical report formulation • Precise description of the specimen for pathology evaluation 	
Performance of individual steps:	
Perform resection in one piece for small papillary tumours (<1 cm) including part from the underlying bladder wall.	B
Perform resection in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area for tumours > 1 cm in diameter.	B
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	C
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, and anterior and posterior bladder walls) are recommended when cytology is positive or when high-risk exophytic tumour is expected (nonpapillary appearance). If equipment is available, use fluorescence-guided (PDD) biopsies.	B
Take biopsy of the prostatic urethra in 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
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between 5 and 7 o'clock positions) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	C
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC, CIS in the bladder (random biopsies or PDD-targeted biopsies), and tumour in prostatic urethra (prostatic urethra biopsy).	C
Perform a second TURB in the following situations:	A
<ul style="list-style-type: none"> • After incomplete initial TURB • If there is no muscle in the specimen after initial resection, with exception of TaG1 tumours and primary CIS • In all T1 tumours • In all HG/G3 tumours, except primary CIS 	
If indicated, perform a second TURB within 2–6 wk after initial resection. It should include the resection of primary tumour site.	C
Pathology report	
The pathology 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 pathology report should specify the presence of LVI or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B
BCa = bladder cancer; CIS = carcinoma <i>in situ</i> ; GR = grade of recommendation; HG = high grade; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder; UTUC = upper tract urothelial carcinoma.	

A complete and correct TURB is essential to achieve a good prognosis [31]. The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence, and tumour understaging [30,32] (LE: 2b). Surgical experience can improve TURB results and thus supports the role of teaching programmes [33].

6.7.2. Office-based fulguration

In patients with a history of small Ta LG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be an option [34,35] (LE: 3).

6.7.3. New resection techniques

Compared with monopolar resection, the bipolar electrocautery system was introduced to reduce the risk of complications and produce better specimens for the pathologist [36] (LE: 3). The results currently remain controversial [37].

6.7.4. Bladder and prostatic urethral biopsies

CIS can present as an area indistinguishable from inflammation, or it may not be visible at all. For this reason, the strategy of taking biopsies from abnormal urothelium and biopsies from normal-looking mucosa (random/mapping biopsies) is recommended (Table 5). The indication for random biopsies reflects the fact that the likelihood of detecting CIS, especially in low-risk tumours, is extremely low (<2%) [38] (LE: 2a). The risk increases in patients with high-risk tumours and with positive cytology [39]. If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy.

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported (11.7% in one study) (LE: 2b) [40]. The risk is higher if the tumour is located on the trigone or bladder neck in the presence of bladder CIS and multiple tumours [41] (LE: 3). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases [40].

6.7.5. New methods of tumour visualisation

As a standard procedure, cystoscopy and TURB are performed using white light (WL). However, the use of WL can lead to missing lesions that are not visible, which is why new technologies are being developed.

6.7.5.1. Photodynamic diagnosis (fluorescence cystoscopy). 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 [42] (LE: 2a). In a systematic review and meta-analysis, PDD had higher sensitivity than WL endoscopy in the pooled estimates for analyses at both the patient level (92% vs 71%) and biopsy level (93% vs 65%) [42]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [43].

PDD had lower specificity than WL endoscopy (63% vs 81%) [42].

False positivity can be induced by inflammation or recent TURB and during the first 3 mo after bacillus Calmette-Guérin (BCG) instillation [44] (LE: 3). Prospective randomised studies evaluating the impact of ALA fluorescence cystoscopy (FC)-guided TURB on disease-recurrence rate provided controversial results [42,45,46].

The beneficial effect of HAL FC on recurrence rate in patients with TURB was confirmed by a multicentre prospective randomised trial and by a meta-analysis based on raw data of controlled trials. A meta-analysis reported an increase in detection of tumour lesions in HAL arms and an absolute reduction < 10% in recurrence rates within 12 mo [47] (LE: 1a). The beneficial effect of HAL FC on recurrence rates in patients with TURB and early intravesical instillation of chemotherapy was not confirmed by prospective randomised trials [48]. The value of FC for improvement of outcome in relation to progression rate and survival remains to be demonstrated.

6.7.5.2. Narrow-band imaging. In narrow-band imaging (NBI), the contrast between normal urothelium and hypervascular cancer tissue is enhanced. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection [49] (LE: 3).

6.8. Second resection

The significant risk of residual tumour after initial TURB of TaT1 lesions was demonstrated [31] (LE: 2a). Persistent disease after resection of T1 tumours was observed in 33–55% of patients, and after resection of TaG3 tumour in 41.4% [50,51]. The tumour is often understaged by initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 4% to 25%, and it increases to 45% if there was no muscle in the initial resection [30]. This risk increased to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [52] (LE: 2a). It has been demonstrated that a second TURB can increase recurrence-free survival [50] (LE: 2a), improve outcomes after BCG treatment [53] (LE: 3), and provide prognostic information [54] (LE: 3). Based on these arguments, a second TURB is recommended in selected cases (Table 5).

6.9. Pathology report

Pathologic investigation of the specimen(s) obtained by TURB is an essential step in the diagnosis and treatment of BCa. Close cooperation between urologists and pathologists is recommended. A high quality of resected and submitted tissue is essential for correct pathologic assessment. The presence of sufficient muscle is necessary for the correct assignment of T category. The specimen collection, handling, and evaluation should respect the recommendations [55]. Table 5 presents the recommendations for TURB and/or biopsies and pathology report.

7. Predicting recurrence and progression

7.1. Prognosis of TaT1 tumours

To predict separately the short- and long-term risks of disease recurrence and progression in individual patients, the European Organisation for the Research and Treatment of Cancer-Genito-Urinary Cancer Group (EORTC-GUCG) developed a scoring system and risk tables [56]. These tables are based on individual patient data from 2596 patients with TaT1 tumours who were randomised into seven EORTC trials and did not undergo a second TURB or receive maintenance BCG.

The 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, and tumour grade (WHO 1973).

Scoring models for BCG-treated patients that predict the short- and long-term risks of recurrence and progression have been developed by the Club Urológico Español de Tratamiento Oncológico (CUETO) and the EORTC.

Using the CUETO 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 [57]. The lower risks in the CUETO tables may be attributable to using BCG, which is a more effective instillation therapy. The CUETO risk calculator is available at <http://www.aeu.es/Cueto.html>.

In 1812 intermediate- and high-risk patients without CIS treated with 1–3 yr of maintenance BCG, the EORTC developed new BCG risk tables. The prior disease-recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and grade were the most important prognostic factors for disease progression and disease-specific survival, and age and grade were the most important prognostic factors for overall survival (OS). T1G3 patients do poorly, with 1- and 5-yr disease-progression rates of 11.4% and 19.8%, respectively [58] (LE: 2a).

Further prognostic factors have been described in selected patient populations. Female sex and CIS in the prostatic urethra are important prognostic factors in T1G3 patients treated with an induction course of BCG, and age, tumour size, and concurrent CIS in BCG-treated patients [40,59] (LE: 2b). Attention must be given to patients with T1G3 tumours in the bladder (pseudo)diverticulum because of an absence of muscle layer in the diverticular wall [60] (LE: 3). In patients with high-risk disease, the tumour stage at the time of the second TURB is an unfavourable prognostic factor [54] (LE: 3). Recurrence at 3 mo was the most important predictor of progression in T1G2 tumours treated with TURB [61] (LE: 2b).

7.2. Prognosis of carcinoma in situ

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [62] (LE: 3). No reliable prognostic factors are available to predict the course of the disease. Some studies have reported a worse

Table 6 – Risk group stratification

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: <ul style="list-style-type: none"> • T1 tumour • HG/G3 tumour • CIS • Multiple and recurrent and large (>3 cm) Ta G1G2 tumours (all conditions must be present in this point)

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

Table 7 – Recommendations for stratification of non-muscle-invasive bladder cancer

Recommendation	GR
Stratify patients into three risk groups according to Table 6.	B
Apply EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B
For individual prediction of the risk of tumour recurrence and progression in patients treated with BCG, use the CUETO risk tables and the new EORTC risk tables.	B

BCG = bacillus Calmette-Guérin; CUETO = Club Urológico Español de Tratamiento Oncológico; EORTC = European Organisation for Research and Treatment of Cancer; GR = grade of recommendation; TURB = transurethral resection of the bladder.

prognosis in concurrent CIS and T1 tumours compared with primary CIS [63], in extended CIS [64], and in CIS in the prostatic urethra [40] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BCa [57,61]. Approximately 10–20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of nonresponders [65] (LE: 2a).

7.3. Patient stratification into risk groups

To facilitate treatment recommendations, it is important to categorise patients into risk groups. Table 6 provides a definition of risk groups that takes into account the EORTC risk tables' probabilities of recurrence and especially progression. Table 7 lists recommendations for NMIBC patient stratification.

8. Disease management

8.1. Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [66,67] (LE: 3).

8.2. Adjuvant treatment

8.2.1. Intravesical chemotherapy

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can

progress to muscle-invasive BCa. It is therefore necessary to consider adjuvant therapy in all patients.

8.2.1.1. Single immediate postoperative intravesical instillation. Immediate single instillation (SI) acts by destroying circulating tumour cells after TURB and by an ablative effect (chemoresection) on residual tumour cells at the resection site and on small overlooked tumours. Four large meta-analyses showed that after TURB, SI significantly reduces the recurrence rate compared with TURB alone [68–71] (LE: 1a). In the most recent systematic review and individual patient data meta-analysis of 2278 eligible patients [68], SI reduced the 5-yr recurrence rate from 59% to 45%. The number to treat (NNT) to prevent one recurrence within 5 yr was seven eligible patients. Only low-risk patients and intermediate-risk patients with a prior recurrence rate of less than or equal to one recurrence per year and an EORTC recurrence score < 5 benefitted from SI. Mitomycin C (MMC), epirubicin, and pirarubicin have all shown a beneficial effect [68] (LE: 1a).

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by extracellular matrix [72] (LE: 3). To maximise the efficacy of SI, flexible practices should be devised that allow the instillation to be given as soon as possible after TURB, preferably within the first 2 h. Because severe complications have been reported in patients with drug extravasation [73], safety measures should be maintained.

8.2.1.2. Additional intravesical chemotherapy instillations. In low-risk patients, an SI reduces the risk of recurrence and is considered the standard and complete treatment. For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression. Evidence from several studies indicated that in intermediate-risk patients, SI might have an impact on recurrence even when further adjuvant instillations are given; however, they do not take into account the EORTC recurrence score [74] (LE: 2a). In one study [75], further chemotherapy instillations after SI improved recurrence-free survival in intermediate-risk patients (LE: 2a). Conversely, a sufficient number of delayed repeat chemotherapy instillations without SI can also reduce recurrences [74].

A meta-analysis of 3703 patients from 11 randomised trials showed a highly significant 44% reduction in the odds of recurrence (corresponding to an absolute difference of approximately 14%) at 1 yr in favour of chemotherapy over TURB alone, but no effect on tumour progression [76]. The length and frequency of chemotherapy instillations is still controversial [74]. The available evidence does not support treatment > 1 yr (LE: 3).

8.2.1.3. Optimising intravesical chemotherapy. Adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution of MMC reduced the recurrence rate [77] (LE: 1b). A 1-h instillation of MMC was more effective than a 30-min instillation, but no efficacy comparisons are available for 1- and 2-h instillations [78] (LE: 3). Another

randomised controlled trial (RCT) using epirubicin documented that concentration is more important than treatment duration [79] (LE: 1b).

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia or the efficacy of MMC using electromotive drug administration in patients with mainly high-risk tumours. The current evidence, however, is limited [80,81], and both treatment modalities are considered experimental (LE: 2b).

8.2.2. Intravesical bacillus Calmette-Guérin immunotherapy

8.2.2.1. Efficacy of bacillus Calmette-Guérin. Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC [82–86] (LE: 1a). Three RCTs of intermediate- and high-risk tumours compared BCG with epirubicin plus interferon [87], MMC [88], or epirubicin alone [89] and confirmed the superiority of BCG for the prevention of tumour recurrence (LE: 1a). The effect is long lasting [88,89] and was also observed in a separate analysis of patients with intermediate-risk tumours [89].

Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [90,91] (LE: 1a). A meta-analysis carried out by the EORTC-GUCG evaluated data from 4863 patients enrolled in 24 RCTs. Five different BCG strains were used, and in 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 yr, in 9.8% of patients treated with BCG, tumours progressed compared with 13.8% in the control groups. The size of the reduction was similar in patients with TaT1 papillary tumours, and in those with CIS [91]. A recent RCT with long-term observation demonstrated significantly fewer distant metastases and better OS and disease-specific survival in patients treated with BCG compared with epirubicin [89] (LE: 1b). On the contrary, 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 [82].

A meta-analysis suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [92]. In the most recent meta-analysis, however, BCG maintenance was more effective than MMC, both in patients previously treated and not previously treated with chemotherapy [82] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 yr of age, but it was still more effective than epirubicin [93] (LE: 1a).

8.2.2.2. Bacillus Calmette-Guérin strain. The EORTC meta-analysis suggested no large differences in efficacy between various BCG strains [91]. Smaller studies without maintenance demonstrated some differences between strains. This clearly needs further evaluation in prospective trials [94,95] (LE: 2a).

8.2.2.3. Bacillus Calmette-Guérin toxicity. BCG intravesical treatment is associated with more side effects compared with intravesical chemotherapy. However, serious side effects

Table 8 – Recommendations for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

Recommendations	GR
Smokers with confirmed NMIBC should be counselled to stop smoking.	B
The type of further therapy after TURB should be based on the risk groups shown in Table 6.	A
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	A
In patients with intermediate-risk tumours (with or without immediate instillation), 1-yr full-dose BCG treatment (induction plus once weekly instillations for 3 wk at 3, 6, and 12 mo), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 yr is recommended. 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.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1–3 yr (induction plus instillations once weekly for 3 wk at 3, 6, 12, 18, 24, 30, and 36 mo) is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconveniences.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG can be offered.	C
In patients at highest risk of tumour progression (sect. 7.1; Table 10), immediate RC should be considered.	C
In patients with BCG failure, RC is indicated.	B
Intravesical chemotherapy	
When given, one immediate instillation of chemotherapy should be administered within 24 h after TURB, preferably within 2 h.	C
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation (after extensive TURB or bleeding requiring bladder irrigation).	C
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not known; 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 by reducing fluid intake before and during instillation.	B
The length of individual instillation should be 1–2 h.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation:	C
<ul style="list-style-type: none"> • During the first 2 wk after TURB • In patients with visible haematuria • After traumatic catheterisation • In patients with symptomatic urinary tract infection 	
The management of side effects after BCG intravesical instillation should reflect their type and grade.	C
BCG = bacillus Calmette-Guérin; CIS = carcinoma <i>in situ</i> ; EORTC = European Organisation for Research and Treatment of Cancer; GR = grade of recommendation; NMIBC = non-muscle-invasive bladder cancer; RC = radical cystectomy; TUR = transurethral resection; TURB = transurethral resection of the bladder.	

are encountered in < 5% of patients and can be treated effectively. Side effects requiring treatment stoppage were seen more often in the first year of therapy [96].

Major complications can appear after systemic absorption of the drug. Thus contraindications of BCG intravesical instillation should be respected (Table 8).

The presence of leukocyturia, nonvisible haematuria, or asymptomatic bacteriuria is not a contraindication for BCG

application, and antibiotic prophylaxis is not necessary in these cases [97] (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (LE: 3). The management of side effects after BCG should reflect their type and grade [98,99].

8.2.2.4. Optimal bacillus Calmette-Guérin schedule. Induction BCG instillations are given according to the empirical schedule of once weekly for 6 wk. For optimal efficacy, BCG must be given in a maintenance schedule [82,86,90,91] (LE: 1a). Many different maintenance schedules have been used; it is not possible, however, to determine which BCG maintenance schedule is the most effective [91,100]. At least 1 yr of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [90] (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations is not fully known. In an RCT of 1355 patients, the EORTC showed that when BCG is given at full dose, 3 yr of maintenance reduces the recurrence rate compared with 1 yr in high-risk but not in intermediate-risk patients [101] (LE: 1b). In an RCT of 397 patients, CUETO suggested that in high-risk tumours, the maintenance schedule with only one instillation every 3 mo for 3 yr may be suboptimal [102] (LE: 1b).

8.2.2.5. Optimal dose of bacillus Calmette-Guérin. To reduce BCG toxicity, instillation of a reduced dose was proposed. The CUETO study compared a one-third dose with full-dose BCG and found no overall difference in efficacy. However, it was suggested that a full dose of BCG is more effective in multifocal tumours [103] (LE: 1b). A further reduction to a one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [104] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full-dose BCG [96,101] (LE: 1b).

8.2.2.6. Indications for bacillus Calmette-Guérin. Table 8 lists the recommendations for individual risk groups. A statement by the panel on BCG shortage can be accessed online at <https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications>.

8.2.3. Combination therapy

In one RCT, a combination of MMC and BCG reduced recurrences but was more toxic compared with BCG monotherapy [105]. In frequently recurrent NMIBC, another RCT demonstrated a significantly higher efficacy of weekly MMC followed by monthly BCG in reduction of the recurrence rate when compared with BCG and interferon [106].

8.2.4. Specific aspects of treatment of carcinoma in situ

8.2.4.1. Treatment strategy. Histologic diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but as many as 40–50% of patients may be overtreated [62] (LE: 3).

8.2.4.2. Intravesical treatment of bladder carcinoma in situ. A meta-analysis of clinical trials comparing intravesical BCG with intravesical chemotherapy in patients with CIS showed a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [107] (LE: 1a).

In an EORTC-GUCC meta-analysis (a subgroup of 403 patients with CIS), BCG reduced the risk of progression by 35% compared with intravesical chemotherapy or different immunotherapy [91] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [108].

8.2.4.3. Treatment of carcinoma in situ in prostatic urethra and upper urinary tract. Patients with CIS are at high risk of extravesical involvement in the upper urinary tract (UUT) and in the prostatic urethra. Patients with extravesical involvement had worse survival than those with bladder CIS alone [109] (LE: 3).

Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [110] (LE: 3).

In patients with prostatic duct involvement, there are promising results after BCG instillation, but the data are insufficient to provide clear treatment recommendations, and radical surgery should be considered [110] (LE: 3).

Treatment of CIS that involves the UUT is discussed in the EAU guidelines on urothelial carcinomas of the upper urinary tract (http://uroweb.org/wp-content/uploads/06-UTUC_druk_LR.pdf).

8.3. Treatment of failure of intravesical therapy

8.3.1. Failure of intravesical chemotherapy

Patients with NMIBC recurrence after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical

Table 9 – Categories of unsuccessful treatment with intravesical bacillus Calmette-Guérin

BCG failure

Whenever a MIBC is detected during follow-up.

BCG-refractory tumour:

1. If HG non-muscle-invasive papillary tumour is present at 3 mo. Further conservative treatment with BCG is associated with increased risk of progression (LE: 3).
2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 mo. If patients with CIS present at 3 mo, an additional BCG course can achieve a complete response in > 50% of cases [11] (LE: 3).
3. If HG tumour appears during BCG therapy.*

HG recurrence after BCG. Recurrence of HG/grade 3 (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.

BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; HG = high grade; LE = level of evidence; MIBC = muscle-invasive bladder cancer; WHO = World Health Organisation.

* Patients with low-grade recurrence during or after BCG treatment are not considered a BCG failure.

Table 10 – Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, G1/PUNLMP/LG, < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All cases between categories of low and high risk	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either 1-yr full-dose BCG treatment (induction plus weekly instillations for 3 wk at 3, 6, and 12 mo), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 yr.
High-risk tumours	Any of the following: <ul style="list-style-type: none"> • T1 tumours • HG/G3 tumours • CIS • Multiple and recurrent and large (>3 cm) Ta G1G2 tumours (all these conditions must be present) 	Intravesical full-dose BCG instillations for 1–3 yr or cystectomy (in highest risk tumours; see below).
Subgroup of highest risk tumours		
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, unusual histology of urothelial carcinoma, LVI (sect. 5.6 and 7.1).	RC should be considered. In those who refuse RC, intravesical full-dose BCG instillations for 1–3 yr.
	BCG failures	RC is recommended.
BCG = bacillus Calmette-Guérin; CIS = carcinoma <i>in situ</i> ; EORTC = European Organisation for Research and Treatment of Cancer; HG = high grade; LG = low grade; LVI = lymphovascular invasion; PUNLMP = papillary urothelial neoplasm of low malignant potential; RC = radical cystectomy; TURB = transurethral resection of the bladder.		

chemotherapy has no impact on the effect of BCG instillation [82] (LE: 1a).

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

Table 9 lists the categories of unsuccessful treatment with intravesical BCG. Patients with BCG failure are unlikely to respond to further BCG therapy; therefore, RC is the preferred option. Several bladder preservation strategies are also now available that can be categorised as immunotherapy [111], chemotherapy, device-assisted therapy, and combination therapy [112]. Changing from BCG to these options can yield responses in selected cases with BCG treatment failure [113–116] (LE: 3).

However, at the present time, treatments other than RC must be considered oncologically inferior in patients with BCG failure (LE: 3).

Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

Non-HG recurrence after BCG is not considered as BCG failure. Treatment decisions should be individualised according to tumour characteristics.

8.4. Radical cystectomy for non-muscle-invasive bladder cancer

If RC is indicated before progression to muscle-invasive tumour, it can be performed as an immediate procedure (right after NMIBC diagnosis) or early procedure (after BCG failure).

There are two reasons to consider immediate RC for selected patients with NMIBC: (1) The staging accuracy for T1 tumours by TURB is low with 27–51% of patients

upstaged to MIBC at RC [52,117,118] (LE: 3), and (2) some patients with NMIBC experience disease progression to muscle-invasive disease.

The potential benefit of RC must be weighed against the risk, morbidity, and impact on quality of life. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of progression based on prognostic tables and additional prognostic factors mentioned in section 7.1 (Table 10) (LE: 3).

Early RC is strongly recommended in patients with BCG-refractory tumours. A delay in RC might lead to decreased disease-specific survival [119] (LE: 3).

Recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS are presented in Table 8.

Treatment principles for NMIBC and for BCG failures are summarised in Tables 10 and 11.

Table 11 – Treatment recommendations for bacillus Calmette-Guérin (BCG) failure and recurrences after BCG

Category	Treatment recommendation	GR
BCG-refractory tumour	1. RC 2. Bladder-preserving strategies in patients not suitable for RC	B
HG/G3 recurrence after BCG	1. RC 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. RC	C
BCG = bacillus Calmette-Guérin; GR = grade of recommendation; HG = high grade; RC = radical cystectomy.		

9. 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. 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 Ta LG/G1 papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy [120,121] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden [40,41] (LE: 3). Some authors have even defended temporary surveillance in selected cases [121] (LE: 3).
- The first cystoscopy after TURB at 3 mo is an important prognostic indicator for recurrence and progression [61,65,122,123] (LE: 1a); therefore, the first cystoscopy should always be performed 3 mo after TURB in all patients with TaT1 tumours and CIS.

- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low [122] (LE: 3). Discontinuation of cystoscopy or its replacement with less invasive methods can be considered [123].
- In tumours originally intermediate or high risk, recurrences after 10 yr tumour free are not unusual [124] (LE: 3); therefore, lifelong follow-up is recommended [123].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT).
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [21] (LE: 3).
- Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy [27] (LE: 1b). It supports the adjunctive role of urine tests during follow-up.

No noninvasive method can replace endoscopy; therefore, follow-up is based on regular cystoscopy. There is a lack of randomised studies that have investigated the possibility of safely reducing the frequency of follow-up cystoscopy.

Multiple biopsies may be necessary in selected cases to confirm the efficacy of intravesical treatment in patients treated for CIS.

Table 12 lists recommendations for the NMIBC follow-up schedule.

Table 12 – Recommendations for follow-up in patients after transurethral resection of the bladder of non-muscle-invasive bladder cancer

Recommendation	GR
The follow-up of TaT1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk Ta 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 Ta tumours should have an in-between follow-up scheme using cystoscopy, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (CT-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
Consider R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 mo) in patients with CIS.	C
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

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

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