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European Association of Urology

Review – Urothelial Cancer

European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update

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Abstract

Context: This overview presents the updated European Association of Urology (EAU) guidelines for non–muscle-invasive bladder cancer (NMIBC), TaT1, and carcinoma in situ (CIS).
Objective: To provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation and recommendations.
Evidence acquisition: A broad and comprehensive scoping exercise covering all areas of the NMIBC guidelines has been performed annually since the last published version in 2017. Databases covered by the search included Medline, EMBASE, and the Cochrane Libraries. Previous guidelines were updated, and the level of evidence and grade of recommendation were assigned.
Evidence synthesis: Tumours staged as Ta, T1, and/or CIS are grouped under the heading of NMIBC. Diagnosis depends on cystoscopy and histological evaluation of the tissue obtained by transurethral resection (TURB) in papillary tumours or by multiple bladder biopsies in CIS. In papillary lesions, a complete TURB is essential for the patient's

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prognosis and correct diagnosis. Where the initial resection is incomplete, where there is no muscle in the specimen, or where a 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. Stratification of patients into low-, intermediate-, and high-risk groups is pivotal to the recommendation of adjuvant treatment. In patients with tumours presumed to be at a low risk and in those presumed to be at an intermediate risk with a low previous recurrence rate and an expected EORTC recurrence score of <5, one immediate chemotherapy instillation is recommended. Patients with intermediate-risk tumours should receive 1 yr of full-dose bacillus Calmette-Guérin (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 the highest risk of tumour progression, immediate radical cystectomy should be considered. Cystectomy is recommended in BCG-unresponsive tumours. The extended version of the guidelines is available at the EAU website: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

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 Non–muscle-invasive Bladder Cancer (NMIBC) Panel has released an updated version of their guidelines, which contains information on classification, risk factors, diagnosis, prognostic factors, and treatment of NMIBC. The recommendations are based on the current literature (until the end of 2018), with emphasis on high-level data from randomised clinical trials and meta-analyses. Stratification of patients into low-, intermediate-, and high-risk groups is essential for deciding appropriate use of adjuvant intravesical chemotherapy or bacillus Calmette-Guérin (BCG) instillations. Surgical removal of the bladder should be considered in case of BCG-unresponsive tumours or in NMIBCs with the highest risk of progression.

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 recommendations on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

It must be emphasised that clinical guidelines present the best evidence available, 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 help focus on decisions—also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

2. Evidence acquisition

For the 2019 NMIBC guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the NMIBC guidelines has been performed annually since the last published version in 2019. Excluded from the search were basic research studies, case series, reports, and editorial comments. Only articles published in English language, addressing adults, were included.

A detailed search strategy is available online: https://uroweb.org/guideline/non-muscle-invasive-bladdercancer/?type=appendices-publications.

For chapters dealing with staging, diagnosis, and prediction, references used in this article were assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (OCEBM) LEs. For the disease management and follow-up chapters, a system modified from the 2009 OCEBM LEs was used.

For each recommendation within the guidelines, there is an accompanying online strength rating form, based on a modified GRADE methodology. These key elements are the basis that panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the word “strong” or “weak”.

3. Evidence synthesis

3.1. Epidemiology, aetiology, and pathology

3.1.1. Epidemiology

Bladder cancer (BC) is the 11th most commonly diagnosed cancer worldwide [1]. The worldwide age-standardised incidence rates (per 100 000 person/yr) are 9.0 for men and 2.2 for women [1]. In the European Union, the age-standardised incidence rates are 19.1 for men and 4.0 for women [1].

Worldwide, the BC age-standardised mortality rate (per 100 000 person/yr) was 3.2 for men versus 0.9 for women [1]. BC incidence and mortality rates vary across countries due to differences in risk factors, diagnostic practices, and availability of treatments, and partly, however, because of the quality of data collection [2]. The incidence and mortality of BC have decreased in some registries, possibly reflecting the decreased impact of causative agents [3].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta and CIS) or submucosa (stage T1) [1,2].

3.1.2. Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [2–4] (LE: 3).

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants, which process paint, dye, metal, and petroleum products [2,3,5].

While family history seems to have little impact [6], genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [2,7].

Chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic; exposure to arsenic in drinking water also increases risk [2,8] (LE: 3). Exposure to ionising radiation is connected with an increased risk; a weak association was also suggested for cyclophosphamide and pioglitazone [2,8,9] (LE: 3). Schistosomiasis is also a cause of BC [2] (LE: 3).

3.1.3. Pathology

The information presented in this article is limited to urothelial carcinoma, unless otherwise specified.

3.2. Staging and classification systems

3.2.1. Definition of NMIBC

Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the tumour, node, metastasis (TNM) classification system [10]. Flat, high-grade (HG) tumours that are confined to the mucosa are classified as CIS (Tis). These tumours are grouped under the heading of NMIBC. The term "non–muscle-invasive BC" presents an overall group definition, and all tumours must be defined according to their T-stage and histological grade. The term "superficial BC" should no longer be used.

3.2.2. TNM classification

The 2009 TNM classification approved by the Union International Contre le Cancer was updated in 2017 (8th edition; Table 1) [10].

Table 1 – 2017 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 stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N—regional 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 regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M—distant metastasis	
M0	No distant metastasis
M1a	Nonregional lymph nodes
M1b	Other distant metastases

TNM = tumour, node, metastasis (classification).

3.2.3. T1 subclassification

The depth of invasion into the lamina propria (T1 substaging) has been demonstrated to be of prognostic value in retrospective cohort studies [11] (LE: 3). Its use is recommended by the 2016 World Health Organization (WHO) classification [12]. The optimal system to substage T1 remains to be defined [12,13].

3.2.4. Histological grading of non–muscle-invasive bladder urothelial carcinomas

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of urothelial carcinomas, which provides different patient stratification between individual categories from the older 1973 WHO classification (Tables 2 and 3) [14,15]. In 2016, an update of the 2004 WHO grading classification was published [12].

A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in the prediction of recurrence and progression. There is a significant shift of patients between the prognostic categories of both systems [16] (LE: 2a). As the 2004 WHO system has not yet been incorporated fully into prognostic models, long-term individual patient data using both classification systems are needed.

3.2.5. CIS and its classification

CIS is a flat, HG, noninvasive urothelial carcinoma. CIS is often multifocal and can occur in the bladder, but also in the

Table 2 – WHO grading in 1973 and in 2004 (papillary lesions) [14,15].

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading system (papillary lesions)
Papillary urothelial neoplasm of low malignant potential
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

WHO = World Health Organization.

Table 3 – WHO 2004 histological classification for flat lesions [15].

• Urothelial proliferation of uncertain malignant potential (flat lesion without atypia or papillary aspects)
• Reactive atypia (flat lesion with atypia)
• Atypia of unknown significance
• Urothelial dysplasia
• Urothelial CIS is always high grade

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

upper urinary tract (UUT), prostatic ducts, and prostatic urethra [17].

Classification of CIS according to clinical type is as follows:

1 Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS.
2 Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS.
3 Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

3.2.6. *Inter- and intraobserver variability in staging and grading*

There is interobserver variability in the diagnosis of CIS with agreement in 70–78% (19), in the classification of stage T1 versus Ta tumours, and in tumour grading in both the 1973 and the 2004 classifications. The general agreement between pathologists in staging and grading is 50–60% [18,19] (LE: 2a). The published comparisons have not confirmed that the WHO 2004 classification provides better reproducibility than the 1973 classification [16].

3.2.7. *Further pathology parameters*

The presence of lymphovascular invasion in transurethral resection (TURB) specimens is associated with an increased risk of pathological upstaging and worse prognosis [20,21] (LE: 3).

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, and sarcomatoid) have a worse prognosis than classical urothelial carcinoma [22,23] (LE: 3).

Molecular markers, in particular complex approaches such as stratification of patients based on molecular classification, are promising but are not yet suitable for routine application [24].

Guidelines for the classification of BC are presented in Table 4.

3.3. *Diagnosis*

3.3.1. *Patient history*

A comprehensive patient history is mandatory.

3.3.2. *Signs and symptoms*

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher-stage disease compared with nonvisible haematuria [25]. CIS might be suspected in patients with lower urinary tract symptoms, especially irritative voiding.

3.3.3. *Physical examination*

A focused urological examination is mandatory, although it does not reveal NMIBC.

3.3.4. *Imaging*

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects and/or hydronephrosis [26]. Intravenous urography is an alternative if CT is not available, but CT urography gives more information (including status of lymph nodes and neighbouring organs). The necessity to perform a baseline CT urography once a bladder tumour has been detected is questionable due to the low incidence of significant findings obtained [27] (LE: 2b). The incidence of upper tract urothelial carcinomas (UTUCs) is low (1.8%), but increases to 7.5% in tumours located in the trigone [27] (LE: 2b). The risk of UTUC during follow-up increases in patients with multiple- and high-risk tumours [28] (LE: 2b).

Ultrasound (US) permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder [29] (LE: 3). It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

The role of multiparametric magnetic resonance imaging has not yet been established in BC diagnosis and staging.

A diagnosis of CIS cannot be made with imaging methods alone.

3.3.5. *Urinary cytology*

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in G3/HG tumours (84%), but low sensitivity in G1/low-grade (LG) tumours (16%) [30]. The sensitivity in CIS detection is 28–100% [31] (LE: 1b). Positive voided urinary cytology can indicate an urothelial carcinoma anywhere in the urinary tract; negative cytology, however, does not

Table 4 – Guidelines for bladder cancer classification.

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO grading systems for histological classification.	Strong
Do not use the term “superficial bladder cancer”.	Strong
Mention the tumour stage and grade whenever the terminology NMIBC is used in individual cases.	Strong

NMIBC = non–muscle-invasive bladder cancer; TNM = tumour, node, metastasis (classification); WHO = World Health Organization.

exclude its presence. Cytological interpretation is user dependent; however, in experienced hands, specificity exceeds 90% [32] (LE: 2b).

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group and is recommended for general application [33].

3.3.6. Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests have been developed [34]. No urinary marker can replace cystoscopy in a routine fashion, but the knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [35] (LE: 1b).

3.3.7. Cystoscopy

The diagnosis of papillary BC depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue. CIS is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies.

Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance compared with a rigid instrument, especially in men [36] (LE: 1b).

Guidelines for the primary assessment of BC are presented in Table 5.

3.3.8. Transurethral resection

3.3.8.1. Strategy of the procedure. The goal of TURB in TaT1 BC is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the management of BC. TURB should be performed systematically in individual steps (see Table 6).

3.3.8.2. Surgical and technical aspects of tumour resection. A complete resection performed by either the fractioned or the en bloc technique is essential to achieve a good prognosis [37]. The technique selected is dependent on the size and location of the tumour and experience of the surgeon.

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence, and tumour understaging [38] (LE: 1b).

Compared with monopolar resection, bipolar resection has been introduced to reduce the risk of complications and produce better specimens. Currently, the results remain controversial [39,40].

In patients with a history of small, TaLG/G1 tumours, fulguration or laser vaporisation of small papillary recurrences on an outpatient basis can reduce the therapeutic burden [41] (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

3.3.8.3. Bladder and prostatic urethral biopsies. CIS can present as a velvet-like, reddish area, indistinguishable from inflammation, or it may not be visible at all. For this reason, biopsies from abnormal urothelium should be taken. In patients with positive urine cytology or a history of HG/G3 NMIBC, and in tumours with nonpapillary appearance, mapping biopsies from normal-looking mucosa in specified areas of the bladder are recommended (see Table 6) [42,43]. If equipment is available, photodynamic diagnosis (PDD) is a useful tool for targeting the biopsy.

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported [44] (LE: 2b). The risk is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [45] (LE: 3b). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Table 6) [44].

3.3.9. New methods of tumour visualisation

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

3.3.9.1. PDD (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

Table 5 – Guidelines for the primary assessment of non–muscle-invasive bladder cancer.

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography (CT) intravenous urography during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (eg, tumours located in the trigone, or multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other noninvasive test.	Strong
In men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (see the figure in the extended version).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 ml fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong

Table 6 – Guidelines for transurethral resection of the bladder, biopsies, and pathology report.

Recommendations	Strength rating
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak
Perform TURB systematically in individual steps:	Strong
• Bimanual palpation under anaesthesia; this step may be omitted in case noninvasive or early treatment for invasive disease is planned	
• Insertion of the resectoscope, under visual control with inspection of the whole urethra	
• Inspection of the whole urothelial lining of the bladder	
• Biopsy from the prostatic urethra (if indicated)	
• Cold-cup bladder biopsies (if indicated)	
• Resection of the tumour	
• Recording of findings in the surgery report/record	
• Precise description of the specimen for pathology evaluation	
Performance of individual steps	
Perform en bloc resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from the abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, and right, left, anterior, and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours, and in tumours with a nonpapillary appearance. If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder CIS is present or suspected, if there is positive cytology without evidence of tumour in the bladder, or if 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.	Strong
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and the 7 o'clock position) using a resection loop. In primary non–muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB record must describe tumour location, appearance, size, and multifocality; all steps of the procedure; as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies), and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations:	Strong
• After incomplete initial TURB, or in case of doubt about completeness of a TURB.	
• If there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS.	
• In T1 tumours.	
If indicated, perform a second TURB within 2–6 wk after initial resection. This second TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
Pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS, and detrusor muscle.	Strong

CIS = carcinoma in situ; HG = high grade; LG = low grade; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

conventional procedures for the detection of malignant tumours, particularly for CIS [46] (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for analyses at both patient level (92% vs71%) and biopsy level (93% vs 65%) [46]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [47].

PDD had lower specificity than white light endoscopy (63% vs 81%) [46] (LE: 1a).

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURB was evaluated. A systematic review and analysis of 14 randomised controlled trials (RCTs) demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates [48] (LE: 1a).

3.3.9.2. Narrow-band imaging. In narrow-band imaging (NBI), the contrast between normal urothelium and hypervascular cancer tissue is enhanced. Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection [49,50] (LE: 3b). An RCT assessed the reduction of recurrence rates if NBI is used during TURB. Although the overall results of the study were negative, a benefit after 3 and 12 mo was observed for low-risk tumours [51] (LE: 1b).

3.3.10. Second resection

3.3.10.1. Detection of residual disease and tumour upstaging. The significant risk of a residual tumour after initial TURB of TaT1 lesions has been demonstrated [37] (LE: 1b).

A systematic review analysing data of 8409 patients with Ta or T1 HG BC demonstrated a 51% risk of disease persistence and an 8% risk of understaging in T1 tumours.

The analysis also showed a high risk of residual disease in Ta tumours, but this observation was based on only a limited number of cases. Most of the residual lesions were detected at the original tumour location [52] (LE: 1a). Another meta-analysis of patients with T1 tumours showed that the prevalence rate of residual tumours and upstaging to invasive disease after TURB remained high in a subgroup with detrusor muscle in the resection specimen [53].

3.3.10.2. Impact of second resection on treatment outcomes. A second TURB can increase recurrence-free survival (RFS) [54] (LE: 2a), improve outcomes after bacillus Calmette-Guérin (BCG) treatment [55] (LE: 3), and provide prognostic information [56,57] (LE: 3).

In a retrospective evaluation of a large multi-institutional cohort of 2451 patients with BCG-treated T1G3/HG tumours, the second resection improved RFS, progression-free survival (PFS), and overall survival (OS) only in patients without detrusor muscle in the specimen of the initial resection [58] (LE: 3).

3.3.10.3. Timing of second resection. A retrospective evaluation showed that a second resection performed 14–42 d after initial resection provides longer RFS and PFS than a second resection performed after 43–90 d [59] (LE: 3).

3.3.11. Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the decision-making process for BC [60]. Close co-operation between urologists and pathologists is required. A high quality of resected tissue and clinical information is essential for correct pathological assessment. The presence of sufficient muscle is necessary for the correct assignment of the T category. To obtain all relevant information, specimen collection, handling, and evaluation should respect the recommendations (see Table 6) [61]. In difficult cases, an additional review by an experienced genitourinary pathologist should be considered. Guidelines for TURB are presented in Table 6.

3.4. Predicting disease recurrence and progression

3.4.1. TaT1 tumours

Treatment should be based on a patient's prognosis. In order to predict both short- and long-term risks of disease recurrence and progression in individual patients, the European Organisation for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancer Group (GUCG) has developed a scoring system and risk tables [62]. The basis for these tables is individual patient data from 2596 patients diagnosed with TaT1 tumours. Of the patients, 78% received intravesical treatment, mostly chemotherapy. However, they did not undergo a second TURB or receive maintenance BCG.

The scoring system is based on the six most significant clinical and pathological factors, which are shown in Table 7. Table 8 shows the total scores stratified into four categories that reflect various probabilities of recurrence and progression at 1 and 5 yr [62] (LE: 2a).

Table 7 – Weighting used to calculate disease recurrence and progression scores.

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

CIS = carcinoma in situ; G = grade.

Table 8 – Probability of recurrence and disease progression according to total score.

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

CI = confidence interval.

The prognosis of intermediate-risk patients treated with chemotherapy has also been calculated [63].

A model that predicts the risk of recurrence and progression after 12 doses of intravesical BCG has been published by the Club Urologico Espanol de Tratamiento Oncologico (CUETO; Spanish Urological Oncology Group). Using this model, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [64] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this sample.

In 1812 intermediate- and high-risk patients without CIS treated with 1–3 yr of maintenance BCG, the EORTC found that the prior disease recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and grade, disease progression, and disease-specific survival, while age and grade were the most important prognostic factors for OS. T1G3 patients do poorly, with 1- and 5-yr disease-progression rates of 11.4% and 19.8%, respectively. Using these data, the new EORTC risk groups and nomograms for BCG-treated patients were designed [65] (LE: 2a).

Further prognostic factors have been described in selected patient populations:

1 In T1G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in patients treated with an induction course of BCG, and age, tumour size, and concurrent CIS in BCG-treated patients [44,66] (LE: 2b).
2 Attention must be given to patients with T1G3 tumours in the bladder (pseudo) diverticulum [67] (LE: 3).
3 In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [56] (LE: 3).
4 In patients with T1G2 tumours treated with TURB, recurrence at 3 mo was the most important predictor of progression [68] (LE: 2b).
5 The prognostic value of pathological factors has been discussed elsewhere (see section 3.2.7).

3.4.2. Carcinoma in situ

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [69] (LE: 3). There are no reliable prognostic factors; some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared with primary CIS [70], in extended CIS [71], and in CIS in the prostatic urethra [44] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [64,68]. Approximately 10–20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of nonresponders [72,73] (LE: 2a).

3.4.3. Patient stratification into risk groups

The Guidelines Panel recommends stratification of patients into three risk groups. Table 9 provides a definition of these risk groups, which takes into account the EORTC risk tables' probabilities of recurrence and, especially, progression.

Based on prognostic factors, it is possible to further stratify patients of the high-risk group and identify those who are at the highest risk of disease progression (see Table 9). Guidelines for stratification of NMIBC are presented in Table 10.

3.5. Disease management

3.5.1. Counselling of smoking cessation

Smoking increases the risk of tumour recurrence and progression [74] (LE: 3). While it is still controversial whether smoking cessation in BC will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general risks connected with tobacco smoking [75,76] (LE: 3).

3.5.2. Adjuvant treatment

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to MIBC. It is therefore necessary to consider adjuvant therapy in all patients.

3.5.2.1. Intravesical chemotherapy

3.5.2.1.1. Single, immediate, postoperative intravesical instillation of chemotherapy. Immediate single instillation (SI) has been shown to act by destroying circulating tumour cells after TURB, and by an ablative effect on residual tumour cells at the resection site and on small overlooked tumours [77] (LE: 3).

In a systematic review and individual patient data meta-analysis of 2278 patients [78], SI reduced the 5-yr recurrence rate by 14%, from 59% to 45%. In patients with an EORTC recurrence score of ≥5 and/or patients with a

Table 9 – Risk group stratification.

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG[a]), <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
	• G3 (HG[b]) tumour
	• CIS
	• Multiple, recurrent, and large (>3 cm) TaG1G2/LG tumours (all features must be present)[a]
	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, some forms of variant histology of urothelial carcinoma, lymphovascular invasion

CIS = carcinoma in situ; HG = high grade; LG = low grade; PUNLMP = papillary urothelial neoplasm of low malignant potential.
Substratification of high-risk tumours for clinical purposes is addressed in Table 13.
[a] Low grade is a mixture of G1 and G2.
[b] High grade is a mixture of some G2 and all G3 (see Fig. 4.1 of 2019 NMIBC guidelines).

Table 10 – Guidelines for stratification of non–muscle-invasive bladder cancer.

Recommendations	Strength rating
Stratify patients with NMIBC into three risk groups according to Table 9.	Strong
Apply the EORTC risk tables and calculator in individual patients for the prediction of the risk of tumour recurrence and progression in different intervals after transurethral resection of the bladder.	Strong
Use the CUETO risk tables and the EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	Strong

CUETO = Club Urologico Espanol de Tratamiento Oncologico; EORTC = European Organisation for Research and Treatment of Cancer; NMIBC = non–muscle-invasive bladder cancer.

prior recurrence rate of more than one recurrence per year, SI was not effective as a single adjuvant treatment.

An SI with mitomycin C (MMC), epirubicin, or pirarubicin has shown a beneficial effect [78]. SI with gemcitabine was superior to placebo control (saline) in an RCT, with remarkably low toxicity rates [79].

Prevention of tumour cell implantation should be initiated within the first few hours after TURB [80] (LE: 3). Safety measures should be maintained (see Table 11).

3.5.2.1.2. Additional adjuvant intravesical chemotherapy instillations. The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Table 9), an SI reduces the risk of recurrence, and is considered to be the standard and complete treatment [78] (LE: 1a). For other patients, however, an SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 7–9).

Efficacy data for the following comparisons of application schemes were published:

1 SI only versus SI and further repeat instillations: In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [81] (LE: 2a).
2 Repeat chemotherapy instillations versus no adjuvant treatment: A large meta-analysis showed a significant reduction in the risk of recurrence at 1 yr (absolute difference of 13–14%) in favour of chemotherapy over TURB alone [82].
3 SI + further repeat instillations versus later repeat instillations only: SI might have an impact on recurrence even when further adjuvant instillations are given [83–85]. An RCT, which compared SI of MMC with an instillation of MMC delayed by 2 wk after TURB (followed by further repeat instillations in both arms), showed a significant reduction of 9% in the risk of recurrence at 3 yr in favour of SI [83,85] (LE: 2a). The results of this study should be considered with caution since some patients did not receive adequate therapy.

The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed 1 yr [84] (LE: 3).

3.5.2.1.3. Options for improving efficacy of intravesical chemotherapy.

1 Adjustment of pH, duration of instillation, and drug concentration: Adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution of MMC reduce the recurrence rate [86] (LE: 1b). Duration of a 1-h instillation of MMC was more effective than that of a 30-min instillation [87] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [88] (LE: 1b). In view of these data, instructions are provided (see Table 11).
2 Device-assisted intravesical chemotherapy:
(3) Microwave-induced hyperthermia: Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [89]. In one RCT comparing 1 yr of BCG with 1 yr of MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, reduced RFS at 24 mo was demonstrated in the MMC group [90] (LE: 1b).
(4) Hyperthermic intravesical chemotherapy: Different technologies that increase the temperature of instilled MMC are available; however, data about their efficacy are still lacking.
(5) Electromotive drug administration: The efficacy of MMC using electromotive drug administration sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [91].

3.5.2.2. Intravesical BCG immunotherapy

3.5.2.2.1. Efficacy of BCG. Recurrence rate: Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing recurrence [92–95] (LE: 1a). Three RCTs in intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (IFN) [96], MMC [97], or epirubicin alone [98], and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting [97,98] and was also observed in a separate analysis of patients with intermediate-risk tumours [98]. One meta-analysis [99] has evaluated the individual data from 2820 patients enrolled in nine RCTs that have compared MMC versus BCG. In trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared with that for MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in trials without BCG maintenance.

Progression rate: Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [100,101] (LE: 1a). A meta-analysis

Table 11 – Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcinoma in situ.

	Strength rating
General recommendations	
Counsel smokers with confirmed non–muscle-invasive bladder cancer to stop smoking.	Strong
The type of further therapy after TURB should be based on the risk groups shown in Tables 9 and 12.	Strong
In patients with tumours presumed to be at a low risk and in those presumed to be at an intermediate risk with previous low recurrence rate (fewer than one recurrence per year) and expected EORTC recurrence score of <5, one immediate chemotherapy instillation is recommended.	Strong
In patients with intermediate-risk tumours (with or without immediate instillation), 1-yr full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6, and 12 mo), or instillations of chemotherapy (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.	Strong
In patients with high-risk tumours, full-dose intravesical BCG for 1–3 yr (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30, and 36 mo) is indicated. The additional beneficial effect of the 2nd and 3rd years of maintenance should be weighed against its added costs and inconveniences.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak
Discuss immediate RC with patients at the highest risk of tumour progression (see Table 12).	Strong
Offer an RC to patients with BCG failure (see Table 14).	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, and preservation strategies (intravesical chemotherapy, chemotherapy, and microwave-induced hyperthermia).	Weak
Recommendations—technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 h after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation are not defined; however, it should not exceed 1 yr.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be 1–2 h.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are the following:	Strong
• During the first 2 wk after TURB	
• In patients with visible haematuria	
• After traumatic catheterisation	
• In patients with symptomatic urinary tract infection	

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; EORTC = European Organisation for Research and Treatment of Cancer; RC = radical cystectomy; TURB = transurethral resection of the bladder.

carried out by the EORTC GUCG has evaluated data from 4863 patients enrolled in 24 RCTs. In 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 yr, tumours progressed in 9.8% patients treated with BCG 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 [101]. An RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better OS and disease-specific survival in patients treated with BCG than in those treated with epirubicin [98] (LE: 1b). In contrast, a meta-analysis of individual patient data was not able to confirm any statistically significant differences between MMC and BCG for progression, survival, and cause of death [99].

The conflicting results in the outcomes of these studies can be explained by different patient characteristics, duration of follow-up, methodology, and statistical power. However, most studies showed a reduction in the risk of progression in high- and intermediate-risk tumours if a BCG maintenance schedule was applied.

3.5.2.2.2. BCG strain. A network meta-analysis identified 10 different BCG strains used for intravesical treatment in the published literature, but was not able to confirm superiority of any BCG strain over another [102]. This conclusion is supported by a meta-analysis of prospective RCTs [101] and data from a prospective registry [103] as well as from a post hoc analysis of large phase 2 prospective trials assessing BCG and IFN-α in both BCG-naive and BCG failure patients [104]. The quality of data, however, does not allow definitive conclusions.

3.5.2.2.3. BCG toxicity. BCG intravesical treatment is associated with more side effects than intravesical chemotherapy [101] (LE: 1a). However, serious side effects are encountered in <5% of patients and can be treated effectively [105] (LE: 1b). A maintenance schedule is not associated with an increased risk of side effects compared with an induction course [105,106]. Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Table 11). 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 [107] (LE: 3).

BCG should be used with caution in immunocompromised patients [108]. Management of side effects after BCG should reflect their type and grade [109].

3.5.2.2.4. Optimal BCG schedule. Induction BCG instillations are given according to the empirical 6-weekly schedule [110]. For optimal efficacy, BCG must be given in a maintenance schedule [95,99–101] (LE: 1a). Many different maintenance schedules have been used [111]. In their meta-analysis, Bohle and Bock [100] concluded that at least 1 yr of maintenance BCG is required to obtain superiority of BCG over MMC (LE: 1a).

The optimal number of induction instillations, and the optimal frequency and duration of maintenance instillations are not fully known. In an RCT of 1355 patients, the EORTC has shown that when BCG is given at full dose, 3-yr maintenance (3-weekly instillations at 3, 6, 12, 18, 24, 30, and 36 mo) reduces the recurrence rate compared with 1-yr maintenance in high-risk but not in intermediate-risk patients. There were no differences in progression or OS [112] (LE: 1b). In an RCT of 397 patients, CUETO suggested that in high-risk tumours, a maintenance schedule with only one instillation every 3 mo for 3 yr may be suboptimal [113] (LE: 1b).

3.5.2.2.5. Optimal dose of BCG. To reduce BCG toxicity, instillation of a reduced dose was proposed. The CUETO study compared one-third dose of BCG with full-dose BCG and found no overall difference in efficacy. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [114,115] (LE: 1b). A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [116] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third dose of BCG and full-dose BCG, but one-third dose of BCG was associated with a higher recurrence rate, especially when it was given only for 1 yr [106,112] (LE: 1b). The routine use of one-third dose of BCG is complicated by potential technical difficulties in preparing the reduced dose reliably.

3.5.2.2.6. Indications for BCG. Recommendations for individual risk groups are provided in Tables 11 and 12.

A statement by the Panel on BCG shortage can be accessed online (https://uroweb.org/guideline/non-muscleinvasive-bladder-cancer/?type=ppendices-publications).

3.5.2.3. Combination therapy. In one RCT, a combination of MMC and BCG was shown to be more effective in reducing recurrences but more toxic compared with BCG monotherapy (LE: 1b) [117]. In a Cochrane meta-analysis of four RCTs, a combination of BCG and IFN-2α did not show a difference in recurrence and progression over BCG alone [118]. Additionally, an RCT comparing BCG monotherapy with a combination of epirubicin and IFN for up to 2 yr showed that the latter was significantly inferior to BCG monotherapy in preventing recurrence [119] (LE: 1b).

3.5.2.4. Specific aspects of treatment of CIS

3.5.2.4.1. Treatment strategy. Detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [62,64]; in this case, further treatment according to the criteria summarised in sections 3.5.2.1, 3.5.2.2, 3.5.3, and 3.5.4 is mandatory.

Table 12 – Treatment recommendations in TaT1 tumours and carcinoma in situ according to risk stratification.

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), <3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and an expected EORTC recurrence score of <5, one immediate instillation of intravesical chemotherapy after TURB; in all patients either 1-yr full-dose BCG treatment (induction plus 3-weekly instillations 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:	Intravesical full-dose BCG instillations for 1–3 yr or radical cystectomy (in highest-risk tumours—see below)
	• T1 tumours	
	• G3 (HG) tumour	
	• CIS	
	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, some forms of variant histology of urothelial carcinoma, LVI (see sections 3.2.7 and 3.4.3)	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for 1–3 yr

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

CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy (RC; LE: 4).

3.5.2.4.2. Prospective randomised trials on intravesical BCG or chemotherapy. A meta-analysis of clinical trials comparing intravesical BCG with intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [120] (LE: 1a).

In an EORTC GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared with intravesical chemotherapy or different immunotherapy [101] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [121].

3.5.2.4.3. Treatment of CIS in prostatic urethra and UUT. Patients with CIS are at a high risk of extravesical involvement in the UUT and the prostatic urethra. Patients with extravesical involvement had worse survival than those with bladder CIS alone [122] (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 [123] (LE: 3).

In patients with prostatic duct involvement, there are promising results using BCG. The data are however insufficient to provide clear treatment recommendations, and radical surgery should be considered [123,124] (LE: 3).

3.5.3. Treatment of failure of intravesical therapy

3.5.3.1. Failure of intravesical chemotherapy. Patients with NMIBC recurrence after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation [99] (LE: 1a).

3.5.3.2. Recurrence and failure after intravesical BCG immunotherapy. HG NMIBC presenting after BCG can be categorised into BCG-refractory, BCG-unresponsive, and BCG relapse NMIBC (Table 13). Recently, an updated definition of BCG-unresponsive tumours was introduced to denote a subgroup of patients at a higher risk of progression for whom further BCG is not feasible [125]. Non-HG recurrence after BCG is not considered as a BCG failure.

3.5.3.3. Treatment of BCG failure. Treatment recommendations and options are provided in Tables 11 and 14, respectively. They reflect the categories listed in Table 13 and tumour characteristics at the time of recurrence.

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; several bladder preservation strategies have been presented, which comprise intravesical immunotherapy [126], intravesical chemotherapy (single-agent or combination therapy) [127], device-assisted therapy (see section 3.5.2.1.3), combination chemoimmunotherapy (see section 3.5.2.3), or gene therapy [128]. Changing from BCG to these options can yield responses in selected cases with BCG-unresponsive disease. Treatments other than RC must however be considered oncologically inferior in such patients at the present time [72,129,130] (LE: 3). Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

Treatment decisions in LG recurrence during or after BCG should be individualised according to tumour characteristics.

3.5.4. RC for NMIBC

There are several 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 being upstaged to muscle-invasive tumour at RC [131–135] (LE: 3).
2 Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 8).
3 Patients who experience disease progression to muscle-invasive stage have a worse prognosis than those who present with "primary" muscle-invasive disease [136,137].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life. Immediate RC

Table 13 – Categories of unsuccessful treatment with intravesical BCG.

BCG failure
Whenever an MIBC is detected during follow-up.
BCG-refractory tumour:
1. If T1G3/HG, non–muscle-invasive papillary tumour is present at 3 mo [129]; further conservative treatment with BCG is associated with increased risk of progression [72,130] (LE: 3).
2. If TaG3/HG or CIS (without concomitant papillary tumour) is present at both 3 and 6 mo (after a second induction course or the first maintenance course of BCG); if patients with CIS present at 3 mo, an additional BCG course can achieve a complete response in >50% of cases [17] (LE: 3).
3. If high-grade tumour appears during BCG therapy.[a]
BCG-relapsing tumour:
1. Recurrence of G3/HG (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response [146] (LE: 3)
BCG-unresponsive tumour:
1. BCG refractory or T1Ta/HG BCG relapse within 6 mo or development of CIS within 12 mo of last BCG exposure [125]
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [109].

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high grade; LE = level of evidence; MIBC = muscle-invasive bladder cancer; WHO = World Health Organization.
[a] Patients with low-grade recurrence during or after BCG treatment are not considered a BCG failure.

Table 14 – Treatment options for bacillus Calmette-Guérin (BCG) failure.

Category	Treatment options
BCG unresponsive (BCG refractory or T1Ta/ HG ≤ 6 mo or CIS ≤ 12 mo of last BCG exposure)	1. RC
	2. Bladder-preserving strategies in patients unsuitable for RC
BCG relapsing: T1Ta/HG recurrence >6 mo or CIS > 12 mo of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation
	2. Bladder-preserving strategies
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy
	2. Radical cystectomy

CIS = carcinoma in situ; HG = high grade; LG = low grade; RC = radical cystectomy.

should be proposed to patients with NMIBC who are at the highest risk of disease progression (see Table 12) [62,64,127] (LE: 3).

Early RC is strongly recommended in patients with BCG-unresponsive tumours, as mentioned above (LE: 3).

Guidelines for adjuvant therapy in TaT1 tumours and for therapy of CIS are presented in Tables 11 and 12, respectively. Table 14 shows treatment options for BCG failure.

3.6. *Follow-up of patients with NMIBC*

As a result of the risk of recurrence and progression, patients with NMIBC need surveillance. However, the frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk (see Tables 7 and 8).

When planning the follow-up schedule and methods, the following aspects should be considered:

1 Prompt detection of muscle-invasive and HG/G3 non–muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life threatening.
2 Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small TaLG/G1/papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy [138,139] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option [41] (LE: 3). Multiple authors have even suggested temporary surveillance in selected cases [140,141] (LE: 3/2a).
3 The first cystoscopy after TURB at 3 mo is an important prognostic indicator for recurrence and progression [68,72,142,143] (LE: 1a). Therefore, the first cystoscopy should always be performed 3 mo after TURB in all patients with TaT1 tumours and CIS.
4 In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low [142] (LE: 3). Therefore, in low-risk tumours, after 5 yr of follow up, discontinuation of cystoscopy or its replacement with less invasive methods can be considered [143].
5 In tumours originally of intermediate or high risk, recurrences after 10 yr of being tumour free are not unusual [144] (LE: 3). Therefore, life-long follow-up is recommended [143].
6 The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders).
7 The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [28] (LE: 3).

Table 15 – Guidelines for follow-up of patients after transurethral resection of the bladder for non–muscle-invasive bladder cancer.

Recommendations	Strength rating
Base follow-up of TaT1 tumours and CIS on regular cystoscopy.	Strong
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.	Weak
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.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.	Weak
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with TaLG/G1–2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; LG = low grade; PDD = photodynamic diagnosis.

8 Positive urine test results have a positive impact on the quality of follow-up cystoscopy [35] (LE: 1b) supporting the adjunctive role of urine tests during follow-up.
9 In patients initially diagnosed with TaG1-2/LG BC, US of the bladder may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [145].
10 No noninvasive method can replace endoscopy.

Guidelines for follow-up of patients after TURB of NMIBC are presented in Table 15.

4. Conclusions

These abridged EAU guidelines present updated information on the diagnosis and treatment of NMIBC for incorporation into clinical practice.

Author contributions: Marko Babjuk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Babjuk.
Acquisition of data: Babjuk, Burger, Compérat, Gontero, Mostafid, Palou, van Rhijn, Rouprêt, Shariat, Sylvester, Zigeuner, Capoun, Cohen, Dominguez Escrig, Peyronnet, Seisen, Soukup.
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Drafting of the manuscript: Babjuk.
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