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European Association of Urology

Review – Bladder Cancer

European Association of Urology Guidelines on Non–muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ)

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Abstract

Context: The European Association of Urology (EAU) has released an updated version of the guidelines on non–muscle-invasive bladder cancer (NMIBC).
Objective: To present the 2021 EAU guidelines on NMIBC.
Evidence acquisition: A broad and comprehensive scoping exercise covering all areas of the NMIBC guidelines since the 2020 version was performed. 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 carcinoma in situ (CIS) are grouped under the heading of NMIBC. Diagnosis depends on cystoscopy and histological evaluation of tissue obtained via transurethral resection of the bladder (TURB) for papillary tumours or via multiple bladder biopsies for CIS. For papillary lesions, a complete TURB is essential for the patient's prognosis and correct diagnosis. In cases for which the initial resection is incomplete, there is no muscle in the specimen, or a T1 tumour is detected, a second TURB should be performed within 2–6 wk. The risk of progression may be estimated for individual patients using the 2021 EAU scoring model. On the basis of their individual risk of progression, patients are stratified as having low, intermediate, high, or very high risk, which is pivotal to recommending adjuvant treatment. For patients with tumours presumed to be at low risk and for small papillary recurrences detected more

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Intravesical chemotherapy
Prognosis
Transurethral resection (TUR)
BCG unresponsive
European Association of Urology (EAU)

than 1 yr after a previous TURB, one immediate chemotherapy instillation is recommended. Patients with an intermediate-risk tumour should receive 1 yr of full-dose intravesical bacillus Calmette-Guérin (BCG) immunotherapy or instillations of chemotherapy for a maximum of 1 yr. For patients with high-risk tumours, full-dose intravesical BCG for 1–3 yr is indicated. For patients at very high risk of tumour progression, immediate radical cystectomy should be considered. Cystectomy is also recommended for BCG-unresponsive tumours. The extended version of the guidelines is available on the EAU website at 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 has released updated guidelines on the classification, risk factors, diagnosis, prognostic factors, and treatment of non–muscle-invasive bladder cancer. The recommendations are based on the literature up to 2020, with emphasis on the highest level of evidence. Classification of patients as having low, intermediate, or and high risk is essential in deciding on suitable treatment. Surgical removal of the bladder should be considered for tumours that do not respond to bacillus Calmette-Guérin (BCG) treatment and tumours with the highest risk of progression.

1. Introduction

Q6 This overview represents the updated European Association of Urology (EAU) guidelines for non–muscle-invasive bladder cancer (NMIBC), comprising Ta, T1, and carcinoma in situ (CIS). The information presented is limited to urothelial carcinoma, unless otherwise specified. The aim is to provide practical recommendations for clinical management of NMIBC, with a focus on clinical presentation and recommendations.

It must be emphasised that 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 help to focus decisions that also take the personal values and references/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 2021 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 since the previous version was published in 2020 was performed. Excluded from the search were basic research studies, case series, reports, and editorial comments. Only articles published in the English language and addressing adults were included. Excluded from the search were basic research studies, case series, reports, and editorial comments. Only articles published in the English language and addressing adults were included. A detailed search strategy is available online at https://uroweb.org/guideline/non-muscle-invasive-bladdercancer/?type=appendices-publications.

For sections dealing with staging, diagnosis, and prediction, references cited in this text were assessed according to their level of evidence (LE) according to the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence [1]. For sections on disease management and follow-up, a system modified from the 2009 CEBM levels of evidence is used.

For each recommendation in the guidelines there is an accompanying online strength rating for which a modified GRADE methodology was used. 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” [2].

3. Epidemiology, aetiology, and pathology

3.1. Epidemiology

Bladder cancer (BC) is the tenth most commonly diagnosed cancer worldwide [3]. The age-standardised incidence rate (per 100 000 person-years) is 9.5 for men and 2.4 for women worldwide, and 20 for men and 4.6 for women in the EU [3].

Worldwide, the BC age-standardised mortality rate (per 100 000 person-years) was 3.3 for men versus 0.86 for women [3]. The incidence and mortality of BC have decreased in some registries, possibly reflecting a decrease in the impact of causative agents [4].

Approximately 75% of patients with BC present with disease confined to the mucosa (stage Ta or CIS) or submucosa (stage T1); for younger patients (<40 yr) this percentage is even higher [5].

3.2. Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for slightly less than 50% of cases [6] (LE: 3), followed with occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons, which are responsible for approximately 10% of all cases [4,7].

While family history seems to have little impact [8], genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [9,10].

Exposure to arsenic in drinking water increases the risk of BC and chlorination of drinking water and subsequent

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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	Microscopic invasion
T3b	Macroscopic invasion (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

levels of trihalomethanes are potentially carcinogenic [11] (LE: 3). A link between dietary habits and BC risk has been suggested [12,13].

Schistosomiasis and exposure to ionising radiation are associated with higher BC risk; a weak association was also suggested for cyclophosphamide and pioglitazone [11,14] (LE: 3).

3.3. Pathology

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

4. Staging and classification systems

4.1. 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 TNM classification system [15]. Flat, high-grade tumours confined to the mucosa are classified as CIS (Tis). All of these tumours are grouped under the heading of NMIBC. The term *non–muscle-invasive BC*, however, represents a group definition; all tumours should be characterised according to their stage, grade, and further pathological characteristics. The term *superficial BC* should no longer be used as it is incorrect.

4.2. TNM classification

The 2009 TNM classification approved by Union International Contre le Cancer was updated in 2017 (8th edition; Table 1) [15].

4.3. T1 subclassification

Retrospective cohort studies have demonstrated that the depth and extent of invasion into the lamina propria (T1 substaging) is of prognostic value [16] (LE: 3). Use of T1 substaging is recommended by the 2016 World Health Organization (WHO) classification [17]. The optimal system for substaging T1 remains to be defined [17,18].

4.4. CIS and its classification

CIS is a flat, high-grade, noninvasive urothelial carcinoma. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. CIS is often multifocal and can occur in the bladder, as well as the upper urinary tract (UUT), prostatic ducts, and prostatic urethra.

From a clinical point of view, CIS can be classified 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; or
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

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

In 2004 the WHO and the International Society of Urological Pathology (ISUP) published and in 2016 updated a histological classification of urothelial carcinomas that provides a different patient stratification between

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Table 2 – World Health Organization (WHO) classification in 1973 and in 2004/2016 [17]

1973 WHO classification system
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004/2016 WHO classification system (papillary lesions)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

Table 3 – World Health Organization 2004 histological classification for flat lesions

Nonmalignant lesions
• Urothelial proliferation of uncertain malignant potential (flat lesion without atypia or papillary aspects).
• Reactive atypia (flat lesion with atypia).
• Atypia of unknown significance.
(Potential) Premalignant lesion
• Urothelial dysplasia.
Malignant lesion
• Urothelial carcinoma in situ is always high grade.

individual categories compared to the older 1973 WHO classification [17] (Tables 2 and 3).

There is a significant shift of patients between the categories of the WHO 1973 and the WHO 2004/2016 systems [19]. The proportion of tumours classified as papillary urothelial neoplasm of low malignant potential (PUNLMP; WHO 2004/2016) has decreased to very low levels in the past decade [20].

4.5.1. *Prognostic value of histological grading*

To compare the prognostic value of both WHO classifications, an individual patient data (IPD) analysis of 5145 primary Ta/T1 NMIBC tumours from patients at 17 centres was conducted. The WHO 1973 and WHO 2004/2016 systems were both prognostic for progression but not for recurrence. When compared, WHO 1973 was a stronger prognosticator of progression in Ta/T1 NMIBC than WHO 2004/2016. However, a four-tier combination (low-grade [LG]/G1, LG/G2, HG/G2, and HG/G3) of both classification systems proved to be superior to either classification system alone [21].

In a subgroup of 3311 patients with primary Ta bladder tumours, similar prognosis was found for PUNLMP and Ta LG carcinomas [22]. Hence, these results do not support the continued use of PUNLMP as a separate grade category in the WHO 2004/2016 system.

To facilitate clinical utilisation in daily practice, these guidelines provide recommendations for tumours in both classification systems.

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

There is interobserver variability in the classification of CIS, with agreement in only 70–78% of cases, in stage T1 versus Ta tumours, and in tumour grading in both the 1973 and 2004/2016 classifications. The general conformity between pathologists in staging and grading is 50–60% [23] (LE: 2a). The WHO 2004/2016 classification provides slightly better reproducibility than the 1973 classification [19].

4.7. *Variants of urothelial carcinoma and lymphovascular invasion*

Several variants of urothelial carcinoma have been identified [24,25]. Most of these variants have worse prognosis than pure HG urothelial carcinoma [26] (LE: 3).

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with higher risk of pathological upstaging and worse prognosis [27] (LE: 3).

4.8. *Molecular classification*

Molecular markers, in particular complex approaches such as stratification of patients on the basis of molecular classification, are promising but are not yet suitable for routine application [28]. Guidelines for the classification of BC are presented in Table 4.

5. Diagnosis

5.1. *Patient history*

A focused patient history is mandatory.

5.2. *Signs and symptoms*

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher-stage disease compared to nonvisible haematuria [29]. CIS might be suspected in patients with lower urinary tract symptoms, especially irritative voiding.

5.3. *Physical examination*

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

Table 4 – Guidelines for bladder cancer classification

Recommendation	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 World Health Organization classification systems.	Weak
Do not use the term “superficial” bladder cancer.	Strong

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

Recommendation	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography (CT) urography during the initial work-up for patients with haematuria.	Strong
Once a bladder tumour has been detected, perform CT urography in selected cases (eg, tumours located in the trigone and multiple or high-risk tumours).	Strong
Perform cystoscopy for patients with symptoms suggestive of bladder cancer or during surveillance. Cystoscopy cannot be replaced by cytology or by any other noninvasive test.	Strong
For men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities observed during cystoscopy. Use a bladder diagram.	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumours.	Strong
Perform cytology on at least 25 ml of 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

5.4. Imaging

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects and/or hydronephrosis [30]. The necessity to perform baseline CT urography once a bladder tumour has been detected is questionable owing to the low incidence of significant findings obtained [31] (LE: 2b). The incidence of simultaneous upper tract urothelial carcinoma (UTUC) is low (1.8%), but increases to 7.5% for tumours located in the trigone [31] (LE: 2b). The risk of UTUC during follow-up is higher for patients with multiple and high-risk tumours [32] (LE: 2b).

Ultrasound (US) permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder, but cannot rule out all potential causes of haematuria [33] (LE: 3). US cannot reliably exclude the presence of UTUC and cannot replace CT urography.

The role of multiparametric magnetic resonance imaging (MRI) in BC diagnosis and staging has not yet been established. A standardised methodology for MRI reporting for patients with BC has been published, but requires validation [34].

5.5. Urinary cytology

Examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in G3 and high-grade tumours (84%), but low sensitivity in G1/LG tumours (16%) [35]. The sensitivity for CIS detection is 28–100% [36] (LE: 1b).

Cytological interpretation is user-dependent [37]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations; however, in experienced hands the specificity exceeds 90% [37] (LE: 2b).

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [38] and validated in retrospective studies [39].

5.6. Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests have been developed [40]. None of these markers can replace cystoscopy in routine practice, but the knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [41] (LE: 1b). Promising novel urinary biomarkers assessing multiple targets have been tested in prospective multicentre studies, with a very high negative predictive value [42–44].

5.7. Cystoscopy

The diagnosis of papillary BC ultimately 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 intraurethral lubricant instillation results in better compliance compared to a rigid instrument, especially in men [45] (LE: 1b). Guidelines for the primary assessment of bladder cancer are presented in Table 5.

5.8. Transurethral resection of Ta/T1 bladder tumours

The goal of TURB in Ta/T1 BC is to make the correct diagnosis and completely remove all visible lesions. TURB should be performed systematically in individual steps [46] (Table 6).

5.8.1. Resection of the tumours

A complete resection, performed using either a fractioned (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) (LE: 2b) or an en-bloc technique (LE: 1b), is essential to achieve good prognosis [47,48].

The technique selected depends on the size and location of the tumour and experience of the surgeon.

The presence of detrusor muscle in the specimen is considered a surrogate criterion of the resection quality and is required (except for Ta G1/LG tumours). The absence of detrusor muscle is associated with a significantly higher risk of residual disease, early recurrence, and tumour understaging [49] (LE: 1b).

In patients with a history of small Ta LG/G1 tumours, fulguration, or laser vaporisation of small papillary

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

Recommendation	Strength rating
In patients suspected of having bladder cancer, perform TURB followed by pathology investigation of the specimen(s) obtained 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 Ta G1/LG tumours.	Weak
Perform TURB systematically in individual steps:	Strong
• Bimanual palpation under anaesthesia. This step may be omitted if 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).	Strong
Avoid cauterisation as much as possible during TURB to minimise tissue deterioration.	Strong
Take biopsies from 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 cases with a history of HG/G3 tumours, and for 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 a prostatic urethral biopsy from the precollicular area (between the 5 and 7 o'clock positions) using a resection loop. If any abnormal-looking areas in the prostatic urethra are observed, these need to be biopsied as well.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Send 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, and the extent and completeness of the resection.	Strong
For patients with positive cytology but negative cystoscopy, exclude UTUC, CIS in the bladder (via mapping biopsies or PDD-guided biopsies), and tumour in the prostatic urethra (via prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations:	Strong
• After incomplete initial TURB, or in the case of doubt about TURB completeness)	
• If there is no detrusor muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS	
• For 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
The pathology report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, and the 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; UTUC = upper tract urothelial carcinoma.

recurrences on an outpatient basis can reduce the therapeutic burden [50] (LE: 3).

5.8.2. Bladder biopsies

CIS can present as a velvet-like, reddish area that is indistinguishable from inflammation, or it may not be visible at all. For this reason, biopsies from suspicious urothelium should be taken. In addition, for patients with positive urine cytology (see Section 5.5) or with a history of HG/G3 NMIBC and for tumours with a nonpapillary appearance, mapping biopsies from normal-looking mucosa are recommended [51]. If equipment is available, photodynamic diagnosis (PDD) is a useful tool for targeting the biopsy.

5.8.3. Prostatic urethral biopsies

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported [52] (LE: 2b). The risk of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS, and in cases with multiple tumours [53] (LE: 3b). On the basis of this observation, a biopsy from the prostatic urethra is necessary in some cases [52,54].

5.9. New methods of tumour visualisation

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

5.9.1. PDD (fluorescence cystoscopy)

PDD is performed using violet light after intravesical instillation of 5-aminolaevulinic acid or hexaminolaevulinic acid (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity for detection of tumour lesions than white light endoscopy at both the patient level (92% vs 71%) and biopsy level (93% vs 65%) [55]. A prospective

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randomised trial did not confirm a higher detection rate among patients with known positive cytology before TURB [56].

PDD had lower specificity than white-light endoscopy (63% vs 81%) [55]. False positivity can be induced by inflammation or recent TURB and during the first 3 mo after bacillus Calmette-Guérin (BCG) instillation [57,58] (LE: 1a).

A systematic review and analysis of 14 randomised controlled trials (RCTs) demonstrated the beneficial effect of fluorescence cystoscopy on the recurrence rate in patients with TURB; however, there were no differences in progression and mortality rates [59] (LE: 1a).

5.9.2. Narrow-band imaging (NBI)

In NBI, the contrast between normal urothelium and hypervascular cancer tissue is enhanced. Improved cancer detection has been observed with NBI flexible cystoscopy and NBI-guided biopsies and resection [60] (LE: 3b). An RCT assessed the reduction in 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 (pTa LG, <30 mm, no CIS) [61] (LE: 1b).

5.10. Second resection

A significant risk of residual tumour after initial TURB of Ta/T1 lesions has been demonstrated [62]. A systematic review demonstrated 51% risk of persistence and 8% risk of understaging for T1 tumours. Most of the residual lesions were detected at the original tumour location [62] (LE: 1a). The prevalence of residual tumours and upstaging to invasive disease after TURB for T1 tumour also remained high in a subgroup with detrusor muscle in the resection specimen [63].

A second TURB can increase recurrence-free survival (RFS) [64] (LE: 2a), improve outcomes after BCG treatment [65] (LE: 3), and provide prognostic information [66,67] (LE: 3). In a retrospective evaluation of a multi-institutional cohort of 2451 patients with BCG-treated T1 G3/HG tumours, the second resection improved RFS, progression-free survival (PFS), and overall survival (OS) only in cases without detrusor muscle in the specimen from the initial resection [68] (LE: 3).

Retrospective evaluation showed that a second resection performed 14–42 d after the initial resection provides longer RFS and PFS compared to a second resection performed after 43–90 d [69] (LE: 3).

5.11. Pathology report

Pathological investigation of the specimen(s) obtained via TURB and biopsies is an essential step in the decision-making process for BC. Close cooperation between urologists and pathologists is required. To obtain all the relevant information, the specimen collection, handling, and evaluation should follow the recommendations (Table 6) [70]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered. Guidelines for TURB, biopsies, and pathology report are presented in Table 6.

6. Predicting disease recurrence and progression

6.1. Ta and T1 tumours

Treatment should take into account a patient's prognosis. In order to predict the risk of disease recurrence and/or progression, several prognostic models for specified patient populations have been introduced.

6.1.1. Scoring models using the WHO 1973 classification system

6.1.1.1. The 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model. The 2006 EORTC scoring model is based on the six most significant clinical and pathological factors for patients mainly treated with intravesical chemotherapy, which are the number of tumours, tumour diameter, prior recurrence rate, category, concurrent CIS, and WHO 1973 tumour grade [71]. Using this model, individual probabilities of recurrence and progression at 1 and 5 yr can be calculated.

6.1.1.2. Model for patients with Ta G1/G2 (WHO 1973) tumours treated with chemotherapy. Patients with Ta G1/G2 tumours receiving chemotherapy were stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours, and adjuvant chemotherapy [72].

6.1.1.3. Club Urologico Español de Tratamiento Oncologico (CUETO) scoring model for BCG-treated patients. The CUETO model predicts the risk of recurrence and progression for patients treated with 12 doses of intravesical BCG over a 5- to 6-mo period following TURB. The scoring system is based on evaluation of seven prognostic factors: gender, age, prior recurrence status, number of tumours, T category, associated CIS, and WHO 1973 tumour grade.

Using this model, the calculated risk of recurrence is lower than that obtained via the EORTC model. For progression, probability is lower only for high-risk patients [73] (LE: 2a). The lower risks in the CUETO model can be attributed to the use of BCG in this sample.

6.1.1.4. The 2016 EORTC scoring model for patients treated with maintenance BCG. In patients with intermediate- and high-risk tumours without CIS treated with 1–3 yr of maintenance BCG, EORTC risk groups and nomograms for BCG-treated patients were developed [74] (LE: 2a).

6.1.2. Scoring model using the WHO 2004/2016 and WHO 1973 classification systems

6.1.2.1. EAU NMIBC 2021 scoring model. To create new prognostic-factor risk groups using both the WHO 1973 and WHO 2004/2016 classification systems, IPD from patients with primary tumours treated with TURB ± intravesical chemotherapy were used [22] (see Section 4.5.1). From the multivariate analysis, tumour stage, WHO 1973 grade, WHO 2004/2016 grade, concomitant CIS, number of tumours, tumour size, and age were independent predictors of disease progression [22].

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Table 7 – Clinical composition of the new European Association of Urology prognostic-factor risk groups for non–muscle-invasive bladder cancer based on the WHO 2004/2016 or WHO 1973 grading classification system [22] [a]

Risk group	
Low risk	• A primary, single, Ta/T1 LG/G1 tumour <3 cm in diameter without CIS in a patient aged ≤70 yr
	• A primary Ta LG/G1 tumour without CIS with at most ONE additional clinical risk factors [b]
Intermediate risk	Patients without CIS who are not included in either the low, high, or very high-risk groups
High risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group
	• All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: [b]
	• Ta LG/G2 or T1 G1 with CIS and all 3 risk factors
	• Ta HG/G3 or T1 LG with no CIS and at least 2 risk factors
	• T1 G2 with no CIS and at least 1 risk factor
Very high risk	**Stage, grade with additional clinical risk factors:** [b]
	• Ta HG/G3 and CIS with all 3 risk factors
	• T1 G2 and CIS with at least 2 risk factors
	• T1 HG/G3 and CIS with at least 1 risk factor
	• T1 HG/G3 with no CIS and all 3 risk factors

CIS = carcinoma in situ; HG = high grade; LG = low grade; LVI = lymphovascular invasion; WHO = World Health Organization.
[a] Only one of the two classification systems (WHO 1973 or WHO 2004/2016) is required to use this table. If both classification systems are available for an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973 system, as it has better prognostic value. The LG category (WHO 2004/2016) also includes tumours classified as papillary urothelial neoplasm of low malignant potential. The scoring model is based on a meta-analysis of individual patient data, but does not consider patients with primary CIS (high risk) or with recurrent tumours, as well as some pathological parameters such as variant histology (micropapillary, plasmacytoid, sarcomatoid, small-cell, neuroendocrine) and LVI. Nevertheless, on the basis of data from the literature, all patients with CIS in the prostatic urethra, with some variant histology of urothelial carcinoma, or with LVI should be included in the very high-risk group. Patients with recurrent tumours should be included in the intermediate-, high-, or very high-risk groups according to the other prognostic factors they have.
[b] Additional risk factors: age >70 yr, multiple papillary tumours, and tumour diameter ≥3 cm.

This model is used for defining risk groups as this is the only model in which the WHO 2004/2016 classification system is included as one of parameters (see Section 6.3).

As the 2021 EAU NMIBC scoring model determines the risk of tumour progression, but not recurrence, any of the models mentioned in Section 6.1.1 may be used to calculate an individual's risk of disease recurrence.

6.1.3. *Further prognostic factors*

Further prognostic factors have been described in selected patient populations:

- For T1 G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size, and concurrent CIS in BCG-treated patients [52,75] (LE: 2b).
- T1 G3 tumours in bladder (pseudo)diverticulum [76] (LE: 3).
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [66,67] (LE: 3).
- In patients with T1 G2 tumours treated with TURB, recurrence at 3 mo was the most important predictor of progression [77] (LE: 2b).
- The prognostic value of pathological factors has been discussed elsewhere (see Section 4.6). More research is needed to determine the role of molecular markers in improving the predictive accuracy of currently available risk tables [78].

6.2. *Carcinoma in situ*

Without any treatment, approximately 54% of patients with CIS experience progression to muscle-invasive disease [79] (LE: 3). There are no reliable prognostic factors, but some studies have reported worse prognosis for concurrent CIS and T1 tumours compared to primary CIS [80,81], for extended CIS [81], and for CIS in the prostatic urethra [52] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [73,77] (LE: 2a).

6.3. *Patient stratification into risk groups*

To be able to facilitate treatment recommendations, the Guidelines Panel recommends the stratification of patients into risk groups according to their probability of progression to muscle-invasive disease (Table 7). The risk group definitions are based on an IPD meta-analysis for primary patients treated with TURB ± intravesical chemotherapy and calculation of their progression scores (2021 EAU NMIBC scoring model) as presented in Sections 4.5.1 and 6.1.2 [22].

For calculation of the risk group for individual patients, either one or both of the WHO 1973 and WHO 2004/2016 classification systems may be used.

For factors for which IPD were not collected, such as variant histology, LVI, primary CIS, and CIS in the prostatic urethra, literature data have been used to classify patients into risk groups.

A web-based calculator (www.nmibc.net) and apps (iOS: https://apps.apple.com/us/app/eau-nmibc-risk-calculator/id1578482687 and Android: https://play.google.com/store/apps/details?id=net.ydeal.nmibc) facilitate determination of a patient's risk group in daily clinical practice. The individual probability of disease progression at 1, 5, and 10 yr for the new EAU NMIBC risk groups is presented in Table 8. Guidelines for stratification of patients with NMIBC are presented in Table 9.

7. Disease management

7.1. *Counselling on smoking cessation*

Smoking increases the risk of tumour recurrence and progression [82] (LE: 3). While it is still controversial whether smoking cessation in BC will favourably influence the outcome of BC treatment, patients should be counselled

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Table 8 – Probability of disease progression at 1, 5, and 10 yr for the new European Association of Urology non–muscle-invasive bladder cancer risk groups [22] [a]

New risk groups	Probability of progression, % (95% confidence interval)		
	1 yr	5 yr	10 yr
With WHO 2004/2016			
Low	0.06 (0.01–0.43)	0.93 (0.49–1.7)	3.7 (2.3–5.9)
Intermediate	1.0 (0.50–2.0)	4.9 (3.4–7.0)	8.5 (5.6–13)
High	3.5 (2.4–5.2)	9.6 (7.4–12)	14 (11–18)
Very High	16 (10–26)	40 (29–54)	53 (36–73)
With WHO 1973			
Low	0.12 (0.02–0.82)	0.57 (0.21–1.5)	3.0 (1.5–6.3)
Intermediate	0.65 (0.36–1.2)	3.6 (2.7–4.9)	7.4 (5.5–10)
High	3.8 (2.6–5.7)	11 (8.1–14)	14 (10–19)
Very High	20 (12–32)	44 (30–61)	59 (39–79)

WHO = World Health Organization.
[a] This table does not include patients with variant histologies, lymphovascular invasion, carcinoma in situ in the prostatic urethra, or primary or recurrent carcinoma in situ.

to stop smoking because of the general risks connected to tobacco smoking [83] (LE: 3).

7.2. Adjuvant treatment

Although TURB by itself can eradicate a Ta/T1 tumour completely, these tumours commonly recur and can progress to MIBC. It is therefore necessary to consider adjuvant therapy for all patients.

7.2.1. Intravesical chemotherapy

7.2.1.1. A single, immediate, postoperative intravesical instillation of chemotherapy. It has been shown that immediate single instillation (SI) acts by destroying circulating/floating tumour cells after TURB, as well as via an ablative effect on residual tumour cells at the resection site and on small overlooked tumours [84,85] (LE: 3).

Four large meta-analyses have consistently shown that after TURB, SI significantly reduces the recurrence rate compared to TURB alone [86–89] (LE: 1a). In a systematic review and IPD meta-analysis, SI reduced the 5-yr recurrence rate by 14%, although only patients with primary tumours or intermediate-risk recurrent tumours with a prior recurrence rate of one or fewer recurrences per year and those with a 2006 EORTC recurrence score of <5 benefited [86].

SIs with mitomycin C (MMC), epirubicin, or pirarubicin have all shown a beneficial effect [86]. SI with gemcitabine was superior to a placebo control (saline) in an RCT with remarkably low toxicity rates [90]. The efficacy of continuous saline irrigation in the prevention of early recurrences has also been suggested [91].

Prevention of tumour cell implantation should be initiated within the first few hours after TURB [92] (LE: 3). Safety measures should be maintained (Table 10).

7.2.1.2. Additional adjuvant intravesical chemotherapy instillations. The need for further adjuvant intravesical therapy depends on prognosis. For patients with low-risk tumours (Table 7), SI reduces the risk of recurrence and is considered to be the standard and complete treatment [86,87] (LE: 1a). For other patients, however, SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (2006 EORTC scoring model and Table 8).

Efficacy data for the following comparisons of application schemes have been published.

7.2.1.2.1. SI alone versus SI and further repeat instillations. In one study, further chemotherapy instillations after SI improved RFS in patients with intermediate-risk tumours [93] (LE: 2a).

7.2.1.2.2. Repeat chemotherapy instillations versus no adjuvant treatment. Meta-analyses showed an absolute reduction of 13–14% for patients treated with TURB and chemotherapy instillations over those with TURB alone [94].

7.2.1.2.3. SI and further repeat instillations versus later repeat instillations only. SI might have an impact on recurrence even when further adjuvant instillations are given [95,96]. An RCT comparing SI of MMC with an instillation of MMC delayed until 2 wk after TURB (followed by further repeat instillations in both treatment arms) showed a significant reduction of 9% in the risk of recurrence at 3 yr in favour of SI [95] (LE: 2a). Since the authors' definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [97]. The results of this study

Table 9 – Guidelines for stratification of patients with non–muscle-invasive bladder cancer

Recommendation	Strength rating
Stratify patients into four risk groups according to Table 7. A patient's risk group can be determined using the EAU risk group calculator available at www.nmibc.net.	Strong
For information about the risk of disease progression in a patient with primary Ta/T1 tumours, use the data from Table 8.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with BCG at www.omnicalculator.com/health/eortc-bladder-cancer.	Strong
Use the 2016 EORTC or the CUETO risk scoring model to predict the risk of tumour recurrence and progression in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1–3 yr of maintenance and the CUETO model for 5–6 m of BCG).	Strong

BCG = bacillus Calmette-Guérin; CUETO = Club Urologico Español de Tratamiento Oncologico; EAU = European Association of Urology; EORTC = European Organisation for Reaearch and Treatment of Cancer.

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Table 10 – Guidelines for adjuvant therapy for Ta/T1 tumours and for carcinoma in situ

General recommendations	Strength rating
Counsel smokers with confirmed NMIBC to stop smoking.	Strong
The type of further therapy after TURB should be based on the risk groups shown in Section 6.3 and Table 7. For determination of a patient's risk group, use the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
For patients with tumours presumed to be at low risk and those with small papillary recurrences (presumably Ta LG/G1) detected more than 1 yr after previous TURB, offer one immediate chemotherapy instillation.	Strong
For 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 (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.	Strong
For 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 second and third years of maintenance should be weighed against added costs, side effects, and problems connected with BCG shortages.	Strong
For patients with very high-risk tumours, discuss immediate RC.	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
The definition of BCG-unresponsive tumours should be respected as it most precisely identifies the patients who are unlikely to respond to further BCG instillations.	Strong
Offer RC to patients with BCG-unresponsive tumours.	Strong
For patients with BCG-unresponsive tumours who are not candidates for RC because of comorbidities, offer preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical or systemic immunotherapy; preferably within clinical trials).	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 for further intravesical chemotherapy instillation are not defined; however, the duration 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 an individual instillation should be 1–2 h.	Weak
BCG intravesical immunotherapy	
Absolute contraindications to BCG intravesical instillation are:	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; EAU = European Association of Urology; LG = low grade; NMIBC = non–muscle-invasive bladder cancer; RC = radical cystectomy; TURB = transurethral resection of the bladder.

should be considered with caution since some patients did not receive adequate therapy. Another RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominantly high-risk BC [98].

7.2.1.2.4. The optimal schedule for intravesical chemotherapy instillations. The length and frequency of repeat chemotherapy instillations are still controversial; however, the duration should not exceed 1 yr [96] (LE: 3).

7.2.1.3. Options for improving the efficacy of intravesical chemotherapy

7.2.1.3.1. Adjustment of pH, duration of instillation, and drug concentration. One RCT showed that adjusting the urinary pH and decreasing urinary excretion reduced the recurrence rate [99] (LE: 1b). Another trial reported that a duration of 1 h for instillation of MMC was more effective than 30-min instillation [100] (LE: 3). Another RCT using epirubicin documented that concentration is more important than treatment duration [101] (LE: 1b).

7.2.1.3.2. Device-assisted intravesical chemotherapy. Microwave-induced hyperthermia effect

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [102]. One RCT comparing 1 yr of BCG with 1 yr of MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC revealed greater RFS at 24 mo in the MMC group [103] (LE: 1b).

Hyperthermic intravesical chemotherapy

Different technologies that increase the temperature of instilled MMC are available, but data on their efficacy are still lacking.

Electromotive drug administration

The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been suggested in one small RCT [104].

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For application of device-assisted instillations in patients with BCG-unresponsive tumours, see Section 7.3.3.

7.2.2. Intravesical BCG immunotherapy

7.2.2.1. Efficacy of BCG

7.2.2.1.1. Recurrence rate. Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy in preventing the recurrence of NMIBC [105–109] (LE: 1a). Three RCTs of intermediate- and high-risk tumours compared BCG with epirubicin and interferon (IFN) [110], epirubicin alone [111], or MMC [112] and confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long-lasting [111,112] and was also observed in a separate analysis of patients with intermediate-risk tumours [111]. An IPD meta-analysis demonstrated a 32% reduction in the risk of recurrence for BCG compared to MMC in trials with BCG maintenance, but a 28% increase for patients treated without BCG maintenance (LE: 1a) [105].

7.2.2.1.2. Progression rate. Two meta-analyses demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [113,114] (LE: 1a). In a meta-analysis carried out by the EORTC Genito-Urinary Cancers Group (GUCG), tumours progressed in 9.8% of patients treated with BCG compared to 13.8% in the control groups (TURB alone, TURB and intravesical chemotherapy, or TURB with other immunotherapy). The magnitude of the reduction was similar in patients with Ta/T1 papillary tumours and in those with CIS [114]. An RCT with long-term follow-up demonstrated significantly fewer distant metastases and better OS and disease-specific survival for patients treated with BCG when compared to epirubicin [111] (LE: 1b). By contrast, an IPD meta-analysis was not able to confirm any significant difference between MMC and BCG for progression, survival, or cause of death [105].

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

7.2.2.2. BCG strain. A network meta-analysis identified ten different BCG strains used for intravesical treatment, but was not able to confirm the superiority of any BCG strain over another [115]. However, the quality of the source data does not allow definitive conclusions.

7.2.2.3. BCG toxicity. BCG intravesical treatment is associated with more side effects than with intravesical chemotherapy [114] (LE: 1a). However, serious side effects are encountered in <5% of patients and can be treated effectively [116] (LE: 1b). The incidence of BCG infections after BCG instillations was 1% in a registry-based cohort analysis [117]. It has been shown that a maintenance schedule is not associated with an increase in the risk of side effects when compared to an induction course [116]. Side effects requiring treatment cessation were seen more often in the first year of therapy [118]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [119] (LE: 2a). No significant difference in toxicity between different BCG strains was demonstrated [120]. Symptoms may be the result of side effects of the BCG treatment or caused by the bladder disease (widespread CIS) itself. Consequently, the burden of symptoms decreases after completion of the treatment in a significant number of patients [121].

Major complications can appear after systemic absorption of the drug. Thus, contraindications to BCG intravesical instillation should be respected (Table 10). The presence of leukocyturia, nonvisible haematuria, or asymptomatic bacteriuria is not a contraindication to BCG application, and antibiotic prophylaxis is not necessary in these cases [122] (LE: 3).

BCG should be used with caution in immunocompromised patients [123]. The management of side effects after BCG should reflect their type and grade according to the recommendations [124].

7.2.2.4. Optimal BCG schedule. Induction BCG instillations are given according to the empirical 6-weekly schedule [125]. For optimal efficacy, the induction course must be followed by maintenance instillations [105,109,113,114] (LE: 1a). Many different maintenance schedules have been used, up to a maximum of 27 instillations over 3 yr [126].

7.2.2.4.1. Optimal number of induction instillations and frequency of instillations during maintenance. The optimal number of induction instillations and frequency of maintenance instillations were evaluated in the NIMBUS trial. A safety analysis after 345 patients had been randomised demonstrated that a lower number of instillations (three instillations for induction and two instillations at 3, 6, and 12 mo) was inferior to the standard schedule (6 instillations for induction and 3 instillations at 3, 6, and 12 mo) regarding the time to first recurrence [127] (LE: 1b). A CUETO RCT showed that for high-risk tumours a maintenance schedule with only one instillation every 3 mo for 3 yr was not superior to induction therapy only, which suggested that one instillation may be suboptimal to three instillations in each maintenance cycle [128] (LE: 1b).

7.2.2.4.2. Optimal length of maintenance. It was demonstrated that at least 1 yr of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [113] (LE: 1a).

An EORTC RCT showed that when BCG is given at full dose, 3 yr of maintenance (3-weekly instillations 3, 6, 12, 18, 24, 30, and 36 mo) reduces the recurrence rate compared to 1 yr for high-risk but not intermediate-risk tumours. There were no differences in progression or OS [129] (LE: 1b).

7.2.2.5. Optimal dose of BCG. To reduce BCG toxicity, instillation of a reduced dose has been proposed. However, it has been suggested that a full dose of BCG is more effective for multifocal tumours [130,131] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. However, a further reduction

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Table 11 – Guidelines for the treatment of Ta/T1 tumours and carcinoma in situ according to risk stratification

Recommendation	Strength rating
EAU low risk group	
Offer one immediate instillation of intravesical chemotherapy after TURB.	Strong
EAU intermediate risk group	
For 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 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. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than 1 yr after previous TURB.	Strong
EAU high risk group	
Offer intravesical full-dose BCG instillations for 1–3 yr or RC.	Strong
EAU very high risk group	
Consider RC and offer intravesical full-dose BCG instillations for 1–3 yr to those who refuse or are unfit for RC.	Strong

BCG = bacillus Calmette-Guérin; EAU = European Association of Urology; RC = radical cystectomy; TURB = transurethral resection of the bladder.

to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [132] (LE: 1b). The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one-third dose BCG was associated with a higher recurrence rate, especially when it was given for only 1 yr [118,129] (LE: 1b). Routine use of one-third dose BCG is complicated by potential technical difficulties in preparing the reduced dose.

7.2.3. Combination therapy

7.2.3.1. Intravesical BCG + chemotherapy versus BCG alone. In one RCT, a combination of MMC and BCG was more effective in reducing recurrences but more toxic compared to BCG monotherapy (LE: 1b). [133]. Improved disease-free survival (DFS) but no difference in PFS for patients treated with combination treatment comparing to BCG alone were observed [134].

7.2.3.2. Combination treatment using IFN. In a Cochrane meta-analysis of four RCTs, a combination of BCG and IFN-2a did not show a clear difference in recurrence and progression when compared to BCG alone [135]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2α showed a higher probability of recurrence compared to MMC followed by BCG alone [136]. In addition, 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 [137] (LE: 1b).

7.2.4. Specific aspects of treatment of CIS

7.2.4.1. Treatment strategy. Detection of concurrent CIS increases the risk of recurrence and progression of Ta/T1 tumours [71,73]. As CIS cannot be cured by an endoscopic procedure alone, the diagnosis of CIS must be followed by further treatment using either intravesical BCG instillations or RC (LE: 4).

7.2.4.2. Prospective randomised trials on intravesical BCG or chemotherapy. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS showed a significantly higher response rate and lower risk of treatment failure after BCG [138] (LE: 1a).

In an EORTC-GUCG meta-analysis, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% when compared to intravesical chemotherapy or immunotherapy [114] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [139].

7.2.4.3. Treatment of CIS in the prostatic urethra. Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra [140]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [140] (LE: 3). Patients with CIS in the epithelial lining of the prostatic urethra can be treated with intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [141] (LE: 3).

For patients with prostatic duct involvement there are promising results with BCG, but only from small series. The data are insufficient to provide clear treatment recommendations, and radical surgery should be considered [141] (LE: 3).

The treatment strategy for primary and recurrent tumours after TURB without previous BCG instillations is presented in Table 11.

7.3. Treatment of failure of intravesical therapy

7.3.1. Recurrence during or after intravesical chemotherapy

Patients with NMIBC recurrence during or after a chemotherapy regimen can benefit from BCG instillations.

Prior intravesical chemotherapy has no impact on the effect of BCG instillations [105] (LE: 1a).

7.3.2. Treatment failure after intravesical BCG immunotherapy

Several categories of BCG failure, broadly defined as any HG disease occurring during or after BCG therapy, have been proposed (Table 12). NMIBC may not respond at all (BCG-refractory) or may relapse after an initial response (BCG-relapsing). Some evidence suggests that patients with BCG relapse have better outcomes than patients with BCG-refractory disease [142].

To be able to specify the subgroup of patients for whom additional BCG is unlikely to provide benefit, the category of BCG-unresponsive tumour was defined [143], which

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Table 12 – Categories of HG recurrence during or after BCG therapy

BCG-refractory tumour
1. If T1 G3/HG tumour is present at 3 mo [144,145] (LE: 3).
2. If TaG3/HG tumour is present after 3 months and/or at 6 mo, after either re-induction or first course of maintenance [146] (LE: 4).
3. If CIS (without concomitant papillary tumour) is present at 3 mo and persists at 6 mo after either reinduction or a first course of maintenance. For patients with CIS present at 3 mo, an additional BCG course can achieve a complete response in >50% of cases [146] (LE: 1b).
4. If HG tumour appears during BCG maintenance therapy. [a]
BCG-relapsing tumour
Recurrence of G3/HG (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response.
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those with T1/Ta HG recurrence within 6 mo of completion of adequate BCG exposure [b] or CIS within 12 mo of completion of adequate BCG exposure [143] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [124].

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high grade; LE = level of evidence; LG = low grade; WHO = World Health Organization.
[a] LG recurrence during or after BCG treatment is not considered to be a BCG failure.
[b] Adequate BCG therapy is defined as completion of at least five of six doses of an initial induction course plus at least two of six doses of a second induction course or two of three doses of maintenance therapy.

comprises BCG-refractory [144–146] and some BCG-relapsing tumours (Table 12).

7.3.3. *Treatment of BCG-unresponsive tumours, late BCG-relapsing tumours, LG recurrences after BCG treatment, and patients with BCG intolerance*

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Several bladder preservation strategies are currently being investigated, including cytotoxic intravesical therapies [147], device-assisted instillations [148,149], intravesical immunotherapy [150], systemic immunotherapy [151], and gene therapy [152].

An RCT including patients with predominantly high-risk NMIBC failing at least one previous BCG induction course demonstrated that MMC combined with microwave-induced hyperthermia provided 35% overall DFS at 2 yr as compared to 41% in the control arm (treated with either BCG, MMC, or MMC and electromotive drug administration at the discretion of the investigator) [149]. The systemic immunotherapy drug pembrolizumab was recently granted US Food and Drug Administration approval on the basis of a phase 2 study showing a 40% complete response rate in BCG-unresponsive CIS [151]. Promising data from a phase 3 multicentre trial with intravesical nadofaragene firadenovec were published, showing a complete response in 53.4% of patients with BCG-unresponsive CIS [152].

Repeat BCG therapy may be appropriate for non-HG and even for some HG recurrent tumours, namely those relapsing beyond 1 yr after BCG exposure [153] (LE: 3).

Treatment decisions in LG recurrences after BCG should be individualised according to the tumour characteristics. Little is known about the optimal treatment for patients with high-risk tumours who could not complete BCG instillations because of intolerance. Treatment options for the various categories of BCG failure are presented in Table 13.

7.4. *Radical cystectomy for NMIBC*

There are several reasons to consider immediate RC for selected patients with NMIBC:

- The staging accuracy for T1 tumours via TURB is low, with 27–51% of patients upstaged to muscle-invasive tumour at RC [154,155] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 8).
- Patients who experience disease progression to the muscle-invasive stage have worse prognosis than those who present with primary muscle-invasive disease [156].

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

Table 13 – Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. RC.
	2. Enrolment in clinical trials assessing new treatment strategies.
	3. Bladder-preserving strategies for patients unsuitable for or refusing RC.
Late BCG-relapsing	1. RC or a repeat BCG course according to the individual situation.
T1/Ta HG recurrence >6 mo or carcinoma in situ >12 mo since last BCG exposure	2. Bladder-preserving strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.
	2. RC.

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Table 14 – Guidelines for follow-up of patients after transurethral resection of the bladder for non–muscle-invasive bladder cancer

Recommendation	Strength rating
Base follow-up of Ta/T1 tumours and carcinoma in situ 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 and those with very high-risk tumours treated conservatively 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, every 6 mo thereafter up to 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 and very 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 for 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
For patients initially diagnosed with Ta LG/G1–2 bladder cancer, use ultrasound of the bladder during surveillance if cystoscopy is not possible or is refused by the patient.	Weak

CT = computed tomography; IVU = intravenous urography; LG = low grade; PDD = photodynamic diagnosis.

discussed with patients. It is reasonable to propose immediate RC for patients with NMIBC who are at very high risk of disease progression (see Sections 6.3 and Table 7) [52,71,73,157] (LE: 3).

Early RC is strongly recommended for patients with BCG-unresponsive tumours and should be considered for late BCG-relapsing HG tumours (Tables 10 and 13). A delay in RC may lead to shorter disease-specific survival [158] (LE: 3).

8. Follow-up of patients with NMIBC

Owing to the risk of recurrence and progression, patients with NMIBC need surveillance following therapy. The frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk (see the guidelines in Table 14).

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

- 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. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology.
- Tumour recurrence in the low-risk group is nearly always of low stage and LG/G1. Small Ta G1/LG papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [159] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be safe [160] (LE: 3). Multiple authors have suggested active surveillance in selected cases [161] (LE: 3/2a).
- The first cystoscopy after TURB at 3 mo is an important prognostic indicator for recurrence and progression [77,162–164] (LE: 1a). Therefore, the first cystoscopy should always be performed 3 mo after TURB in all patients with Ta or T1 tumours or CIS.
- For low-risk tumours, the risk of recurrence after 5 yr of recurrence-free status is low [163] (LE: 3). Therefore, for low-risk tumours, discontinuation of cystoscopy or replacement with less invasive methods can be considered after 5 yr of follow-up [164].
- For tumours originally classified as intermediate, high, or very high risk and treated conservatively, recurrences after 10 yr of tumour-free status are not unusual [165] (LE: 3). Therefore, life-long follow-up is recommended [164].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders).
- The risk of UUT recurrence is higher for patients with multiple and high-risk tumours [32] (LE: 3).
- Research has been carried out into the usefulness of urinary cytology versus urinary markers as an adjunct to cystoscopy in NMIBC follow-up [42,43,166]. One prospective randomised study found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [41] (LE: 1b), supporting the adjunctive role of a noninvasive urine test performed before follow-up cystoscopy [41] (see Section 5.7.3). Q8
- For patients initially diagnosed with Ta G1–2/LG BC, US of the bladder or a urinary marker may be used for surveillance if cystoscopy is not possible or is refused by the patient [167].
- According to current knowledge, no urinary marker can replace cystoscopy during follow-up or reduce the cystoscopy frequency on a routine basis.

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Study concept and design: Babjuk.
Acquisition of data: Babjuk, Burger, Capoun, Cohen, Compérat, Dominguez Escrig, Gontero, Liedberg, Masson-Lecomte, Mostafid, Palou, van Rhijn, Rouprêt, Shariat, Seisen, Soukup, Sylvester.
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