EAU Guidelines on

Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

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1. INTRODUCTION

1.1 Aim and scope

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.

Separate EAU guidelines documents are available addressing upper tract urothelial carcinoma (UTUC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3]. 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 - 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.

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of suffering from bladder cancer. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the NMIBC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2016 [4], as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU Guidelines on Bladder Cancer were first published in 2000. This 2017 NMIBC guidelines document presents a limited update of the 2016 publication.

1.4.2 Summary of changes

New references have been added throughout the 2017 NMIBC Guidelines document.
Key changes in this 2017 print:
- Section 4.3 - T1 subclassification. This is a new section.
- Section 5.5 - Urinary Cytology. Diagnostic categories based on the Paris Working Group Classification have been added.
- Section 5.10.2 - Surgical and technical aspects of tumour resection. This section has been revised and enlarged, resulting in changes in the recommendations (Section 5.14).
- Section 5.12 - Second resection. Additional literature has been included, resulting in changes in the recommendations (Section 5.14).
- Section 6.4 - Subgroup of highest risk tumours. This is a new section.
- Section 7.2.1.3.2 - Device-assisted intravesical chemotherapy. This is a new section.

Changes in recommendations

Section 5.9: A new recommendation has been added.

Recommendations for the primary assessment of NMIBC	GR
Repeat urine cytology in patients with suspicious initial cytology results.	C

Section 5.14: Additional information has been included.

Recommendations for transurethral resection of the bladder (TURB) and/or biopsies and pathology report	
Perform *en-block* 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.	B
Perform a second TURB in the following situations: • after (suspicion of) incomplete initial TURB (in the case of any doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with exception of TaLG/G1 tumours and primary CIS; • In T1 tumours.	A
Register the results of a second TURB as it reflects the quality of the initial resection.	A

Section 7.5: A new recommendation have been included.

Recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS	GR
In patients with bacillus Calmette-Guérin failure, who are not candidates of radical cystectomy due to comorbidities, use preservation strategies (device-assisted instillations of chemotherapy, intravesical chemotherapy, intravesical immunotherapy).	C

Section 8.1: A new recommendation has been added.

Recommendations for follow-up of patients after transurethral resection of the bladder for NMIBC	GR
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.	C

2. METHODS

2.1 Data Identification

For the 2017 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 was performed. Excluded from the search were basic research studies, case series, reports and editorial comments. Only articles published in the English language, addressing adults, were included. The search was restricted to articles published between June 1st 2015 and April 22nd 2016. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 973 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available on line:
https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/. A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Review

Chapter 7, Disease Management was peer reviewed prior to publication in 2016. All other chapters of the NMIBC Guidelines were peer-reviewed in 2015.

2.3 Future goals

The results of an ongoing systematic review will be included in the 2018 update of the NMIBC Guidelines. These reviews are performed using standard Cochrane systematic review methodology;
http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Ongoing systematic review:
1.   Is there a difference between the 2004 WHO grading system and the 1973 WHO grading system for NMIBC in terms of prognostic performance and reproducibility? [6].

3.   EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1   Epidemiology
Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered [7]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [7]. In the European Union the age-standardised incidence rate is 19.1 for men and 4.0 for women [7]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [7]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, partly caused by the different methodologies used and the quality of data collection [8]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [9].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); in younger patients (< 40) this percentage is even higher [10]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to T2-4 tumours [7, 8].

3.2   Aetiology
Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [8, 9, 11] (LE: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

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 [8, 9, 12, 13]. In developed industrial settings, these risks have been reduced by work-safety guidelines, therefore, chemical workers no longer have a higher incidence of BC compared to the general population [8, 12, 13].

While family history seems to have little impact [14] and, to date, no overt significance of any genetic variation for BC has been shown, genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [8, 15, 16].

Although the significance of fluid intake is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, also exposure to arsenic in drinking water increases risk [8, 17] (LE: 3). The association between personal hair dye use and risk remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow NAT2 acetylation phenotype [8]. Dietary habits seem to have little impact [18-20].

Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [8, 17] (LE: 3). Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is also a cause of BC [8] (LE: 3).

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

3.4   Summary of evidence for epidemiology, aetiology and pathology

Summary of evidence	LE
Worldwide, bladder cancer is the eleventh most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of bladder cancer diagnosis have been identified.	3

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

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 [21]. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis). These tumours can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. However, molecular biology techniques and clinical experience have demonstrated the highly malignant potential of CIS and T1 lesions as compared to Ta lesions. The terms "NMIBC" and "superficial BC" are therefore suboptimal descriptions.

4.2 Tumour, Node, Metastasis Classification (TNM)

The 2009 TNM classification approved by the Union International Contre le Cancer (UICC) was updated in 2017 (8th Edn.), but with no changes in relation to bladder tumours (Table 4.1) [21].

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate 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	Non-regional lymph nodes
	M1b	Other distant metastases

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 substaging) has been demonstrated to be of prognostic value in retrospective cohort studies [22, 23] (LE: 3). Its use is recommended by the most recent 2016 World Health Organization (WHO) classification [24]. The optimal system to substage T1 remains to be defined.

4.4 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 a different patient stratification between individual categories compared to the older 1973 WHO classification [25, 26] (Tables 4.2 and 4.3, Fig 4.1). Recently an update of the 2004 WHO grading classification was published [24] but the following guidelines are still based on the 1973 and 2004 WHO classifications since most published data rely on these two classifications [25, 26].

Table 4.2: WHO grading in 1973 and in 2004 [25, 26]

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 (PUNLMP) Low-grade (LG) papillary urothelial carcinoma High-grade (HG) papillary urothelial carcinoma

The prognostic value of both WHO 1973 and 2004 grading systems has been confirmed. Attempts to demonstrate better prognostic value of one over the other, however, have yielded controversial results [27-29]. (LE: 2a). Moreover, the 2004 WHO system have not been fully incorporated into prognostic models yet.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications [30]*

Histologic Spectrum of urothelial carcinoma [UC]
1973 WHO Grade 1 carcinomas have been reassigned to papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade (LG) carcinomas in the 2004 WHO classification, and Grade 2 carcinomas to LG and high-grade (HG) carcinomas. All 1973 WHO Grade 3 carcinomas have been reassigned to HG carcinomas (Reproduced with permission from Elsevier).

4.5 Carcinoma *in situ* and its classification

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract, prostatic ducts, and prostatic urethra [31].

Classification of CIS according to clinical type [32]:
* Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
* Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
* Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

Table 4.3: WHO 2004 histological classification for flat lesions

• 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.

4.6 Inter- and intra-observer variability in staging and grading

There is significant variability among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70-78% of cases [33] (LE: 2a). There is also interobserver variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2004 classifications. The general conformity in staging and grading is between 50% and 60% [28, 34-36] (LE: 2a). The published comparisons have not clearly confirmed that the WHO 2004 classification provides better reproducibility than the 1973 classification [27, 28, 36, 37].

4.7 Further pathology parameters

According to a meta-analysis of retrospective trials, the presence of lymphovascular invasion (LVI) in TURB specimens is connected with an increased risk of pathological upstaging [38] (LE: 3). Lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours [38] (LE: 3). Some variants of urothelial carcinoma (micropapillary, plasmocytoid, nested, sarcomatoid, microcystic, squamous and adeno variants, have a worse prognosis than classical urothelial carcinoma [2, 39-46] (LE: 3).

Molecular markers, particularly FGFR3 mutation status, are promising but need further validation [47-51].

4.8 Summary of evidence and recommendations for bladder cancer classification

Summary of evidence	LE
The depth of invasion (staging) is classified according to the TNM classification.	2a
Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis).	2a
T1 and CIS, as compared to Ta, have high malignant potential, the term non-muscle-invasive bladder cancer (NMIBC) is therefore a suboptimal description.	3
For histological classification of NMIBC, both the WHO 1973 and 2004 grading systems are used.	2a

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

5. DIAGNOSIS

5.1 Patient history

A comprehensive 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 non-visible haematuria at first presentation [52]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding.

5.3 Physical examination

Physical examination does not reveal NMIBC.

5.4 Imaging

5.4.1 *Computed tomography urography and intravenous urography*

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects or hydronephrosis.

Intravenous urography (IVU) is an alternative if CT is not available [53] (LE: 3), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography gives more information than IVU (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography or IVU once a bladder tumour has been detected is questionable due to the low incidence of significant findings obtained [54-56] (LE: 2a). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [55] (LE: 2b). The risk of UTUC during follow up increases in patients with multiple- and high-risk tumours [57] (LE: 3).

5.4.2 *Ultrasound (US)*

Transabdominal US permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder [58] (LE: 3). Ultrasound is therefore a useful tool for detection of obstruction in patients with haematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

The diagnosis of CIS cannot be made with imaging methods (CT urography, IVU or US) (LE: 4).

5.5 Urinary cytology

The 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 and low-grade tumours (16%) [59]. The sensitivity in CIS detection is 28-100% [60] (LE: 2b). Cytology is useful, particularly as an adjunct to cystoscopy, if G3/CIS malignancy is present. Positive voided urinary cytology can indicate an urothelial tumour anywhere in the urinary tract; negative cytology, however, does not exclude the presence of a tumour.

Cytological interpretation is user-dependent [61]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, but in experienced hands specificity exceeds 90% [61] (LE: 2b).

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [62]:
- Adequacy of urine specimens (Adequacy);
- Negative for high-grade urothelial carcinoma (Negative);
- Atypical urothelial cells (AUC);
- Suspicious for high-grade urothelial carcinoma (Suspicious);
- High-grade urothelial carcinoma (HGUC);
- Low-grade urothelial neoplasia (LGUN).

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [63]. In patients with suspicious cytology repeat investigation is advised [64] (LE: 3).

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests were developed [65-69]. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines. A list of the more established urine tests (US Food and Drug Administration [FDA] approved and those for which multi-institutional data are available) is listed in Table 5.1.

The following conclusions can be drawn regarding the existing tests:
- Sensitivity is usually higher at the cost of lower specificity, compared to urine cytology [65, 67-72] (LE: 3).
- Benign conditions and bacillus Calmette-Guérin (BCG) influence many urinary marker tests [65-69] (LE: 3).
- Requirements for sensitivity and specificity of a urinary marker test depend on the clinical context of the patient (screening, primary detection, follow up [high risk, low/intermediate risk]) [67, 68, 73] (LE: 3).
- Patient selection explains the wide range in performance of the markers listed in Table 5.1.
- Positive results of Cytology, UroVysion (FISH), NMP-22, Ucyt+ and microsatellite analysis in patients with negative cystoscopy and upper tract workup, may identify patients more likely to experience recurrence [74-77] and possibly progression [74-78] (LE: 3).

Table 5.1: Summary of more established urinary markers

Markers (or test specifications)	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumours (%)	Point-of-care test	LE
UroVysion (FISH)*	30-86	63-95	66-70	No	2b
Microsatellite analysis	58-92	73-100	90-92	No	1b
Immunocyt/uCyt +*	52-100	63-79	62-92	No	2a
Nuclear matrix Protein 22*	47-100	55-98	75-92	Yes	2a
BTA stat*	29-83	56-86	62-91	Yes	3
BTA TRAK*	53-91	28-83	74-77	No	3
Cytokeratins	12-88	73-95	33-100	No	3

BTA = bladder tumour antigen.
* FDA approved.

5.7 Potential application of urinary cytology and markers

The following objectives of urinary cytology or molecular tests must be considered.

5.7.1 Screening of the population at risk of bladder cancer

The application of haematuria dipstick, NMP22 or UroVysion in BC screening in high-risk populations has been

reported [79]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [77, 79]. Routine screening for BC is not recommended [80].

5.7.2 *Exploration of patients after haematuria or other symptoms suggestive of bladder cancer (primary detection)*

It is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or markers can be used as an adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, sensitivity for high-grade tumours and specificity are particularly important. Urinary cytology is highly specific, but urinary markers lack such high specificity and are not recommended for primary detection.

5.7.3 *Surveillance of non-muscle-invasive bladder cancer*

Research has been carried out into the usefulness of urinary cytology vs. markers in the follow up of NMIBC [69, 81, 82].

5.7.3.1 *Follow-up of high-risk non-muscle-invasive bladder cancer*

High-risk tumours should be detected early in follow up, and the percentage of tumours missed should be as low as possible. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology.

5.7.3.2 *Follow-up of low/intermediate-risk non-muscle-invasive bladder cancer*

To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology is its low sensitivity for low-grade recurrences. Several urinary markers are better, but still do not detect half of the low-grade tumours identified by cystoscopy [67] (LE: 3).

According to current knowledge, no urinary marker can replace cystoscopy during follow up or help to lower cystoscopy frequency in a routine fashion. One prospective randomised study found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [83] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy [83].

5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection. Carcinoma *in situ* is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies [84]. Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intra-urethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [85].

Figure 5.1: Bladder diagram

1 = Trigone	6 = Anterior wall
2 = Right ureteral orifice	7 = Posterior wall
3 = Left ureteral orifice	8 = Dome
4 = Right wall	9 = Neck
5 = Left wall	10 = Posterior urethra
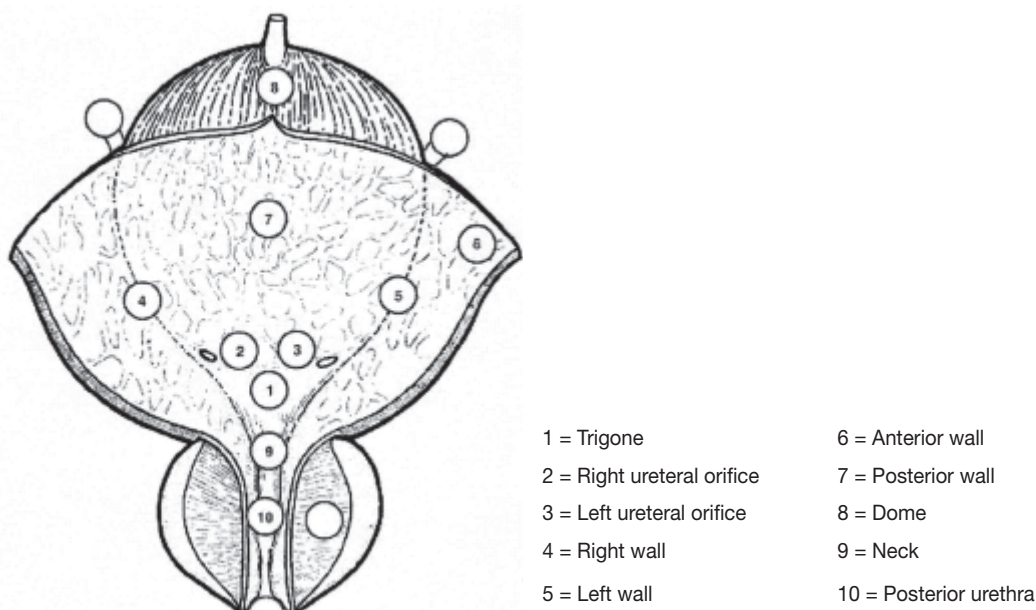
5.9 Summary of evidence and recommendations for the primary assessment of non-muscle-invasive bladder cancer

Summary of evidence	LE
The diagnosis of bladder cancer depends on cystoscopy examination.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b

Recommendations	GR
Take a patient history.	A
Renal and bladder ultrasound may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of non-muscle-invasive bladder cancer (NMIBC), perform computed tomography urography (or intravenous urography [IVU]) in selected cases (e.g., tumours located in the trigone, multiple or high-risk tumours).	B
Perform cystoscopy in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or by any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended (see Figure 5.1).	C
Voided urine cytology is advocated as an adjunct to cystoscopy to detect high-grade tumour.	C
Perform cystoscopy on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C
Repeat urine cytology in patients with suspicious initial cytology results.	C

5.10 Transurethral resection of TaT1 bladder tumours

5.10.1 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 diagnosis and treatment of BC. TURB should be performed systematically in individual steps (see Section 5.14).

5.10.2 Surgical and technical aspects of tumour resection
5.10.2.1 Surgical strategy of resection (resection in fractions, en-bloc resection)
A complete resection is essential to achieve a good prognosis [86]. A complete resection can be achieved by either resection in fractions or *en-bloc* resection.
- Resection in fractions (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) provides good information about the vertical and horizontal extent of the tumour [87] (LE: 3).
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is feasible in selected exophytic tumours. It provides high quality resected specimens with the presence of detrusor muscle in 96-100% of cases [88-91] (LE 3).

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

5.10.2.2 Evaluation of resection quality
It has been confirmed that the absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumour understaging [92] (LE: 2b). The presence of detrusor muscle in the specimen is considered as the surrogate criterion of the resection quality and is required (except of TaG1/LG tumours). It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [93].

5.10.2.3 Monopolar and bipolar resection
Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and to produce better specimens for the pathologist [94] (LE: 3). Currently, the results remain controversial [95-97].

5.10.2.4 Office-based fulguration and laser vaporisation
In patients with a history of small, TaLG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and is a treatment option [94, 98] (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

Potassium titanyl-phosphate (KTP) laser vaporisation is associated with a low risk of complications. Its oncologic outcomes need to be confirmed in a larger patient population [99].

5.10.2.5   Resection of small papillary bladder tumours at the time of transurethral resection of the prostate (TURP)

Only limited, retrospective, data exist on the outcome of incidentally detected papillary bladder tumour during cystoscopy as the initial step of TURP. Provided these tumours are papillary by aspect, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate. However, no exact risk-assessment can be provided [100, 101].

*5.10.3   **Bladder and prostatic urethral biopsies and incidental papillary tumours during transurethral resection of the prostate***

Carcinoma *in situ* can present as a velvet-like, reddish, area indistinguishable from inflammation, or it may not be visible at all. For this reason, the strategy of taking biopsies from abnormal urothelium and biopsies from normal-looking mucosa (random/mapping biopsies) is recommended (see Section 5.14). The indication for random biopsies reflects the very low likelihood of detecting CIS, especially in low-risk tumours (< 2%) [102] (LE: 2a). The risk increases in patients with high-risk tumours and with positive cytology [103].

If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy (see Section 5.11.1).

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.* [104] showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% (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 multiple tumours [105] (LE: 3). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Section 5.14) [104, 106].

5.11   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.

*5.11.1   **Photodynamic diagnosis (fluorescence cystoscopy)***

Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly for CIS [107, 108] (LE: 2a). In a systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for analyses at both the patient-level (92% vs.71%) and biopsy-level (93% vs. 65%) [108]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [109].

Photodynamic diagnosis had lower specificity than white-light endoscopy (63% vs. 81%) [108]. False-positivity can be induced by inflammation or recent TURB and during the first three months after BCG instillation [110, 111] (LE: 3). Prospective randomised studies evaluating the impact of ALA fluorescence-guided (FC) TURB on disease-recurrence rate provided controversial results [108, 112, 113].

The beneficial effect of HAL FC on recurrence rate in patients with TURB was confirmed by a multicentre, prospective, randomised trial and by a raw-data-based meta-analysis of controlled trials. A meta-analysis reported in the HAL arms an increase in detection of tumour lesions across all risk groups and an absolute reduction of < 10% in recurrence rates within twelve months [114] (LE: 1a). The beneficial effect of HAL FC on recurrence rate in patients with TURB and early intravesical instillation of chemotherapy was not confirmed by two prospective randomised trials [115, 116]. In the prospective controlled analysis of patients receiving early instillation in a real-life clinical setting, the beneficial effect of HAL FC on early recurrence rate was confirmed for low- and intermediate-risk tumours [117]. The value of fluorescence-guided TURB for the improvement of outcome in relation to progression rate, survival and clinical management remains to be demonstrated.

*5.11.2   **Narrow-band imaging***

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection [118, 119] (LE: 3). The reduction of recurrence rate if NBI is used during TURB has been confirmed after three and twelve months only for low-risk tumours (pTaLG, < 30 mm, no CIS) [120].

5.12 Second resection

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [86] (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-55% of patients, after resection of TaG3 tumour in 41.4% [121-124]. Moreover, the tumour is often understaged in the initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 1.3-25%, and increases to 45% if there was no muscle in the initial resection [109, 125-128]. This risk increased to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [129-131] (LE: 2a). Treatment of a TaT1 high-grade tumour and a T2 tumour is completely different; correct staging is therefore important. It has been demonstrated that a second TURB can increase recurrence-free survival [121, 122] (LE: 2a), improve outcomes after BCG treatment [132] (LE: 3) and provide prognostic information [127, 129, 133] (LE: 3).

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1G3/HG tumours (second resection was performed in 935 patients), the second resection improved recurrence-free survival (RFS), progression-free survival (PFS) and overall survival (OS) only in patients without muscle in the specimen from initial resection [134] (LE:3).

Retrospective evaluation showed that a second resection performed 14-42 days after initial resection provides longer RFS and PFS comparing to second resection performed after 43-90 days [135] (LE:3). Based on these arguments, a second TURB is recommended in selected cases two-six weeks after initial resection (for recommendations on patient selection, see Section 5.14).

The results of the second resection (residual tumours and understaging) reflect the quality of the initial TURB. As the goal is to improve the quality of the initial TURB, the results of the second resection should be recorded.

5.13 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the diagnosis and treatment decision-making process for BC. Close co-operation between urologists and pathologists is required. A high quality of resected and submitted 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, the specimen collection, handling and evaluation should respect the recommendations provided below (see Section 5.14) [136].

5.14 Summary of evidence and recommendations for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	LE
Transurethral resection of the bladder (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the treatment of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour understaging.	2b
In patients with a history of small, TaLG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis is feasible and safe.	3
A second TURB can detect residual tumours and tumour understaging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2

Recommendations	GR
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.	A
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from 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.	C

Performance of individual steps	
Perform *en-block* 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.	B
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	C
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder wall) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance). If equipment is available, perform fluorescence-guided (PDD) biopsies.	B
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 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.	C
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
The TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (random biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (prostatic urethra biopsy).	C
Perform a second TURB in the following situations: • after (suspicion of) incomplete initial TURB (in the case of any 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.	A
If indicated, perform a second TURB within two-six weeks after initial resection. This second TURB should include resection of the primary tumour site.	C
Register the results of a second TURB as it reflects the quality of the initial resection.	A
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	A
Pathological report	
The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathological report should specify the presence of lymphovascular invasion or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

In order to predict, separately, the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group has developed a scoring system and risk tables [137]. The basis for these tables are individual patient data from 2,596 patients diagnosed with TaT1 tumours, who were randomised into seven EORTC trials. Patients with CIS alone were not included. Seventy-eight percent of patients 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 6.1. It also illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 6.2 shows the total scores stratified, into four categories that reflect various probabilities of recurrence and progression at one and five years [137] (LE: 2a).

Table 6.1: 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		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	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**

Table 6.2: Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(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 year		Probability of progression at 5 years	
	%	(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)

NB: Electronic calculators for Tables 6.1 and 6.2, which have been updated for the Apple and Android phones and tablets, are available at http://www.eortc.be/tools/bladdercalculator/.

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received twelve instillations over five to six months. No immediate post-operative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:
- gender;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- tumour grade.

Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [138] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this sample, which is a more effective instillation therapy. The CUETO risk calculator is available at: http://www.aeu.es/Cueto.html.

The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG and by long-term follow up in an independent patient population [139, 140] (LE: 2a). In 1,812 intermediate- and high-risk patients without CIS treated with one to three years 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 were the most important prognostic factors for disease progression and disease-specific survival, while age and grade were the most important prognostic factors for OS. T1G3 patients do poorly, with one- and five-year 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 [141] (LE: 2a).

Further prognostic factors have been described in selected patient populations:
- In T1G3 tumours important prognostic factors were female sex and 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 (62% with induction course only) [104, 142] (LE: 2b).
- Attention must be given to patients with T1G3 tumours in bladder (pseudo) diverticulum because of the absence of muscle layer in the diverticular wall [143] (LE: 3).
- In patients with high-risk disease, the tumour stage at the time of the second TURB is an unfavourable prognostic factor [129, 133] (LE: 3)
- In patients with T1G2 tumours treated with TURB, recurrence at three months was the most important predictor of progression [144] (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 [139, 145].

6.2 Carcinoma *in situ*
Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [146] (LE: 3). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease. Publications are based on retrospective analyses of small series of patients and conclusions are not homogeneous. Some studies have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [147, 148], extended CIS [149] and CIS in the prostatic urethra [104] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [138-140, 144]. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [150, 151] (LE: 2a).

6.3 Patient stratification into risk groups

To facilitate treatment recommendations it is important to categorise patients into risk groups. Based on available prognostic factors and in particular data from the EORTC risk tables, the Guidelines Panel recommends stratification of patients into three risk groups. Table 6.3 provides a definition of these risk groups, which takes into account the EORTC risk tables' probabilities of recurrence and especially progression.

6.4 Subgroup of highest-risk tumours

Based on prognostic factors, it is possible to substratify high-risk group patients, and identify those that are at the highest risk of disease progression. Patients diagnosed with T1G3/HG tumours associated with concurrent bladder CIS, multiple and/or largeT1G3/HG tumours and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma and T1 tumours with LVI (Table 6.3) are at the highest risk of progression.

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG*), < 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**) tumour • carcinoma *in situ* (CIS) • Multiple, recurrent and large (> 3 cm) TaG1G2 /LG tumours (all features must be present)*.
	Subgroup of highest risk tumours:
	T1G3/HG associated with concurrent bladder CIS, multiple and/or largeT1G3/HG and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.

Substratification of high-risk tumours for clinical purposes is addressed in Table 7.2.
*Low grade is a mixture of G1 and G2.
** High grade is a mixture of some G2 and all G3 (see Figure 4.1).

6.5 Summary of evidence and recommendations for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EORTC scoring system and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with non-muscle-invasive bladder cancer (NMIBC).	2a
In patients treated with BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression.	2a
In patients receiving BCG maintenance: prior recurrence rate and number of tumours are the most important prognostic factors for disease recurrence.	2a
Stage and grade are the most important prognostic factors for disease progression and disease specific survival.	2a
Patient age and grade are the most important prognostic factors for overall survival.	2a

Recommendations	GR
Stratify patients into three risk groups according to Table 6.3.	B
Apply the EORTC risk tables and calculator for the prediction of the risk of tumour recurrence and progression in different intervals after transurethral resection of the bladder, in individual patients.	B
Use the CUETO risk tables and the new EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	B

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation
It has been confirmed that smoking increases the risk of tumour recurrence and progression [152, 153] (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 [154-157] (LE: 3).

7.2 Adjuvant treatment
7.2.1 Intravesical chemotherapy
Although TURB by itself can eradicate a Ta, T1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the three-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [86]. It is therefore necessary to consider adjuvant therapy in all patients.

7.2.1.1 A single, immediate, post-operative 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 (chemo resection) on residual tumour cells at the resection site and on small overlooked tumours [158-161] (LE: 3).

Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURB, SI significantly reduces the recurrence rate compared to TURB alone [162-165] (LE: 1a). In the most recent systematic review and individual patient data meta-analysis of 2,278 eligible patients [162], SI reduced the five-year recurrence rate by 14%, from 59% to 45%. The number to treat (NNT) to prevent one recurrence within five years was seven eligible patients. Only patients with a prior recurrence rate of less than or equal to one recurrence per year and those with an EORTC recurrence score < 5 benefited from SI. In patients with an EORTC recurrence score ≥ 5 and/or patients with a prior recurrence rate of > 1 recurrence per year, SI was not effective as a single adjuvant treatment. Mitomycin C (MMC), epirubicin, and pirarubicin have all shown a beneficial effect [162]. No randomised comparisons of individual drugs have been conducted [162-165] (LE: 1a).

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by extracellular matrix [158, 166, 167] (LE: 3). In all SI studies, the installation was administered within 24 hours. To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre. As severe complications have been reported in patients with drug extravasation [168, 169] safety measures should be maintained (see Section 7.5).

7.2.1.2 Additional adjuvant intravesical chemotherapy instillations
The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1, 6.2 and 6.3), a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [162, 163] (LE: 1a). For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1, 6.2 and 6.3). The individual patient data meta-analysis also showed that a SI reduced recurrences in intermediate-risk patients with an EORTC recurrence score < 5, none of whom received further treatment prior to recurrence [162]. There is evidence from several studies in intermediate-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given; however, they do not take into account the EORTC recurrence score [170-172] (LE: 2a). In one study [173], further chemotherapy instillations after SI improved recurrence-free survival in intermediate-risk patients (LE: 2a). Conversely, a sufficient number of delayed repeat chemotherapy instillations without SI can also reduce recurrences [170, 172].

A large meta-analysis of 3,703 patients from eleven randomised trials showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [174]. This

corresponds to an absolute difference of 13-14% in the number of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may reduce the risk of tumour progression [175, 176] (LE: 1a) (see Section 7.2.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [177-179] (see Section 7.2.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy [179] (LE: 1a).

The length and frequency of chemotherapy instillations is still controversial. A systematic review of RCTs, comparing different schedules of intravesical chemotherapy instillations, concluded that the ideal duration and intensity of the schedule remains undefined because of conflicting data [172]. The available evidence does not support treatment longer than one year (LE: 3).

7.2.1.3 Options for improving efficacy of intravesical chemotherapy
7.2.1.3.1 Adjustment of pH, duration of instillation, and drug concentration
One RCT using MMC has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduced the recurrence rate [180] (LE: 1b). Another trial reported that duration of a one hour instillation of MCC was more effective compared to a 30 minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [181] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [182] (LE: 1b). In view of these data, instructions are provided (see Section 7.5).

7.2.1.3.2 Device-assisted intravesical chemotherapy
Hyperthermia
Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [183]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate and high-risk bladder cancer, a reduced RFS at 24 months in the MMC group was demonstrated [184] (LE: 1b). Different technologies which increase the temperature of instilled MMC are available, however, data about their efficacy are still lacking.

Electromotive drug administration (EMDA)
The efficacy of MMC using EMDA in patients with high-risk tumours has been demonstrated in one small RCT [185]. The definitive conclusion however, needs further confirmation.

7.2.1.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	LE
In patients with non-muscle-invasive bladder cancer and a prior low recurrence rate (≤ to one recurrence per year) and in those with an EORTC recurrence score < 5, a single instillation (SI) significantly reduces the recurrence rate compared to transurethral resection of the bladder alone.	1a
In intermediate-risk patients, SI might have an impact on recurrence even when further adjuvant instillations are given.	3
Further chemotherapy instillations after SI improve recurrence-free survival in intermediate-risk patients.	2a

7.2.2 Intravesical bacillus Calmette-Guérin (BCG) immunotherapy
7.2.2.1 Efficacy of BCG
Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing the recurrence of NMIBC [177, 186-188] [189] (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin + interferon [190], MMC [191], or epirubicin alone [178] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long-lasting [178, 191] and was also observed in a separate analysis of patients with intermediate-risk tumours [178]. One meta-analysis [177] has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC vs. BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance.

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [175, 176] (LE: 1a). A meta-analysis carried out by the EORTC-GUCG has evaluated data from 4,863 patients enrolled in 24 RCTs. Five different BCG strains were used, and in 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, in 260 out of 2,658 patients (9.8%) treated with BCG, tumours progressed, compared to 304 out of 2,205 (13.8%) in the control groups (TURB alone, TURB + intravesical chemotherapy, or TURB + other immunotherapy). This shows a reduction

of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [176]. A recent RCT with long-term observation has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [178] (LE: 1b). On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [177].

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 BCG was applied including a maintenance schedule.

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [192]. In the most recent meta-analysis, however, BCG maintenance was more effective than MMC, both in patients previously treated and not previously treated with chemotherapy [177] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 years of age, but still more effective than epirubicin in a cohort of elderly patients [193] (LE: 1a).

7.2.2.2 BCG strain
The EORTC meta-analysis suggested no large differences in efficacy between various BCG strains [176]. Recently published smaller studies without maintenance demonstrated some differences between strains. This clearly needs further evaluation in prospective trials [194, 195] (LE: 2a).

7.2.2.3 BCG toxicity
BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy [176] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [196] (LE: 1b). It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [196]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [197]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [198] (LE: 2a).

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.5). The presence of leukocyturia, non-visible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [199, 200] (LE: 3).

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients; e.g. immunosuppression, human immunodeficiency virus [HIV] infection pose relative contraindications [201], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients. The role of prophylactic anti-tuberculosis medication in these patients remains unclear [202-204] (LE: 3). The management of side effects after BCG should reflect their type and grade according to the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [205, 206] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical bacillus Calmette-Guérin (BCG) [206-209]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs)
	If symptoms improve within a few days: continue instillations
	If symptoms persist or worsen: 　a. Postpone the instillation 　b. Perform a urine culture 　c. Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: 　a. With positive culture: adjust antibiotic treatment according to sensitivity 　b. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [207].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for three months.
	Cessation of intravesical therapy.
Epididymo-orchitis [208]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.
Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or anti-tuberculosis drugs [209].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: 　• High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. 　• Early, high-dose corticosteroids as long as symptoms persist. 　• Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or *Enterococcus*.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

7.2.2.4　Optimal BCG schedule
Induction BCG instillations are given according to the empirical six-weekly schedule introduced by Morales [210]. For optimal efficacy, BCG must be given in a maintenance schedule [175-177, 189] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of ten instillations given in eighteen

weeks to 27 over three years [211]. The EORTC meta-analysis was unable to determine which BCG maintenance schedule was the most effective [176]. In their meta-analysis, Böhle *et al.* concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [175] (LE: 1a).

The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations is not fully known. Moreover, it can be different in each individual patient [212]. In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, three years' maintenance (three-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS. In the three-year arm, however, 36.1% of patients did not complete the three-year schedule [213] (LE: 1b). In a RCT of 397 patients CUETO suggested that in high-risk tumours, the maintenance schedule with only one instillation every three months for three years may be suboptimal [214] (LE: 1b).

7.2.2.5 Optimal dose of BCG
To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [215, 216] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [217] (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 only for one year [197, 213] (LE: 1b). The routine use of one-third dose BCG is complicated by potential technical difficulties in preparing the reduced dose reliably, given uneven distribution of colony-forming-units in the dry product formulation.

7.2.2.6 Indications for BCG
Although BCG is a very effective treatment, there is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends upon the patient's risk (Table 6.2). The recommendation for individual risk groups is provided in Section 7.5.

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

7.2.2.7 Summary of evidence - BCG treatment

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical bacillus Calmette-Guérin (BCG) after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB + intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

7.2.3 Combination therapy
In one RCT, a combination of MMC and BCG was shown to be more effective in reducing recurrences but more toxic compared to BCG monotherapy (LE: 1b). Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by one MMC instillation [218]. Another RCT in frequently recurrent NMIBC demonstrated significantly higher efficacy of weekly MMC followed by monthly BCG in reduction of the recurrence rate when compared to BCG and interferon [219] (LE: 1b). In contrast a recent RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and interferon for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [220] (LE: 1b). In an RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [185, 221] (LE: 2).

7.2.4 Specific aspects of treatment of Carcinoma in situ
7.2.4.1 Treatment strategy
The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [137, 138], in this case further treatment according to the criteria summarised in Sections 7.2.1, 7.2.2, 7.3 and 7.4 is mandatory. CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of Carcinoma *in*

situ must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific-survival rates after immediate RC for CIS are excellent, but as many as 40-50% of patients might be over treated [146] (LE: 3).

7.2.4.2 Cohort studies on intravesical BCG or chemotherapy
In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG [146-149, 222] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [149, 211, 222, 223] (LE: 3).

7.2.4.3 Prospective randomised trials on intravesical BCG or chemotherapy
Unfortunately, there have been few randomised trials in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to 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 [224] (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 to intravesical chemotherapy or different immunotherapy [176] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [225]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1b).

7.2.4.4 Treatment of CIS in prostatic urethra and upper urinary tract
Patients with CIS are at high risk of extravesical involvement in the upper urinary tract (UUT) and in the prostatic urethra. Solsona *et al.* found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [226]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [226] (LE: 3). In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [31]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours), and for which immediate radical cystoprostatectomy is mandatory. 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 [85, 227] (LE: 3). However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement, there are promising results after BCG instillation, but only from small series, so the data are insufficient to provide clear treatment recommendations and radical surgery should be considered [227, 228] (LE: 3). Treatment of CIS that involves the UUT is discussed in the EAU Guidelines on Urothelial Tumours of the Upper Urinary Tract [1].

7.2.4.5 Summary of evidence – treatment of carcinoma in situ

Summary of evidence	LE
Carcinoma *in situ* (CIS) cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, bacillus Calmette-Guérin treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression.	1b

Flowchart 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*

TURB

Consider tumour appearance and early postoperative situation

Presumably low- or intermediate-risk tumour with low previous recurrence rate (≤ 1 recurrence per year) and EORTC recurrence score < 5

No perforation, no extensive resection, no bleeding with clots after TURB

Apparently muscle-invasive or high-risk tumour (sessile appearance etc.)

Bladder perforation, bleeding with clots

Single instillation of chemotherapy (GR: A)

Consider completeness of the resection and pathological report

Incomplete resection or no muscle (except for monofocal TaG1/LG) or T1 or G3/HG (except for primary CIS)

Macroscopically complete resection and TaG1-2/LG with muscle in the specimen or in TaG1/LG even without muscle or in primary CIS

Muscle invasive tumour

second TURB (GR: A) in 2-6 weeks (GR: C)

See guidelines for MIBC

Stratify patients into risk groups (GR: B)
• Previous history
• Endoscopic appearance (number and size of tumours)
• Pathological report the worst stage and grade from either initial or second TURB (GR: B)

Low-risk tumour (primary solitary TaG1/LG < 3 cm)

Intermediate-risk tumour

High-risk tumour (T1 or Tis or 3/HG or multiple and recurrent and > 3 cm TaG1-2/LG)

Cystoscopy (GR: A) at 3 mo

If negative, cystoscopy (GR: A) at 12 mo. and then yearly for 5 yr. (GR: C)

Primary or recurrent tumour without previous chemotherapy: Intravesical BCG for 1 yr. (6 weekly and 3 weekly at 3, 6 and 12 mo.) or intravesical chemotherapy for up to 12 mo. (GR: A)

Recurrent tumour with previous chemotherapy: Intravesical BCG for 1 yr. (6 weekly and 3 weekly at 3, 6 and 12 mo.) (GR: A), in late recurrence of small TaG1/LG consider repeating intravesical Chemotherapy

In all cases: Cystoscopy (GR: A) and cytology (GR: B) at 3 mo. If negative, cystoscopy and cytology at 3-6 mo. intervals until 5 yr. and then yearly (GR: C)

Highest-risk tumour (T1G3/HG + CIS, T1G3/HG + CIS in prostatic urethra, multiple T1G3/HG, T1G3/HG > 3 cm, micropapillary variant)

Positive or suspect cystoscopy during follow-up

No

Yes

Explain the risk and consider radical cystectomy

Tiny papillary recurrence

Larger or non papillary recurrence

Positive or suspect cystoscopy during follow-up

Intravesical BCG for 1-3 yr. (GR: A)

Cystoscopy (GR: A) and cytology (GR: B) at 3 mo.

If negative, cystoscopy and cytology every 3 mo. for 2 yr., every 6 mo. thereafter until 5 yr. and then yearly (GR: C), CT-IVU or IVU yearly (GR: C)

Consider patients´ age, comorbidities and preferences

Office fulguration or surveillance

Positive cytology with no visible tumour in the bladder during follow-up

Follow-up: cystoscopy (GR: A)

Schedule: individual (GR: C)

TURB + biopsies from abnormal looking mucosa (GR: B), bladder random biopsies if indicated* (GR: C), prostatic urethra biopsy if indicated* (GR: C) (See text in guidelines)

Re-check upper tract (GR: B)

Bladder random biopsies (GR: B), prostatic urethra biopsy in men (GR: B), if available use PDD (GR: B)

Consider pathological report

Non-muscle invasive recurrence

Muscle invasive recurrence

Consider previous history and pathological report (see flow-chart II)

See MIBC guidelines

*For details and explanations see the text of the guidelines
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; GR = grade of recommendation; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.3 Treatment of failure of intravesical therapy

7.3.1 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 [177] (LE: 1a).

7.3.2 Recurrence and failure after intravesical bacillus Calmette-Guérin (BCG) immunotherapy

Categories of unsuccessful treatment with intravesical BCG are presented in Table 7.2.

Table 7.2: Categories of unsuccessful treatment with intravesical BCG

BCG failure
Whenever a MIBC is detected during follow-up.
BCG-refractory tumour: 1. If high-grade, non-muscle-invasive papillary tumour is present at three months [229]. Further conservative treatment with BCG is associated with increased risk of progression [150, 230] (LE: 3). 2. If CIS (without concomitant papillary tumour) is present at both three and six months. If patients with CIS present at three months, an additional BCG course can achieve a complete response in > 50% of cases [31] (LE: 3). 3. If high-grade tumour appears during BCG therapy*.
High-grade recurrence after BCG. Recurrence of high-grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response [231] (LE: 3).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [206].

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

7.3.3 Treatment of BCG failure and recurrences after BCG

Treatment recommendations are provided in Sections 7.5 and 7.7. They reflect the categories mentioned in Table 7.2 and tumour characteristics at the time of recurrence.

Patients with BCG failure are unlikely to respond to further BCG therapy; RC is therefore the preferred option. Various studies suggest that repeat BCG therapy is appropriate for non-high-grade and even for some high-grade recurrent tumours [232, 233] (LE: 3). Additionally, there are now several bladder preservation strategies available that can be categorised as intravesical immunotherapy [234], intravesical chemotherapy, device-assisted therapy (see Section 7.2.1.3.2), and combination therapy (see Section 7.2.3) [235]. Changing from BCG to these options can yield responses in selected cases with BCG treatment failure [232, 234-242] (LE: 3).

Treatments other than RC must be considered oncologically inferior in patients with BCG failure at the present time [150, 229, 230] (LE: 3).

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

Non-high-grade recurrence after BCG is not considered as BCG failure. Treatment decision should be individualised according to tumour characteristics. It could include chemotherapy or repeat BCG instillations, but the published evidence is very low.

7.3.4 Summary of evidence - treatment failure of intravesical therapy

Summary of evidence	LE
Prior intravesical chemotherapy has no impact on the effect of bacillus Calmette-Guérin (BCG) instillation.	1a
Treatments other than radical cystectomy must be considered oncologically inferior in patients with BCG failure.	3

Flowchart 7.2: Treatment strategy in recurrence during or after intravesical BCG*
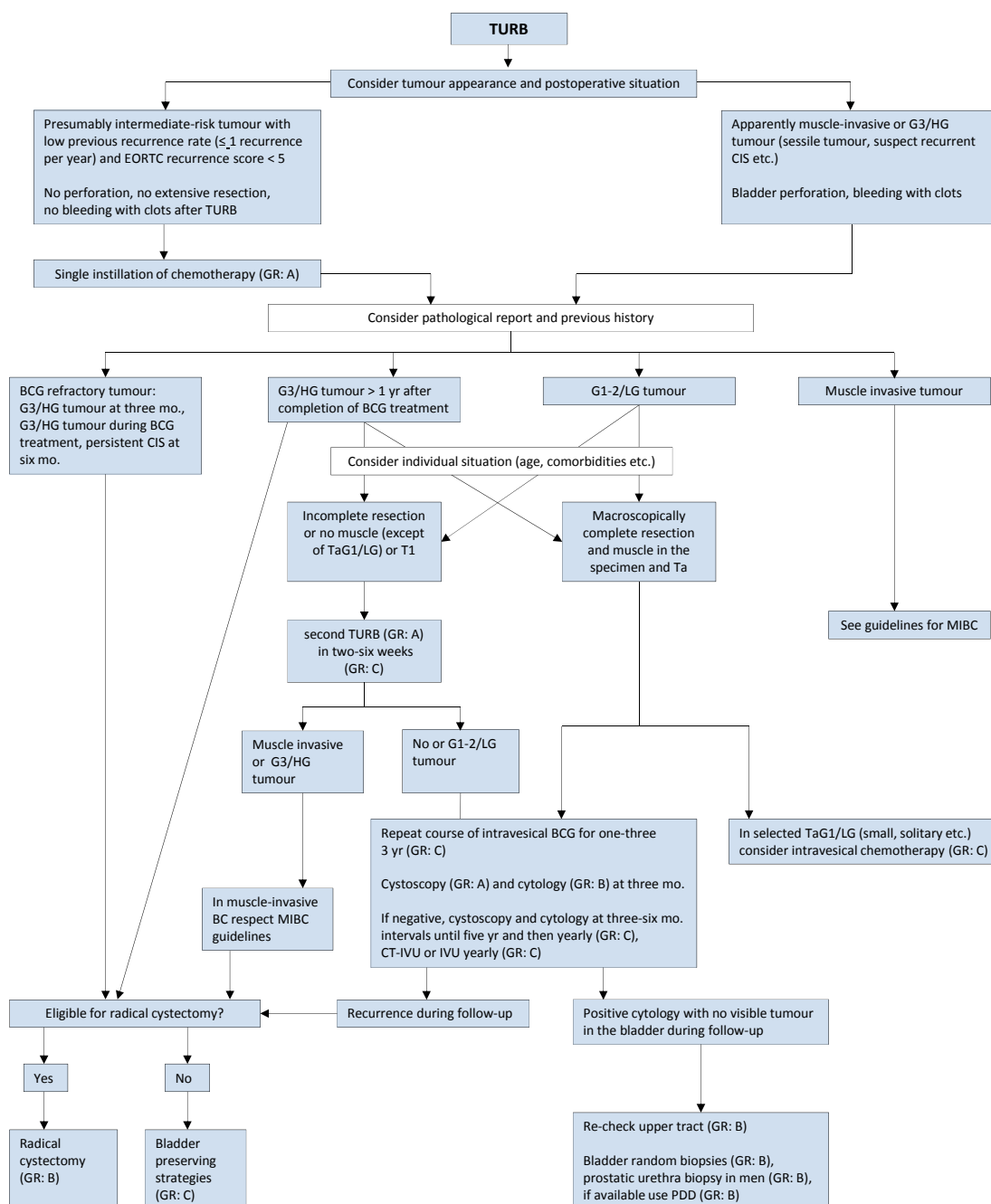
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; IVU = intravenous urography;
LG = low-grade; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.4 Radical cystectomy for NMIBC

If RC is indicated before progression to muscle-invasive tumour, it can be performed as an immediate (immediately after NMIBC diagnosis) or early procedure (after intravesical therapy failure, see Section 7.3).

There are several reasons to consider immediate RC for selected patients with NMIBC:
• The staging accuracy for T1 tumours by TURB is low with 27-51% of patients being upstaged to muscle-invasive tumour at RC [106, 130, 243-246] (LE: 3).
• Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
Patients who experience disease progression to muscle-invasive stage, have a worse prognosis than those who present with 'primary' muscle-invasive disease [247, 248].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of disease

progression (see Section 7.6) [46, 104, 137, 138, 249] (LE: 3).

The benefits and risks of immediate and delayed RC should be discussed with patients, in a shared decision-making process. Individual additional prognostic factors in T1 tumours mentioned in Sections 4.7 and 6.4 should be considered. Early RC is strongly recommended in patients with BCG-refractory tumours, as mentioned above. A delay in RC may lead to decreased disease-specific survival [250] (LE: 3).

In patients in whom RC is performed before progression to MIBC, the five-year disease-free survival rate exceeds 80% [251-253] (LE: 3).

7.5 Recommendations for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

	GR
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	B
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Table 6.3 and Section 7.6.	A
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (≤ one recurrence per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	A
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus three-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for one-three years (induction plus three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconveniences.	A
In patients with CIS in the epithelial lining of the prostatic urethra, transurethral resection of the prostate followed by intravesical instillation of BCG can be offered.	C
Discuss immediate radical cystectomy with patients at highest risk of tumour progression (see Section 7.6).	C
Offer radical cystectomy (RC) to patients with BCG failure (see Section 7.7).	B
In patients with BCG failure, who are not candidates for RC due to comorbidities, use preservation strategies (device-assisted instillations of chemotherapy, intravesical chemotherapy, intravesical immunotherapy).	C
Intravesical chemotherapy	
When given, a single immediate instillation of chemotherapy should be administered within 24 hours after TURB, preferably within two hours.	C
A single immediate instillation of chemotherapy should be omitted in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	C
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined, it should not exceed one year.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug by reducing fluid intake before and during instillation.	B
The length of individual instillation should be one-two hours.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	C
The management of side effects after BCG intravesical instillation should reflect their type and grade (see Table 7.1).	C

7.6 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 expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either one-year full-dose BCG treatment (induction plus three-weekly instillations at three, six and twelve months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: • T1 tumours; • G3 (HG) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present).	Intravesical full-dose BCG instillations for one-three years or radical cystectomy (in highest-risk tumours - *see below*).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or largeT1G3/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 4.7 and 6.4).	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for one-three years.
	BCG failures.	Radical cystectomy is recommended.

7.7 Treatment recommendations for bacillus Calmette-Guérin (BCG) failure and recurrences after BCG

Category	Treatment recommendation	GR
BCG-refractory tumour	1. Radical cystectomy 2. Bladder-preserving strategies in patients unsuitable for radical cystectomy	B
High-grade (HG) recurrence after BCG	1. Radical cystectomy 2. Bladder-preserving strategies 3. Repeat BCG course	C
Non-HG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

8. 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 should reflect the individual patient's degree of risk. Using risk tables (see Tables 6.1 and 6.2), the short- and long-term risks of recurrence and progression in individual patients may be predicted and the follow-up schedule adapted accordingly [137, 138].

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

- 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 [254, 255] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden [98] (LE: 3). Some authors have even defended temporary surveillance in selected cases [255-257] (LE: 3).
- The first cystoscopy after TURB at three months is an important prognostic indicator for recurrence and progression [144, 150, 258-260] (LE: 1a). Therefore, the first cystoscopy should always be performed three months after TURB in all patients with TaT1 tumours and CIS.
- In tumours at low risk, the risk of recurrence after five recurrence-free years is low [259] (LE: 3).
- Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [260].
- In tumours originally intermediate- or high risk, recurrences after ten years tumour-free are not unusual [261] (LE: 3). Therefore, life-long follow-up is recommended [260].
- 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 increases in patients with multiple- and high-risk tumours [57] (LE: 3).
- Positive urine test results have a positive impact on the quality of follow-up cystoscopy [83] (LE: 1b) supporting the adjunctive role of urine tests during follow-up.
- In patients initially diagnosed with TaLG/G1-2 BC, ultrasound of the bladder may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [262].

No non-invasive method can replace endoscopy. Follow-up is therefore based on regular cystoscopy (see Section 5.7). There is a lack of randomised studies investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

As CIS is often not visible, multiple biopsies may be necessary in selected cases to confirm the efficacy of intravesical treatment in patients treated for CIS [84]. The recommendations for follow-up are mainly based on retrospective data (see Section 8.1).

8.1 Summary of evidence and recommendations for follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer

Summary of evidence	LE
The first cystoscopy after transurethral resection of the bladder at 3 months is an important prognostic indicator for recurrence and progression.	1a
The risk of upper urinary tract (UUT) recurrence increases in patients with multiple- and high-risk tumours.	3

Recommendations	GR
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly.	C
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy and cytology.	C
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
Consider random (R)-biopsies or photodynamic diagnosis (PDD)-guided biopsies after intravesical treatment (at three or six months) in patients with CIS.	C
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B
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.	C

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10.   CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=panel.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.