

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/nonmuscleinvasive-bladder-cancer/>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2019 [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 2020 NMIBC Guidelines document presents a limited update of the 2019 publication.

1.4.2 Summary of changes

Additional data has been included throughout this document text. In particular in sections:

- 4.7 - Variants of urothelial carcinoma and lymphovascular invasion: this section has been expanded to include further information on variant histologies.
- 7.3 - Treatment of failure of intravesical therapy. This section has been considerably expanded, alongside a revision of Figure 7.2, Table 7.2 (Categories of unsuccessful treatment with intravesical BCG) and 7.7 Guidelines for the treatment of BCG failure.

Recommendations have been changed in sections:

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

General recommendations	Strength rating
Offer a RC to patients with BCG unresponsive tumours (see Section 7.7).	Strong
Offer patients with BCG unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak

7.7 Guidelines for the treatment of BCG failure

Category	Treatment options	Strength rating
BCG-unresponsive	1. Radical cystectomy (RC)	Strong
	2. Enrollment in clinical trials assessing new treatment strategies.	Weak
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.	Weak
Late BCG relapsing: T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation.	Strong
	2. Bladder-preserving strategies	Weak
LG recurrence after BCG for primary	1. Repeat BCG or intravesical chemotherapy	Weak
	2. Radical cystectomy	Weak

2. METHODS

2.1 Data Identification

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

A broad and comprehensive scoping exercise covering all areas of the NMIBC Guidelines 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 8th 2018 and May 16th, 2019. 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 1,124 unique records were identified, retrieved and screened for relevance.

A total of 29 new publications were added to the 2020 NMIBC Guidelines. A detailed search strategy is available online: <https://uroweb.org/guideline/non-muscle-invasive-bladdercancer/?type=appendices-publications>.

For Chapters 3-6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis, Predicting disease recurrence and progression) references used in this text were assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [5]. For the Disease Management and Follow-up chapters (Chapters 7 and 8) a system modified from the 2009 CEBM levels of evidence was being used [5].

For each recommendation within the guidelines there is an accompanying online strength rating form based on a modified GRADE methodology [6, 7]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; <http://www.uroweb.org/guideline/>. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

Publications of systematic reviews were peer reviewed prior to publication. The NMIBC Guidelines were peer-reviewed prior to publication in 2019.

2.3 Future goals

The results of ongoing reviews will be included in the 2020 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 projects:

- Individual Patient Data Prognostic Factor Study on WHO 1973 & 2004 Grade and EORTC 2006 risk score in primary TaT1 Bladder Cancer.

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 [8]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [8]. In the European Union the age-standardised incidence rate is 19.1 for men and 4.0 for women [8]. 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) [8].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [8]. 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 [9]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [10].

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 [11]. 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 [8, 9].

3.2 Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [9, 10, 12, 13] (LE: 3). Low-tar cigarettes are not associated with a lower risk of developing bladder cancer [13]. The risk associated with electronic cigarettes is not adequately assessed; however, carcinogens have been identified in urine [13]. Environmental exposure to tobacco smoke is also associated with an increased risk for BC [9]. 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 [9, 10, 14, 15]. 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 [9, 14, 15].

While family history seems to have little impact [16] 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 [9, 17-21]. This has been suggested to lead to familial clustering of BC with an increased risk for first- and second-degree relatives (hazard ratio [HR]: 1/4 1.69, 95% confidence interval [CI]: 1/4, 1.47-1.95, $p < 0.001$) [22].

Although the impact of drinking habits is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, also exposure to arsenic in drinking water increases risk [9, 23] (LE: 3). Arsenic intake and smoking has a combined effect [24]. 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 [9]. Dietary habits seem to have little impact, recently protective impact of flavonoids have been suggested and a Mediterranean diet, characterised by a high

consumption of vegetables and non-saturated fat (olive oil) and moderate consumption of protein, was linked to some reduction of BC risk (HR: 0.85 [95% CI: 0.77, 0.93]) [25-30].

Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [9, 23, 31] (LE: 3). The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol and triglycerides) is uncertain [32]. Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is also a cause of BC [9] (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 (BC) is the eleventh most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC 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 [33]. 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. The term “Non-muscle-invasive BC” represents a group definition and all tumours should be characterised according to their stage, grade, and further pathological characteristics (see Sections 4.5 and 4.7 and the International Collaboration on Cancer Reporting website: <http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/carcinoma-of-the-bladder-cystectomy-cystoprostatec>). The term ‘superficial BC’ should no longer be used as it is incorrect.

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) [33].

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 <i>in situ</i> : ‘flat tumour’
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate 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 [34, 35] (LE: 3). Its use is recommended by the most recent 2016 World Health Organization (WHO) classification [36]. The optimal system to substage T1 remains to be defined [36, 37].

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 [36, 38] (Tables 4.2 and 4.3, Figure 4.1). In 2016, an update of the 2004 WHO grading classification was published without major changes [36]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [39].

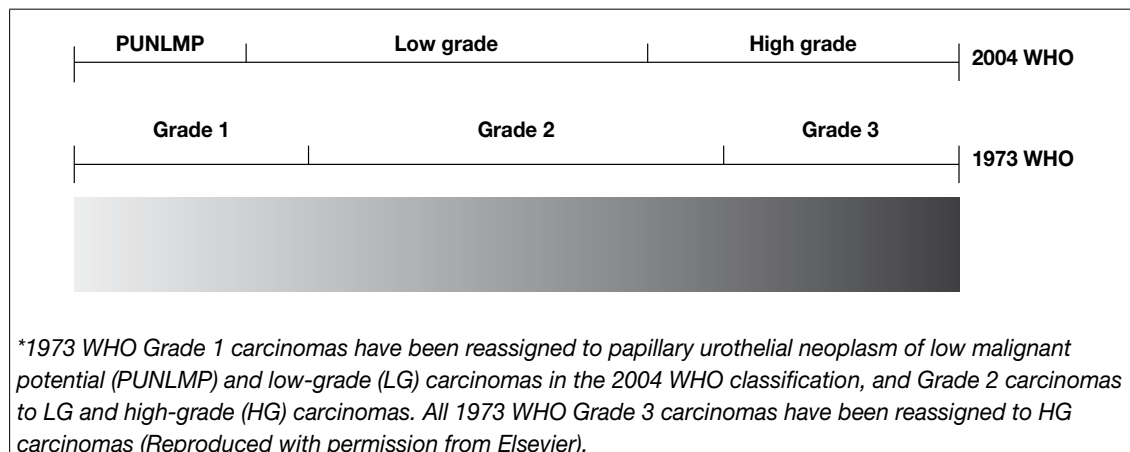
Table 4.2: WHO grading in 1973 and in 2004/2016 [36]

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004/2016 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

A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression [39] (LE: 2a).

There is a significant shift of patients between the prognostic categories of both systems, for example an increase in the number of HG patients (WHO 2004/2016) due to inclusion of some G2 patients with their better prognosis compared to the G3 category (WHO 1973) [39]. According to a recent multi-institutional IPD analysis, the proportion of tumours classified as PUNLMP has decreased to very low levels in the last decade [40]. As the 2004 WHO system has not been fully incorporated into prognostic models yet, long term individual patient data using both classification systems are needed.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications [41]*



4.5 Carcinoma *in situ* and its classification

Carcinoma *in situ* 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 (UUT), prostatic ducts, and prostatic urethra [42].

Classification of CIS according to clinical type [43]:

- 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

<p>Non-malignant lesions</p> <ul style="list-style-type: none"> • 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. <p>Malignant lesion</p> <ul style="list-style-type: none"> • Urothelial CIS is always high grade.
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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 [44] (LE: 2a). There is also inter-observer variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2004 classifications. The general conformity between pathologists in staging and grading is 50-60% [45-48] (LE: 2a). The WHO 2004 classification provides slightly better reproducibility than the 1973 classification [39].

4.7 Variants of urothelial carcinoma and lymphovascular invasion

Currently the following differentiations are used [49, 50]:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation;
3. micropapillary urothelial carcinoma;
4. nested variant (including large nested variant) and microcystic urothelial carcinoma;
5. plasmocytoid, giant cell, signet ring, diffuse, undifferentiated;
6. lymphoepithelioma-like;
7. some urothelial carcinomas with other rare differentiation;
8. small-cell carcinomas;
9. sarcomatoid urothelial carcinoma.

Other, extremely rare, variants exist which are not detailed.

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, sarcomatoid) have a worse prognosis than

pure HG urothelial carcinoma [2, 51-58] (LE: 3).

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with an increased risk of pathological upstaging and worse prognosis [59-63] (LE: 3).

4.8 Molecular classification

Molecular markers and their prognostic role have been investigated [64-68]. These methods, in particular complex approaches such as the stratification of patients based on molecular classification are promising, but are not yet suitable for routine application [69, 70].

4.9 Summary of evidence and guidelines 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
For histological classification of NMIBC, both the WHO 1973 and 2004 grading systems are used.	2a

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO grading systems.	Strong
Do not use the term 'superficial' bladder cancer.	Strong

5. DIAGNOSIS

5.1 Patient history

A focused patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher stage disease compared to nonvisible haematuria [71]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding.

5.3 Physical examination

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

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 and/or hydronephrosis [72].

Intravenous urography (IVU) is an alternative if CT is not available [73] (LE: 2b), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography provides more information (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography once a bladder tumour has been detected is questionable due to the low incidence of significant findings obtained [74-76] (LE: 2b). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [75] (LE: 2b). The risk of UTUC during follow up increases in patients with multiple- and high-risk tumours [77] (LE: 2b).

5.4.2 Ultrasound

Ultrasound (US) may be performed as an adjunct to physical examination as it has moderate sensitivity to a wide range of abnormalities in the upper and lower urinary tract. It permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder, but cannot rule out all potential causes of haematuria [78, 79] (LE: 3). It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

5.4.3 **Multiparametric magnetic resonance imaging**

The role of multiparametric magnetic resonance imaging (mpMRI) has not yet been established in BC diagnosis and staging. A standardised methodology of MRI reporting in patients with BC was recently published but requires validation [80].

A diagnosis of CIS cannot be made with imaging methods alone (CT urography, IVU, US or MRI) (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/LG tumours (16%) [81]. The sensitivity in CIS detection is 28-100% [82] (LE: 1b). Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours. Positive voided urinary cytology can indicate an urothelial carcinoma anywhere in the urinary tract; negative cytology, however, does not exclude its presence.

Cytological interpretation is user-dependent [83, 84]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, however, in experienced hands specificity exceeds 90% [83] (LE: 2b).

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [85]:

- 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).

The Paris system for reporting urinary cytology has been validated in several retrospective studies [86, 87].

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [88]. In patients with suspicious cytology repeat investigation is advised [89] (LE: 2b).

5.6 **Urinary molecular marker tests**

Driven by the low sensitivity of urine cytology, numerous urinary tests have been developed [90]. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines.

The following conclusions can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity, compared to urine cytology [91-96] (LE: 3).
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests [91-93] (LE: 1b).
- Requirements for sensitivity and specificity of a urinary marker test largely depend on the clinical context of the patient (screening, primary detection, follow up [high risk, low/intermediate risk]) [92, 93] (LE: 3).
- The wide range in performance of the markers and low reproducibility may be explained by patient selection and complicated laboratory methods required [93, 94, 97-104].
- Positive results of cytology, UroVysion (FISH), Nuclear Matrix Protein (NMP)22®, *Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT)* and microsatellite analysis in patients with negative cystoscopy and upper tract work-up, may identify patients more likely to experience disease recurrence and possibly progression [98, 100, 103-107] (LE: 2b).
- If main aim is to avoid unnecessary cystoscopies, rather than looking for markers with a high sensitivity and specificity, focus should be on identifying a marker with a very high negative predictive value. A test able to predict absence of tumour will have great utility in daily clinical practice [108].
- Promising novel urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies, with a very high negative predictive value [97, 99, 109-112].

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, followed by *FGFR3*, NMP22® or UroVysion tests if dipstick is positive has been reported in BC screening in high-risk populations [113, 114]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [106, 114]. Routine screening for BC is not recommended [106, 113, 114].

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 biomarkers can be used as an adjunct to cystoscopy to detect missed tumours, particularly CIS. In this setting, sensitivity for high-grade tumours and specificity are particularly important.

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 [97, 98, 110, 111, 115].

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 and current urinary markers is their low sensitivity for low-grade recurrences [92, 98] (LE: 1b).

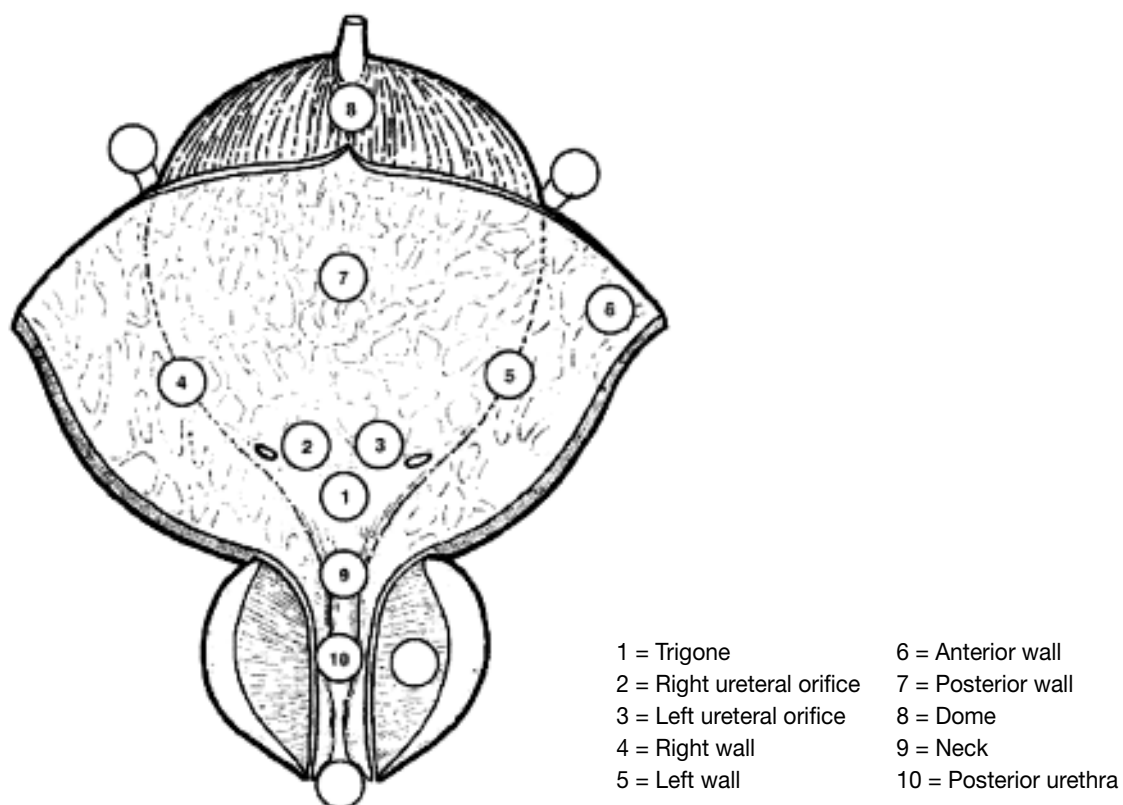
According to current knowledge, no urinary marker can replace cystoscopy during follow up or lower cystoscopy frequency in a routine fashion. One prospective randomised study found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [116] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed prior to follow-up cystoscopy [116] (see Section 8.1).

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 [117].

Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [118, 119] (LE: 1b).

Figure 5.1: Bladder diagram



5.9 Summary of evidence and guidelines for the primary assessment of non-muscle-invasive bladder cancer

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of bladder cancer.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i> .	2b

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong

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 management of BC. Transurethral resection of the bladder should be performed systematically in individual steps [120, 121] (see Section 5.14).

The operative steps necessary to achieve a successful TURB include identifying the factors required to assign disease risk (number of tumours, size, multifocality, characteristics, concern for the presence of CIS, recurrent vs. primary tumour), clinical stage (bimanual examination under anaesthesia, assignment of clinical tumour stage), adequacy of the resection (visually complete resection, visualisation of muscle at the resection base), and presence of complications (assessment for perforation) [121, 122]. To measure the size of the largest tumour, one can use the end of cutting loop, which is approximately 1 cm wide as a reference. The characteristics of the tumour are described as sessile, nodular, papillary or flat.

5.10.2 Surgical and technical aspects of tumour resection

5.10.2.1 Surgical strategy of resection (*piecemeal/separate resection, en-bloc resection*)

A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis [120, 123].

- Piecemeal 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 [124] (LE: 2b).
- *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 [120, 125-128] (LE: 1b).

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

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumour understaging [129] (LE: 1b). The presence of detrusor muscle in the specimen is considered as the surrogate criterion of the resection quality and is required (except in TaG1/LG tumours).

It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [130]. Virtual training on simulators is an emerging approach [131]. Its role in the teaching process still needs to be established [121].

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. Currently, the results remain controversial [132-135].

5.10.2.4 *Office-based fulguration and laser vaporisation*

In patients with a history of small, TaLG/G1 tumours, fulguration or laser vaporisation of small papillary recurrences on an outpatient basis can reduce the therapeutic burden [136, 137] (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

5.10.2.5 *Resection of small papillary bladder tumours at the time of transurethral resection of the prostate*

Only limited, retrospective, data exist on the outcome of incidentally detected papillary bladder tumour during cystoscopy as the initial step of transurethral resection of the prostate. 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 [138, 139].

5.10.3 **Bladder biopsies**

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 biopsies from suspicious urothelium should be taken. However, in patients with positive urine cytology, or with a history of HG/G3 NMIBC and in tumours with non-papillary appearance, mapping biopsies from normal-looking mucosa is recommended [140, 141]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [140, 141]. If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy.

5.10.4 **Prostatic urethral biopsies**

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.* showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% [142] (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 [143] (LE: 3b). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Section 5.14) [142, 144, 145].

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 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 [146, 147] (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [147]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [148].

Photodynamic diagnosis had lower specificity than white-light endoscopy (63% vs. 81%) [147]. False-positivity can be induced by inflammation or recent TURB and during the first three months after BCG instillation [149, 150] (LE: 1a).

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURB was evaluated. A systematic review and analysis of 14 RCTs including 2,906 patients, six using 5-ALA and nine HAL, demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates. The analysis demonstrated inconsistency between trials and potential susceptibility to performance and publication bias [151] (LE: 1a).

One RCT has shown a reduction in recurrence and progression with fluorescence guided TURB as compared to white light TURB [152]. These results need to be validated by further studies.

5.11.2 **Narrow-band imaging**

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection [153-156] (LE: 3b). An RCT assessed the reduction of recurrence rates if NBI is used during TURB. Although the overall results of the study were negative, a benefit after three and twelve months was observed for low-risk tumours (pTa/LG, < 30 mm, no CIS) [157] (LE: 1b).

5.11.3 **Additional technologies**

Confocal laser micro-endoscopy is a high resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [158]. The Storz professional image enhancement system (IMAGE1 S, formally called SPIES) is an image enhancement system using four different light spectra but prospective data using this system are lacking [159].

5.12 **Second resection**

5.12.1 **Detection of residual disease and tumour upstaging**

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [123] (LE: 1b).

A SR analysing data of 8,409 patients with Ta or T1 HG BC demonstrated a 51% risk of disease persistence and an 8% risk of understaging in T1 tumours. The analysis also showed a high risk of residual disease in Ta tumours, but this observation was based only on a limited number of cases. Most of the residual lesions were detected at the original tumour location [160] (LE: 1a).

Another meta-analysis of 3,556 patients with T1 tumours showed that the prevalence rate of residual tumours and upstaging to invasive disease after TURB remained high in a subgroup with detrusor muscle in the resection specimen. In the subgroup of 1,565 T1 tumours with detrusor muscle present, persistent tumour was found in 58% and understaging occurred in 11% of cases [161].

5.12.2 **The impact of second resection on treatment outcomes**

A second TURB can increase recurrence-free survival (RFS) [162, 163] (LE: 2a), improve outcomes after BCG treatment [164] (LE: 3) and provide prognostic information [165-168] (LE: 3).

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1G3/HG tumours (a second resection was performed in 935 patients), the second resection improved RFS, progression-free survival (PFS) and overall survival (OS) only in patients without detrusor muscle in the specimen of the initial resection [169] (LE: 3).

5.12.3 **Timing of second resection**

Retrospective evaluation showed that a second resection performed 14-42 days after initial resection provides longer RFS and PFS compared to second resection performed after 43-90 days [170] (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).

5.12.4 **Recording of results**

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 decision-making process for BC [171]. 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) [172, 173]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered.

5.14 Summary of evidence and guidelines 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 management of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour understaging (with the exception of TaLG tumours).	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	Strength rating
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak
Perform TURB systematically in individual steps: <ul style="list-style-type: none"> • bimanual palpation under anaesthesia. This step may be omitted in case non-invasive or early treatment for invasive disease is planned; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen for pathology evaluation. 	Strong
Performance of individual steps	
Perform <i>en-bloc</i> resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours and in tumours with non-papillary appearance. If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma <i>in situ</i> is present or suspected, if there is positive cytology without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong

Perform a second TURB in the following situations: <ul style="list-style-type: none"> • after incomplete initial TURB, or in case of doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours. 	Strong
If indicated, perform a second TURB within two-six weeks after initial resection. This second TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS and detrusor muscle.	Strong

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

Treatment should be based on a patient's prognosis. In order to predict, both 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 [174]. 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 [174] (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 Apple and Android phones and tables, are available for download: https://www.eortc.be/tools/bladdercalculator/download_disclaimer.htm.

The prognosis of intermediate-risk patients treated with chemotherapy has been calculated. Patients with Ta G1/G2 tumours receiving chemotherapy were further stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade, number of tumours and adjuvant chemotherapy [175].

A model that predicts the risk of recurrence and progression, based on 12 doses of intravesical BCG over a 5 to 6 month period following TURB, 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-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 this model, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [176] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this sample.

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 [177, 178] (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 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 5-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 [179] (LE: 2a).

Further prognostic factors have been described in selected patient populations:

- In T1G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with induction course only) [142, 180] (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 [181] (LE: 3).
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [166-168] (LE: 3).
- In patients with T1G2 tumours treated with TURB, recurrence at three months was the most important predictor of progression [182] (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 [177, 183].
- Preoperative neutrophil-to-lymphocyte ratio may have prognostic value in NMIBC. This data, however, needs further validation [184].

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [185] (LE: 3). There are no reliable prognostic factors, some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [186, 187] in extended CIS [188] and in CIS in the prostatic urethra [142] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [176-178, 182]. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [189, 190] (LE: 2a).

6.3 Patient stratification into risk groups

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 sub-stratify 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 large T1G3/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	<p>Any of the following:</p> <ul style="list-style-type: none"> • T1 tumour • G3 (HG**) tumour • carcinoma <i>in situ</i> (CIS) • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present)*. <p>Subgroup of highest risk tumours:</p> <p>T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.</p>

Sub-stratification 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 guidelines 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
Patients with Ta G1/G2 tumours receiving chemotherapy have been further stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade, number of tumours and adjuvant chemotherapy.	2a-b
In patients treated with 5-6 months of 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. Stage and grade are the most important prognostic factors for disease progression and disease-specific survival; patient age and grade are the most important prognostic factors for overall survival.	2a

Recommendations	Strength rating
Stratify patients into three risk groups according to Table 6.3.	Strong
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.	Strong
Use the CUETO risk tables and the EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	Strong

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [191, 192] (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 [181, 193-195] (LE: 3).

7.2 Adjuvant treatment

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the 3-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [123]. It is therefore necessary to consider adjuvant therapy in all patients.

7.2.1 Intravesical chemotherapy

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 on residual tumour cells at the resection site and on small overlooked tumours [196-199] (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 [200-203] (LE: 1a). In a SR and individual patient data meta-analysis of 2,278 eligible patients [200], SI reduced the 5-year recurrence rate by 14%, from 59% to 45%. 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.

No randomised comparisons of individual drugs have been conducted [200-203].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin, have all shown a beneficial effect [200]. Single instillation with gemcitabine was superior to placebo control (saline) in an RCT with approximately 200 patients per arm [204], with remarkably low toxicity rates [204]. These findings are in contrast with a previous study, which, however, used a shorter instillation time [205]. In the Böhle *et al.* study, continuous saline irrigation was used for 24 hours post-operatively in both arms, which could explain the low

recurrence rate in the control arm [205]. Two meta-analyses suggest efficacy of continuous saline irrigation in the prevention of early recurrences [206, 207].

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 the extracellular matrix [196, 208-210] (LE: 3). In all SI studies, the instillation was administered within 24 hours. Two RCTs found no overall impact of SI with apaziquone; in contrast, a *post-hoc* analysis did find a reduction of recurrence risk in patients receiving apaziquone within 90 minutes following TURB [211]. 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 [212, 213] 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 [200, 201] (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).

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

Single installation only vs. SI and further repeat instillations

In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [214] (LE: 2a).

Repeat chemotherapy instillations vs. no adjuvant treatment

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 [215]. 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 [216, 217] (see Section 7.2.2.1) (LE: 1a). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [218-220] (see Section 7.2.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy [220] (LE: 1a).

Single instillation + further repeat instillations vs. later repeat instillations only

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 [221-224]. An RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURB (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at three years in favour of SI, from 36% to 27%. The effect was significant in the intermediate- and high-risk groups of patients receiving additional adjuvant MMC instillations [221] (LE: 2a). Since the author's definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [225]. The results of this study should be considered with caution since some patients did not receive adequate therapy. An RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC [226].

The optimal schedule of intravesical chemotherapy instillations

The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed one year [224] (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*

The intravesical solution reduced the recurrence rate [227] (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 [228] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [229] (LE: 1b). In view of these data, instructions are provided (see Section 7.5).

7.2.1.3.2 Device-assisted intravesical chemotherapy

Microwave-induced hyperthermia

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [230]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [231] (LE: 1b).

Hyperthermic intravesical chemotherapy

Different technologies which increase the temperature of instilled MMC are available, however, data about their efficacy are still lacking.

Electromotive drug administration

The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [232]. The definitive conclusion, however, needs further confirmation.

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

7.2.1.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	LE
In patients with low-risk NMIBC and in those with a prior low recurrence rate (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
Single instillation might have an impact on recurrence even when further adjuvant chemotherapy instillations are given.	3
Repeat chemotherapy instillations (with or without previous 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*

Recurrence rate

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing the recurrence of NMIBC [218, 233-236] (LE: 1a). Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (INF) [237], MMC [238], or epirubicin alone [219] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting [219, 238] and was also observed in a separate analysis of patients with intermediate-risk tumours [219]. One meta-analysis [218] 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.

It has been suggested that the efficacy of MMC may be improved by optimising application through the adjustment of urine pH, in addition to the use of alternative maintenance schedules. Neither aspect is reflected in the literature quoted above since most published studies do not support this approach.

Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [216, 217, 236] (LE: 1a). A meta-analysis carried out by the EORTC Genito-Urinary Cancers Group (GUCG) has evaluated data from 4,863 patients enrolled in 24 RCTs. In 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, tumours progressed in 9.8% of the patients treated with BCG compared to 13.8% in the control groups (TURB alone, TURB and intravesical chemotherapy, or TURB with the addition of 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 [217]. An RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [219] (LE: 1b). In contrast, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [218].

The conflicting results in the outcomes of these studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. However, most studies showed a

reduction in the risk of progression in high- and intermediate-risk tumours if a BCG maintenance schedule was applied.

Influence of further factors

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [239]. In the IPD meta-analysis, however, BCG maintenance was more effective than MMC in reduction of recurrence rate, both in patients previously treated and not previously treated with chemotherapy [218] (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 [240] (LE: 1a). According to a cohort analysis, the risk of tumour recurrence after BCG was shown to be higher in patients with a previous history of UTUC [241].

7.2.2.2 BCG strain

Although smaller studies without maintenance demonstrated some differences between strains [241-243], a network meta-analysis identified ten different BCG strains used for intravesical treatment in the published literature but was not able to confirm superiority of any BCG strain over another [244].

Similarly, a published meta-analysis of prospective RCTs [217], recently published data from a prospective registry [245] as well as from a *post-hoc* analysis of a large phase 2 prospective trial assessing BCG and INF- α in both BCG-naive and BCG-failure patients [246] did not suggest any clear difference in efficacy between the different BCG-strains (LE: 2a). The quality of data, however, does not allow definitive conclusions.

7.2.2.3 BCG toxicity

Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [217] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [247] (LE: 1b). The incidence of BCG infections after BCG instillations was 1% in a register-based cohort analysis [248]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [247]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [249]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [250] (LE: 2a). No significant difference in toxicity between different BCG strains was demonstrated [245]. Symptoms may be the result of side-effects of the BCG-treatment or caused by bladder disease (widespread CIS) itself. Consequently, the burden of symptoms is reduced after completion of the treatment in a significant number of patients [251].

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, nonvisible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [100, 252, 253] (LE: 3).

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients; e.g. immunosuppression, human immunodeficiency virus (HIV) infection pose relative contraindications [254], 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 [255-257] (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 [258, 259] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [259-262]

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: <ol style="list-style-type: none"> Postpone the instillation Perform a urine culture Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: <ol style="list-style-type: none"> With positive culture: adjust antibiotic treatment according to sensitivity With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [260].
	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 [261]	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 antituberculosis drugs [262].
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: <ul style="list-style-type: none"> 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 <i>Enterococcus</i>.
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 6-weekly schedule introduced by Morales *et al.* [263]. For optimal efficacy, BCG must be given in a maintenance schedule [216-218, 236] (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 [264]. The EORTC meta-analysis was unable to determine which BCG maintenance schedule was the most effective [217]. In their meta-analysis, Bohle *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 [216] (LE: 1a).

The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations are not fully known. Moreover, it can be different in each individual patient [265]. In an RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, three years' maintenance (3-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 3-year arm, however, 36.1% of patients did not complete the 3-year schedule [266] (LE: 1b). In an 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 [267] (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 [268, 269] (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 [270] (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 [249, 266] (LE: 1b). The routine use of one-third dose BCG is complicated by potential technical difficulties in preparing the reduced dose reliably.

7.2.2.6 *Indications for BCG*

Although BCG is very effective, there is 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). Recommendations for individual risk groups are provided in Section 7.5.

A statement by the Panel on BCG shortage can be accessed online:

<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 and 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**

7.2.3.1 *Intravesical BCG + chemotherapy versus BCG alone*

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 [271]. 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 [232, 272] (LE: 2). Two meta-analyses demonstrated improved DFS, but no difference in PFS in patients treated with combination treatment comparing to BCG alone [272, 273].

7.2.3.2 *Combination treatment using interferon*

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2 α did not show a clear difference in recurrence and progression over BCG alone [274]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2 α showed a higher probability of recurrence compared to MMC followed by BCG alone [275]. Additionally, an RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and INF for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [276] (LE: 1b).

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 [174, 176], 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. Carcinoma *in situ* cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [185] (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 [185-188, 277] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [188, 210, 264, 277] (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 [278] (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 [217] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [279]. 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*

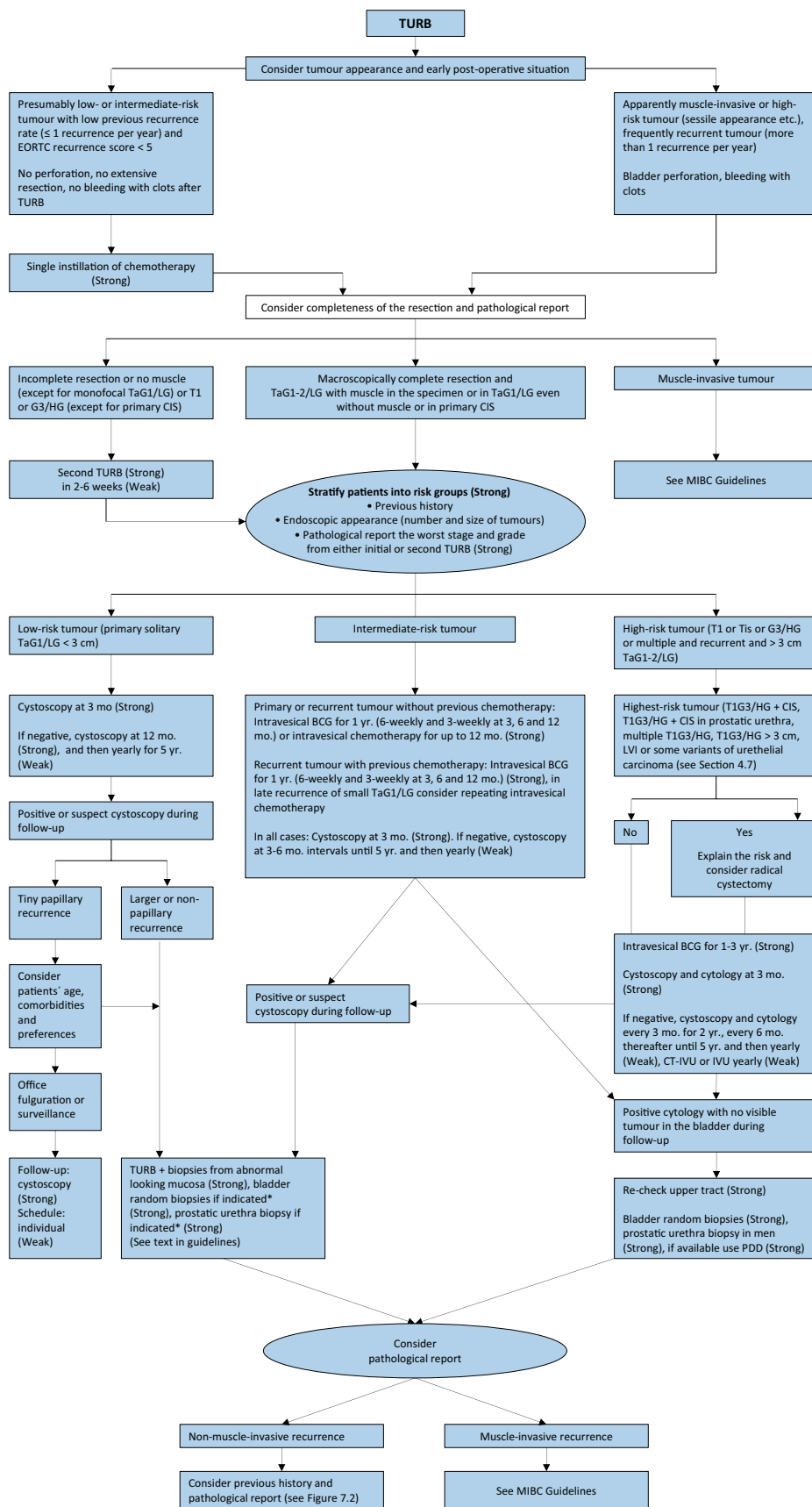
Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra. Solsona *et al.* found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [280]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [280] (LE: 3). In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [42]. 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 [119, 281] (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 of BCG, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [281, 282] (LE: 3).

7.2.4.5 *Summary of evidence - treatment of carcinoma in situ*

Summary of evidence	LE
Carcinoma <i>in situ</i> (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

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



* For details and explanations see the text of the guidelines.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; 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 [218] (LE: 1a).

7.3.2 Recurrence and failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any disease occurrence following therapy, have been proposed (Table 7.2). Non-muscle-invasive BC presenting after BCG can be categorised into BCG refractory, BCG unresponsive and BCG relapse. Some evidence suggests that patients with BCG relapse have better outcomes than BCG refractory patients [283]. Recently an updated definition of BCG-unresponsive tumours was introduced to denote a subgroup of patients at higher risk of progression for whom further BCG is not feasible [284]. This definition was developed in consultation with the FDA to allow for single-arm trials to provide primary evidence of effectiveness to support a marketing application since no effective therapy is available for BCG-unresponsive NMIBC [285].

Table 7.2: Categories of unsuccessful treatment with intravesical BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1G3/HG tumour is present at 3 months [286]. Further conservative treatment with BCG is associated with an increased risk of progression [189, 287] (LE: 3).
2. If TaG3/HG tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [42] (LE: 4).
3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [42, 43, 277] (LE: 1b).
4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of G3/HG (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response [288] (LE: 3).
BCG unresponsive tumour
BCG refractory or T1Ta/HG BCG recurrence within 6 months of completion of adequate BCG exposure** or development of CIS within 12 months of completion of adequate BCG exposure [284] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [259].

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

** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.

7.3.3 Treatment of BCG failure

Treatment recommendations and options 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 unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the preferred option. Additionally, several bladder preservation strategies are under different stages of investigation such as cytotoxic intravesical therapies (271), device assisted instillations (see below), intravesical immunotherapy [289], systemic immunotherapy [290] or gene therapy [291-293].

Changing from BCG to these options can yield responses in selected cases with BCG unresponsive disease [289, 294-303] (LE: 3). In the only RCT on a series of predominantly high-risk NMIBC failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia yielded an overall 35% disease-free survival (DFS) at 2 years as compared to 41% of the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave-induced thermotherapy showed lower response rate in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [304]. Recently, the systemic immunotherapy pembrolizumab was granted FDA approval based on currently unpublished data.

At the present time, treatments other than RC must, however, be considered oncologically inferior in patients with BCG unresponsive disease [189, 286, 287] (LE: 3). Various studies suggest that repeat-BCG therapy is appropriate for non-high-grade and even for some high-grade recurrent tumours, namely those relapsing beyond one year after BCG exposure [294, 305] (LE: 3).

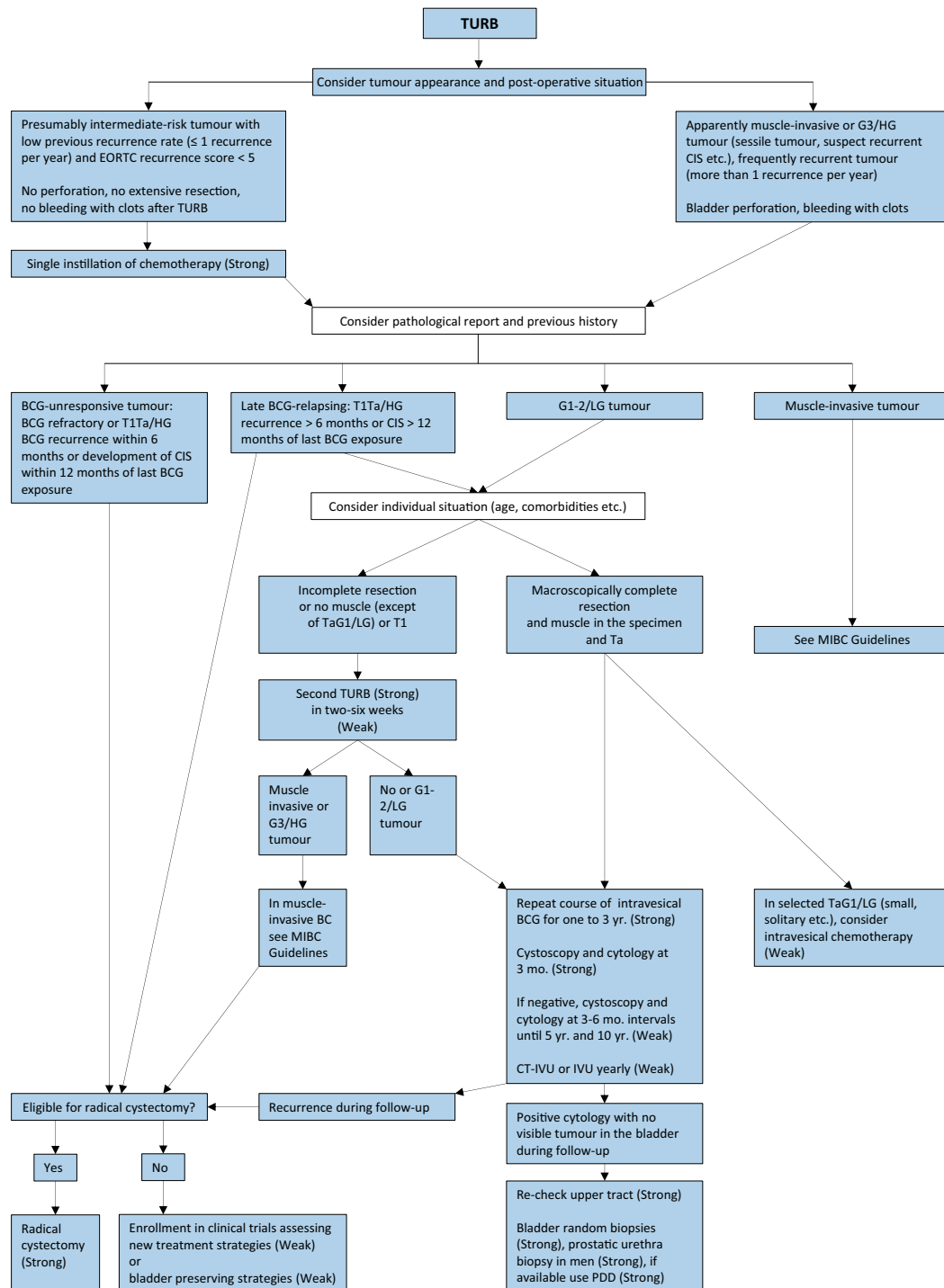
Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

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

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 unresponsive tumours.	3

Figure 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 non-muscle-invasive bladder cancer

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 [145, 306-310] (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 [311, 312].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life and discussed with patients, in a shared decision-making process. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of disease progression (see Section 7.6) [58, 142, 174, 176, 313] (LE: 3).

Early RC is strongly recommended in patients with BCG unresponsive tumours, as mentioned above. A delay in RC may lead to decreased disease-specific survival [314] (LE: 3).

In patients in whom RC is performed before progression to MIBC, the 5-year DFS rate exceeds 80% [315-317] (LE: 3).

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

General recommendations	Strength rating
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	Strong
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.	Strong
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (less than one recurrence per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	Strong
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-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.	Strong
In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus 3-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, side-effects and problems connected with BCG shortage.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak
Discuss immediate radical cystectomy (RC) with patients at the highest risk of tumour progression (see Section 7.6).	Strong
Offer a RC to patients with BCG unresponsive tumours (see Section 7.7).	Strong
Offer patients with BCG unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be one to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: <ul style="list-style-type: none"> during the first two weeks after TURB; in patients with visible haematuria; after traumatic catheterisation; in patients with symptomatic urinary tract infection. 	Strong

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 3weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: <ul style="list-style-type: none"> • 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 to 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 large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI (see Sections 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 to three years.

7.7 Guidelines for the treatment of BCG failure

Category	Treatment options	Strength rating
BCG-unresponsive	1. Radical cystectomy (RC).	Strong
	2. Enrollment in clinical trials assessing new treatment strategies.	Weak
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.	Weak
Late BCG relapsing: T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation.	Strong
	2. Bladder-preserving strategies.	Weak
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.	Weak
	2. Radical cystectomy.	Weak

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need surveillance, following therapy. However, the frequency and duration of cystoscopy and imaging follow-up 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 (see Section 8.1) [174, 176]. However, recommendations for follow-up are mainly based on retrospective data and there is a lack of randomised studies investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

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, TaG1/LG papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [318, 319] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be safe [320] (LE: 3). Multiple authors have suggested active surveillance in selected cases [321-323] (LE: 3/2a).
- The first cystoscopy after TURB at three months is an important prognostic indicator for recurrence and progression [182, 189, 324-326] (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 [325] (LE: 3). Therefore, in low-risk tumours, after five years of follow up, discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [326].
- In tumours originally intermediate- or high risk, recurrences after ten years tumour-free are not unusual [327] (LE: 3). Therefore, life-long follow-up is recommended [326].
- 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 [77] (LE: 3).
- Positive urine test results have a positive impact on the quality of follow-up cystoscopy [116] (LE: 1b) supporting the adjunctive role of urine tests during follow-up.
- In patients initially diagnosed with TaG1-2/LG BC, US of the bladder may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [328].
- No non-invasive method can replace endoscopy.

8.1 Summary of evidence and guidelines 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 recurrence increases in patients with multiple- and high-risk tumours.	3

Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma <i>in situ</i> (CIS) on regular cystoscopy.	Strong
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.	Weak
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.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	Weak
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong

During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with TaLG/G1-2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

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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>.

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