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 (UC), unless specified otherwise. The aim is to provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation. Separate EAU Guidelines 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 references/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 patient representative. 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/guidelines/non-muscle-invasive-bladder-cancer/panel.

1.3 Available publications

A quick reference document, the Pocket guidelines), is available in print. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2022 [4]. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guidelines/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. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates This 2024 NMIBC Guidelines present a limited update of the 2023 publication.

*1.4.2 **Summary of changes***

For the 2024 NMIBC Guidelines new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. This resulted in the inclusion of 36 updated studies across the Guidelines. Key changes include the addition of:

- a new category of high-grade recurrence during or after BCG (table 7.2): the BCG-exposed tumour category;
- updates on the proposed treatment options for late BCG relapses and low grade (LG) recurrence after bacillus Calmette-Guérin (BCG) for primary intermediate-risk bladder cancer in table 7.3;
- a proposed follow-up schedule based on patient's risk category in Table 8.2;
- a new section on patient reported outcome measures and quality indicators for NMIBC (section 9).

In addition, minor adaptions and updates to multiple recommendations have been made and users are advised to review all sections in full. A summary of key recommendation changes include:

- an update in the evidence and guidelines in section 4.10 on bladder cancer classification;
- new summary of evidence and recommendations updates in section 5.15 on the transurethral resection of the bladder, biopsies and pathology report;
- guidelines updates in section 7.10 on adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*;
- a new update to the very high risk EAU risk group, in section 7.11 on the guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification;

- new updates in section 8.2 on the summary of evidence and recommendations for the follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer.

2. METHODS

2.1 Data Identification

For the 2024 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. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between the 5th of May 2022 and 1st May 2023. A total of 788 unique records were identified, retrieved, and screened for relevance. A total of 36 new references were added to the 2024 NMIBC Guidelines. A detailed search strategy is available online: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/publications-appendices.

For Chapters 3 through 6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis, Predicting disease recurrence and progression) the 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 chapters 7 and 8 (Disease Management and Follow-up) chapters a system modified from the 2009 CEBM levels of evidence was used [5].

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. 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 the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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 and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [6].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The 2024 publication was peer reviewed prior to publication.

2.3 Future goals

The Panel are currently conducting two individual patient data (IPD) analyses to validate the definition of bacillus Calmette-Guérin (BCG) failure/BCG unresponsive in patients with non-muscle invasive urothelial carcinoma of the bladder and the impact of BCG on progression in the BCG treated subgroup of the original cohort that served to generate the 2021 risk stratification. The results of both analyses will be included in the future update of the NMIBC Guidelines.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, and it is the tenth when both genders are considered [7]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women [7]. In the European Union, the age-standardised incidence rate is 20 in men and 4.6 in women [7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) is 3.3 for men vs. 0.86 for women [7]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and variations in access to, and delivery of, healthcare. Additionally, epidemiological variations have been attributed to differing methodologies and the quality of data from individual datasets [8]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative factors [9].

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

3.2 Aetiology

*3.2.1 **Main risk factors***

3.2.1.1 Tobacco

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [8, 9, 11, 12]. The aromatic amines and polycyclic aromatic hydrocarbons within the tobacco smoke, which undergo renal excretion, are linked to the development of BC. The risk of BC increases with smoking duration and intensity [18]. Low-tar cigarettes are not associated with a lower risk of developing BC [13]. The risk associated with electronic cigarettes has not been adequately assessed; however, carcinogens have been identified in the urine with electronic cigarettes [14]. 'Second-hand' exposure to tobacco smoke is also associated with an increased risk of BC [8].

3.2.1.2 Occupational exposure

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants which process paint, dye, metal, and petroleum products [8, 9, 15, 16]. In developed industrial settings these risks have been reduced by work-safety guidelines; therefore, chemical workers no longer have a higher incidence of BC compared to the general population [8, 15, 16]. Recently, greater occupational exposure to diesel exhaust has been suggested as a significant risk factor (odds ratio [OR]: 1.61; 95% confidence interval [CI]: 1.08–2.40) [17]. Additionally, a large registry-based study of over one million people, with a follow up of 21 years, found that residents in the Haifa Bay Area of Israel (which is a centre for petrochemical industry) had a significantly higher incidence of several cancers, including bladder cancer (hazard ratio [HR] 1.11; 95% CI: 1.01–1.23), compared with non-residents [18].

*3.2.2 **Genetic***

Family history seems to have little impact [19]. To date, no clinically relevant genetic alteration has been linked to BC. Genetic predisposition may lead to a higher susceptibility to other risk factors, and thereby explain the familiar clustering of BC in first- and second-degree relatives (HR: 1.69; 95% CI: 1.47–1.95) [8, 20-25] that has been confirmed more recently [26]. A recent study identified three single nucleotide polymorphisms related to the development of aggressive NMIBC [27]. Currently, there is insufficient evidence to support genetic screening for BC.

*3.2.3 **Dietary habits***

Dietary habits seem to have limited impact on the risk of developing BC. A protective impact of flavonoids has been suggested [28]. The Mediterranean diet, characterised by a high consumption of vegetables and non-saturated fat (olive oil) with moderate consumption of protein, has been linked to some reduction of BC risk (HR: 0.85; 95% CI: 0.77–0.93) [29-33]. Western diet (high in saturated fats) and organ meat has been shown to increase the risk of BC in a recent meta-analysis [34, 35]. The impact of an increased consumption of fruits has been suggested to reduce the risk of BC. This effect has been demonstrated to be significant in women only (HR: 0.92; 95% CI: 0.85–0.99) [36]. This gender discrepancy was also evident in the BLEND study which showed that in men moderate or high intake of vitamins B1, B2 and vitamins related to energy metabolism were found to be associated with an increased BC risk, whereas in women high intake of the same vitamins and vitamin combinations was shown to have a protective effect with the exception of the entire B group vitamin

complex [37]. One possible explanation for this gender discrepancies is the difference in the main source of vitamin intake among study participants, being meat in men and fruits/vegetables in women. In addition, higher consumption of tea has also been associated with a reduction in risk of BC in men but through an interaction with tobacco smoking; therefore, making the protective effect of this compound questionable [38].

*3.2.4 **Environmental exposure***

Although the impact of drinking habits remains uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic. Additionally, exposure to arsenic in drinking water has been suggested to increase the risk of BC [8, 39]. Arsenic intake and smoking have a combined effect [40]. Conversely, chronic exposure to nitrate in drinking water does not seem to be associated with increased risk of BC [41].

The association between personal hair dye use and risk of BC remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow NAT2 acetylation phenotype [8] but a large prospective cohort study could not identify an association between hair dye and risk of cancer and cancer-related mortality [42].

*3.2.5 **Pelvic radiation***

Exposure to pelvic ionizing radiation is associated with an increased risk of BC [43, 44]. In a retrospective analysis of patients with localised prostate cancer, external beam radiotherapy (EBRT) was independently associated with a risk of developing a second primary BC [43]. A single centre study of 583 prostate cancer patients treated with brachytherapy revealed that the risk of developing BC increased in those who received additional EBRT (n=255) (HR 3.29; 95% CI 1.03–10.52). The BC specific mortality was also higher when combination therapy was used [44].

*3.2.6 **Other***

The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol, and triglycerides) remains uncertain [45]. However, data suggest that high circulating levels of vitamin D are associated with a reduction in the risk of BC [46]. Schistosomiasis, which is an infection caused by a parasitic trematode, can lead to BC [8]. A weak association was also suggested for cyclophosphamide and pioglitazone [8, 39, 47].

3.3 Summary of evidence for epidemiology and aetiology

Summary of evidence	**LE**
Worldwide, bladder cancer (BC) is the tenth most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC diagnosis have been identified.	3
Tobacco smoking is the most important risk factor for BC.	3

4. PATHOLOGICAL STAGING, GRADING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Urothelial 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 [48]. Intra-epithelial, high-grade (HG) tumours confined to the mucosa are classified as CIS (Tis). All of 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/bladder. The term 'superficial BC' should no longer be used as it is incorrect.

4.2 Tumour, Node, Metastasis Classification (TNM)

The latest TNM classification approved by the Union International Contre le Cancer (UICC) (8th Edn.) is referred to (Table 4.1) [48].

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 sub-staging) has been demonstrated to be of prognostic value in retrospective cohort studies [48, 49] (LE: 3). Its use is recommended by the most recent 2022 World Health Organization (WHO) classification [50, 51]. T1 sub-staging methods are based either on micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles; the optimal classification system, however, remains to be defined [52, 53] .

4.4 Lymphovascular invasion

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with an increased risk of pathological upstaging and worse prognosis [54-58] (LE: 3). Immunohistochemistry for confirmation is not mandatory [50].

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

4.5.1 Types of histological grading systems

In 2004 the WHO published a histological classification system for UCs including papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive papillary carcinoma low grade (LG) and HG. This system was also taken into the updated 2016/2022 WHO classifications [50, 51]. It provides a different patient stratification between individual categories compared to the older 1973 WHO classification, which distinguished between grade 1 (G1), grade 2 (G2) and grade 3 (G3) categories [52, 59].

There is a significant shift of patients between the categories of the WHO 1973 and the WHO 2004/2022 systems (see Figure 4.1), for example an increase in the number of HG patients (WHO 2004/2022) due to inclusion of a subset of G2 patients with a more favourable prognosis compared to the G3 category (WHO 1973) [60, 61]. According to a multi-institutional individual patient data analysis, the proportion of tumours classified as PUNLMP (WHO 2004/2016) has decreased to very low levels in the last decade [62].

4.5.2 Prognostic value of histological grading

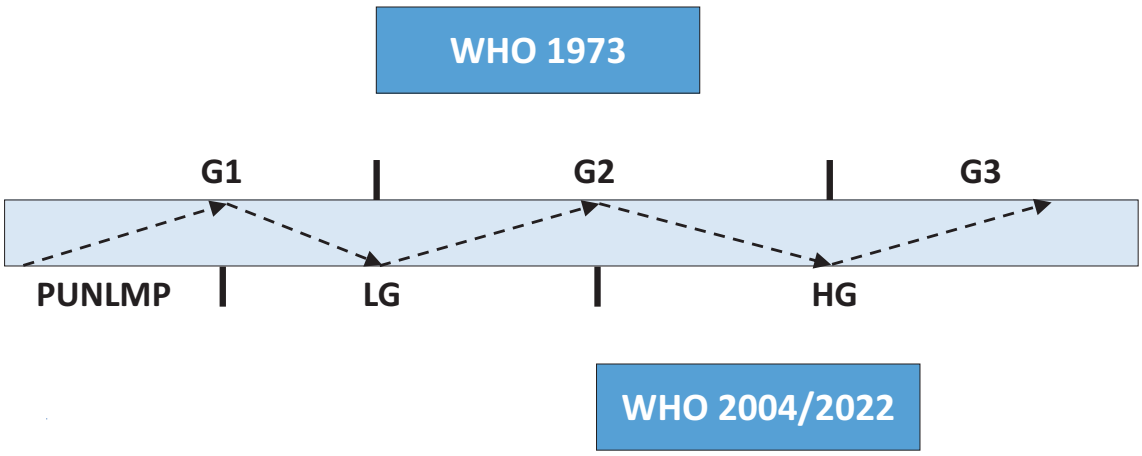
A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression [60].

To compare the prognostic value of both WHO classifications, an individual patient data analysis of 5,145 primary TaT1 NMIBC patients from sixteen centres throughout Europe and one in Canada was conducted. Patients had a transurethral resection of bladder tumour (TURBT) followed by intravesical instillations at the physician's discretion. In this large study, the WHO 1973 and the WHO 2004/2016 were both prognostic for progression but not for recurrence. When compared, the WHO 1973 was a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 3-tier (LG/G1-G2, HG/G2 & HG/G3) or a 4-tier hybrid combination LG/G1, LG/G2, HG/G2 and HG/G3) of both classification systems proved to be superior to either classification system alone, as it divides the large group of G2 patients into two subgroups (LG/HG) with different prognoses [63]. In a subgroup of 3,311 patients with primary Ta bladder tumours, a similar prognosis was found for PUNLMP and Ta LG carcinomas [62].

4.5.3 Clinical application of histological grading systems

- The WHO 2004/2022 classification system is currently supported by the WHO for clinical application. Nevertheless, the WHO 1973 is still being used.
- The most important parameters, which must be considered for clinical application of any grading system are its inter-observer reproducibility and prognostic value (see Sections 4.5.1 and 4.6).
- These guidelines provide recommendations for tumours classified by both classification systems.

Figure 4.1: Schematic representation of tumours according to grade in the WHO 1973 and 2004/2022 classifications [63]*



**Grade shifts from the WHO 1973 (G1–G3) to the WHO 2004/2022 (PUNLMP, LG and HG) classification for Ta/T1 bladder tumours are displayed with dotted lines and arrows. Along the dotted lines, both the degree of anaplasia and the 5-year progression rates increased in LG/G1, LG/G2, HG/G2, and HG/G3 patients.*

Note: the 2004/2022 WHO classification is the updated version of 2004/2016 WHO classification. According to a series of 5145 primary Ta-T1 patients, the distribution of G1, G2 and G3 in the WHO 1973 classification is 23.5, 49.3 and 27.2% respectively while the corresponding PUNLMP, LG and HG rates for the WHO 2004/2022 system are 1.5, 49.8 and 48,7% respectively [63]. Figure reproduced with permission from Elsevier from [63] .

4.6 Carcinoma *in situ*

Carcinoma *in situ* is an intra-epithelial, HG, non-invasive UC. 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 urethra [64].

From a clinical point of view, CIS may be classified as [65]:

- 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.

4.7 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 [66]. There is also inter-observer variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2022 classifications. The general conformity between pathologists in staging and grading is 50–60% [67-70]. The WHO 2004/2022 classification provides slightly better reproducibility than the 1973 classification [60].

4.8 Subtypes of urothelial carcinoma

Currently the following differentiations of urothelial carcinoma (UC) are used [71, 72]:

1. Pure UC (more than 90% of all cases);
2. UC with partial (squamous-glandular or trophoblastic) divergent differentiation;
3. UC with micropapillary divergent differentiation;
4. UC with nested/microcystic divergent differentiation;
5. UC with microtubular divergent differentiation;
6. UC with large nested divergent differentiation;
7. UC with plasmacytoid divergent differentiation;
8. UC with lymphoepithelioma-like divergent differentiation;
9. UC with giant cell, diffuse, undifferentiated divergent differentiation;
10. UC with sarcomatoid divergent differentiation;
11. some UCs with other rare differentiations;
12. UCs with partial NE (neuroendocrine differentiation, % to be given);
13. pure neuroendocrine carcinoma (including small and large cell neuroendocrine carcinomas.

In the new WHO 2022 all subtypes are considered HG [51]. The percentage of subtype in the specimen should be reported since it has been shown to be of prognostic value [73]. The WHO 2022 classification considers all subtypes UC (LG and HG) with more than 5% of HG as a HG tumour [2, 73-80].

4.9 Tumour markers and molecular classification

Tumour markers and their prognostic role have been investigated [81-85]. These methods, in particular complex approaches such as the stratification of patients based on molecular classification, are promising but have not yet been recommended by any pathological organisation and are therefore not suitable for routine application [53, 86, 87].

4.10 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
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
Histological grading of urothelial NMIBC is classified according to the WHO 2004/2016/2022 (PUNLMP, LG/HG) systems and/or WHO 1973 (G1–G3).	2a
The WHO 2004/2016/2022 classification provides slightly better reproducibility than the 1973 classification.	2a

Both the WHO 1973 and the 2004/2016/2022 classification systems are prognostic for progression, but not for recurrence.	2a
The WHO 1973 is a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 3-tier hybrid (LG/G1-G2, HG/G2 & HG/G3) or a 4-tier hybrid LG/G1, LG/G2, HG/G2 and HG/G3) combination of both classification systems proved to be superior to either classification system alone.	2a

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Provide T1 sub-stage if the lamina propria is adequately sampled using either micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles.	Weak
Use both the 1973 and 2004/2022 WHO grading classification systems, or a hybrid system.	Weak
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 at diagnosis disease compared to nonvisible haematuria [88]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding symptoms.

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 [89].

Intravenous urography (IVU) is an alternative if CT is not available [90], but CT urography provides more information particularly in muscle-invasive tumours of the bladder and in UTUCs (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 which can be obtained [91-93]. The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [92]. The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [94].

*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 [95, 96]. It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

*5.4.3 **Multi-parametric magnetic resonance imaging***

The role of multi-parametric magnetic resonance imaging (mpMRI) has not yet been established in BC diagnosis and staging. A standardised methodology of MRI reporting (Vesical Imaging-Reporting and Data System [VI-RADS]) in patients with BC has recently been published and requires further validation [97]. A systematic review of 8 studies showed that the VI-RADS scoring system can accurately differentiate NMIBC from MIBC with high inter-observer agreement rates [98]. A diagnosis of CIS cannot be made with imaging methods alone (CT urography, IVU, US or MRI).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG and G3 tumours (84%), but low sensitivity in LG/G1 tumours (16%) [99]. The sensitivity in CIS detection is 28–100% [100]. A recent report applying the Paris system found a sensitivity of 46% for HG disease [101]. Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours; it is not designed to detect LG tumours. Positive voided urinary cytology can indicate an UC anywhere in the urinary tract; negative cytology, however, does not exclude its presence.

Cytological interpretation is user-dependent [102, 103] and evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations: although in experienced hands specificity exceeds 90% [104]. Artificial intelligence algorithms combined with digital image processing (VisioCyt test) improved the sensitivity of cytology for HG tumours up to 92% [105].

A standardised reporting system known as The Paris System published in 2022 (2nd Edn.) redefined urinary cytology diagnostic categories as follows [106]:

- No adequate diagnosis possible (No diagnosis);
- Negative for UC (Negative);
- Atypical urothelial cells (Atypia);
- Suspicious for HG UC (Suspicious);
- High-grade/G3 UC (Malignant).

The principle of the system and its terminology underlines the role of urinary cytology in detection of G3 and HG tumours. The Paris system for reporting urinary cytology has been validated in several retrospective studies [107, 108].

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [106]. In patients with suspicious cytology repeat investigation is advised as the underlying risk of a high grade lesion is between 24-53% [109].

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology in LG/G1 tumours, numerous urinary tests have been developed [110]. None of these markers have been accepted as routine practice by any clinical guidelines for diagnosis or follow-up.

The following general statements can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity compared to urine cytology [106].
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests [111].
- 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]) [106].
- Several urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies [112, 113]. Four of the commercially available urine biomarkers, Cx-Bladder [114, 115], ADX-BladderTM [116, 117], Xpert Bladder® [118-120] and EpiCheckTM [112], although not tested in RCTs, have such high sensitivities and negative predictive values in the referenced studies for HG disease that these biomarkers may approach the sensitivity of cystoscopy. These 4 tests might be used in the initial diagnostic workup to avoid/implement cystoscopy [114, 121, 122], or in follow-up to replace or postpone cystoscopy [116, 117, 120, 123]. See section 8 for more details on the use of urine markers in the follow up.
- In patients with negative cystoscopy and upper tract work-up, positive results of urine cytology or molecular urine tests such as UroVysion™ (FISH), Nuclear Matrix Protein (NMP)22®, Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT) and microsatellite analysis may identify patients more likely to experience disease recurrence and possibly progression [124-131].

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, or UroVysionTM tests if dipstick is positive has been reported in BC screening in high-risk populations [132, 133]. However, the low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness of BC screening [127, 133]. Thus, routine screening for BC is not recommended [127, 132, 133].

5.7.2 ***Investigation 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, specificity is particularly important. Recently, CellDetect® and UroVysion™ have shown similar performance to detect BC and were both superior to cytology [134]. In addition, Xpert Bladder® had higher sensitivity and negative-predictive value than both cytology or UroVysion™ for the detection of BC in patients with haematuria [121].

5.7.3 ***Follow-up of non-muscle-invasive bladder cancer***

The current status of urine cytology and urinary molecular marker tests in follow-up for non-muscle-invasive bladder cancer is discussed in Section 8.

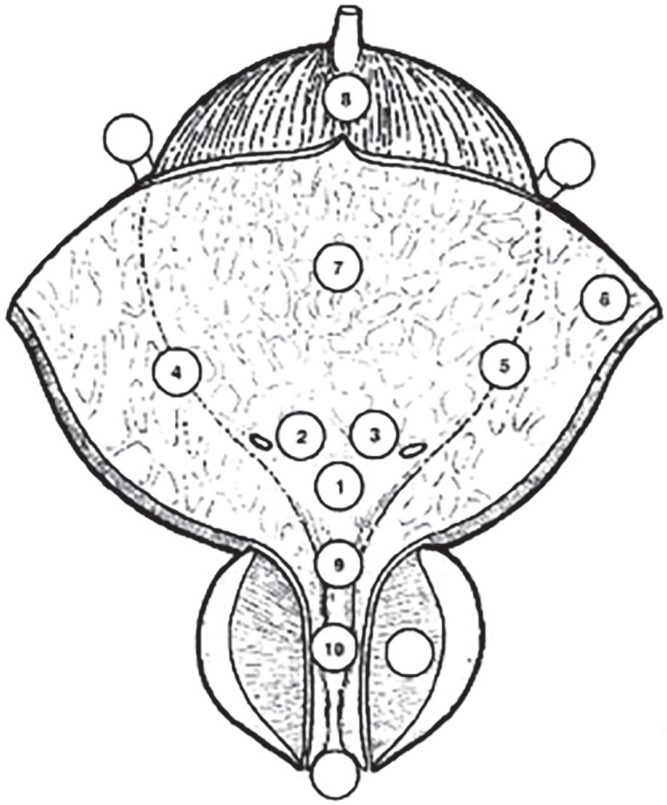
5.8 Cystoscopy

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* can be suspected through cystoscopy and urine cytology and confirmed by histological evaluation of multiple bladder biopsies [135].

Cystoscopy can be 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 [136, 137].

To temporary increase the urethral pressure by irrigation 'bag squeeze' when passing membranous and prostatic urethra with a flexible cystoscope in males also decreases pain during the procedure [138, 139].

Figure 5.1: Bladder diagram



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

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of BC.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	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, and apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	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. First morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris System 2nd Edn. for cytology reporting.	Strong

5.10 Transurethral resection of TaT1 bladder tumours

*5.10.1 **Strategy of the procedure***

The goals of TURB in TaT1 BC is to establish accurate pathological diagnosis/staging and completely remove all visible lesions. It is a crucial procedure in the management of BC. Transurethral resection of the bladder tumours should be performed systematically in individual steps [140, 141] (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, architecture, location, 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), visualisation of tumour in the distal ureter and presence of complications (assessment for perforation) [140, 142]. Documentation of cystoscopic tumour characteristics and consequent clinically predicted tumour grade and stage can help assign patients to post-TURB single instillation of chemotherapy (low grade non-invasive) and muscle invasive cancers to be fast tracked to definitive treatment [143]. To measure the size of the largest tumour, one can use the end of the cutting loop, which is approximately 1 cm wide, as a reference. Tumour architecture can be sessile, nodular, papillary, mixed papillary/solid 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 [141, 144].

- 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 [145]. Whilst this technique is carried out using a loop with diathermy (monopolar or bipolar), the Thulium-YAG laser is potentially a feasible alternative [146].
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG or KTP-Green Light lasers is feasible in selected exophytic tumours. It provides high-quality resected specimens with the presence of detrusor muscle in 96–100% of cases [141, 147-154]; however, its superiority over conventional TURB remains debatable [155, 156]. Detrusor muscle sampling rates were no different between these techniques in a systematic review of 1,142 patients [157], and in a single centre RCT showing similar detrusor muscle sampling rates of 95% between conventional TURB and *en-bloc* resection [155]. Conversely, another systematic review of 4,484 patients revealed higher detrusor muscle sampling

rates in favour of *en-bloc* resection [147], and a multicentre RCT found significantly higher detrusor muscle rates with *en-bloc* compared to conventional TURB (80.7 vs 71.1) [156]. Respect for tumour architecture increases the accuracy of T1 staging and the possibility of sub-staging while potentially reducing the risk of bladder perforation [147, 152-155]. With regards oncological outcomes, two RCTs did not reveal a difference in time to recurrence between *en-bloc* resection and conventional TURB [155, 156]. This has also been shown in two systematic reviews [147, 157].

The technique selected is dependent on the size and location of the tumour and experience of the surgeon. The tumour size feasible for retrieval *en-bloc* is limited by the currently available endoscopic equipment and it has been shown that technical success declines with tumours larger than three cm [158]. With better detection of tumours and abnormal margins, methods of optical enhancement are expected to improve complete resection rates (see Section 5.11).

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 under-staging [159] (LE: 1b). The presence of detrusor muscle in the specimen is considered as a surrogate criterion of the resection quality [159] and is required (except in Ta LG/ G1 tumours). Surgical checklists and quality performance indicator programmes have been shown to increase surgical quality (accurate documentation of factors required to assign risk and sample detrusor muscle) and decrease recurrence rates [140, 142, 160-162]. The Panel have included a sample TURB checklist in Table 5.1 and reported quality indicators for the procedure in Table 9.1.

It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [159, 163]. Virtual training on simulators is an emerging approach [164]. Its role in the teaching process still needs to be established [140]. Surgical experience and/or volume has been associated with risk of complications [165], recurrence [166] and survival [167] in retrospective studies. Despite a relatively low overall rate of detrusor muscle (DM) sampling, a collaborative study of 503 patients demonstrated that higher utilisation of surgical checklists by residents was associated with a higher rate of detrusor muscle sampling (62.9%) vs. 'experts' (50.6%) who's utilisation of checklists was lower [140, 162].

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 [168-170], with significant inherent limitations due to selection bias, heterogeneity of surgical approach or inability to qualify surgeon experience. A systematic review of 13 RCTs (2,379 patients) showed no benefit of bipolar vs. monopolar TURB for efficacy and safety [170] while one meta-analysis of RCTs (n = 2,099) suggests a lower fall in haemoglobin and shorter hospital stay with bipolar resections [168] and another systematic review of RCTs and observational studies (n = 19,927) suggests lesser thermal artifacts in the specimen [169].

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

It is not uncommon to incidentally detect bladder tumours during TURP in men with benign prostatic hyperplasia. Provided these tumours are papillary, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate [171, 172]. Simultaneous TURB and TURP does not appear to lead to any increased risk of tumour recurrence or progression [173]. Whilst most reports have suggested surgeons prefer to undertake saline irrigation following the combined TURBT and TURP, post-operative single instillation of chemotherapy also appears to be feasible and safe provided there is no capsular or bladder perforation [174].

5.11 Endoscopic biopsies

*5.11.1 **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. In patients with positive urine cytology (see Section 5.5), and normal-looking mucosa at cystoscopy, mapping biopsies are recommended [175, 176]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [175, 176]. If the equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy (see section 5.12.1).

*5.11.2 **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 UC, the incidence of CIS in the prostatic urethra was 11.7% [177]. 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 [178]. Based on this observation, a biopsy from the prostatic urethra is necessary in some cases [177, 179, 180]. Biopsies should preferably be from the pre-collicular area (between 5 and 7 o'clock position next to the veru montanum) using a resection loop.

5.12 New methods of tumour visualisation

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

*5.12.1 **Photodynamic diagnosis (fluorescence cystoscopy or blue light cystoscopy)***

Photodynamic diagnosis is performed using blue light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL).

5.12.1.1 Impact on bladder cancer detection

It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly CIS [181, 182] (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity than WL endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [182]. A prospective RCT did not confirm a higher detection rate in patients with known positive cytology before TURB [183].

Photodynamic diagnosis had lower specificity than WL endoscopy (63% vs. 81%) and it does not help to rule out prostatic involvement [182]. False- positivity can be induced by inflammation or recent TURB and during the first 3 months after BCG instillation [184, 185].

5.12.1.2 Impact on bladder cancer recurrence

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, 6 using 5-ALA and 9 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 [186]. While a recent systematic review and meta-analysis of 12 RCTs (n = 2,288) revealed lower risk of recurrence and improved time to recurrence (at least in the first 2 years and possibly up to 5 years) with PDD [187], the most recent Cochrane systematic review and meta-analysis of 16 RCTs (n = 4,325) demonstrated that PDD-assisted TURBT may prolong not only recurrence over time but also risk of progression, albeit supported only by low certainty evidence [188]. This finding has been corroborated in a systematic review and meta-analysis of 12 RCTs involving 2,775 patients [189].

Contrary to previous evidence, a multicenter RCT from UK showed that PDD-guided TURBT did not reduce recurrence rates, nor was it cost-effective compared with WL cystoscopy at three years [190] .

*5.12.2 **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 [191-194] (LE: 3b). Two RCTs assessed the reduction of recurrence rates if NBI is used during TURB [194, 195]. Although the overall results were negative, a benefit after three and twelve months was observed for low-risk tumours (pTa LG, < 30 mm, no CIS) [195].

A systematic review and meta-analysis by Russo *et al.*, (17 RCTs and non-RCTs) demonstrated improved detection (diagnostic accuracy) of bladder tumours with either PDD or NBI over WL cystoscopy [196], while another one (including 5,217 patients) showed improved RFS with either enhancement technique [197]. Conversely, a systematic review and network meta-analysis that took into account the use of single post-operative instillation of chemotherapy, concluded that there was a lower likelihood of recurrence at one year only following PDD-guided TURB (with or without single instillation) but not with NBI-guided surgery [198].

5.12.3 IMAGE1 S™, and other technologies

IMAGE1 S™ (formerly named SPIES) is an image enhancement system based on a computerized processing of different colour components that uses specific light filters. Limited evidence has been produced so far in an attempt to validate the 4 different light spectra modalities, suggesting an improvement in the diagnostic accuracy of WL [199, 200]. Early (18 months) follow-up data of an RCT failed to show an advantage in recurrence rate in the IMAGE1 S™ arm over WL, except in a subgroup of primary low intermediate-risk NMIBCs [201].

Confocal laser micro-endoscopy is a high-resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [202].

5.13 Second resection (second TURB)

5.13.1 Detection of residual disease and tumour upstaging

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [144]. This residual cancer has the potential to worsen oncological outcomes and therefore further emphasises the importance of an effective initial TURB. As patients with an initial incomplete TURB (either from extensive tumour or intra-operative complications) will require a second completion resection, documentation of resection completeness at the time of the initial TURB is essential.

The main purposes of a second TURB are to: (1) clear any residual cancer; (2) re-resect the previous resection site to establish correct pathological staging; and (3) obtain any missing elements of the clinical information (e.g. extent of cancer, involvement of prostatic urethra).

A systematic review analysing data of 8,409 patients with Ta or T1 HG UC demonstrated a 51% risk of persistence and an 8% risk of under-staging 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 [203].

Another systematic review and 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 even in a subgroup with detrusor muscle sampled at the initial TURB. In the subgroup of 1,565 T1 tumours with detrusor muscle present, persistent tumour was found in 58% and under-staging occurred in 11% of cases [204].

Prospective trials suggest that post-operative positive urine cytology [205] and Xpert Bladder® (urine mRNA test) [206] are independently associated with residual disease at second resection and risk of future recurrences, respectively. These data, however, need to be confirmed in further studies.

5.13.2 The impact of second resection on treatment outcomes

A second TURB can increase recurrence-free survival (RFS) [207-209], improve outcomes after BCG treatment [210] and provide prognostic information [211-214].

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1 G3/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 initial resection specimen [215]. In a retrospective analysis of 7,666 patients diagnosed with T1 cancer in Ontario, 2,162 underwent a second resection; after adjusting for the effects of confounding variables, only OS (and not CSS) was better in patients who underwent second resection [167]. This apparent improved survival could also be the result of selection bias with fitter patients undergoing second resections. Whilst a single centre retrospective review revealed survival benefit in 209 HGTa patients who underwent a second TURB [216], further evidence is required to identify specific sub-groups of patients with high-grade cancer who are most likely to benefit from a second resection.

5.13.3 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 [217]. Based on this currently available evidence, a second TURB is recommended in selected cases 2 to 6 weeks after initial resection [217] (for recommendations on patient selection, see Section 5.14).

5.13.4 Recording of results

The results of the second resection (residual tumours and under-staging) reflect the quality and effectiveness 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.

5.14 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the decision-making process for BC [218]. Close co-operation between urologists and pathologists is required. Clinical information and high quality of resected and submitted tissue is essential for correct pathological assessment. To obtain all relevant information, the specimen collection, handling and evaluation, should respect the recommendations provided below (see Section 5.14) [219]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered.

Table 5.1 TURBT checklist*

TURBT checklist - In the Operating Room	
Check the operating room setup	Instruments (sheath, resectoscope, loops, roller if needed, monopolar/ bipolar), camera, video, strainer, specimen container, catheter if needed
Decide irrigation fluid	Saline, Glycine, Water
Disease characteristics checklist	History of bladder cancer, tumour characteristics at cystoscopy if any, imaging results if any, first or second look, visual optimisation planned (PDD/NBI), risk classification
Cystoscopy/ TURBT	
Cystoscopy	Urethra/prostate (males)
	Ureteral orifices
	Diverticula
	Tumour location, number, size, appearance (papillary/sessile), CIS (yes/no)
	White light/PDD/NBI/IMAGE1 S™
	Urine for cytology/bladder wash
TURBT	Resection technique (standard/*en bloc*/cold cup/roller ball cautery)
	Depth of resection
	Complete/incomplete resection
	Prostatic urethra biopsy if performed
	Any additional procedure, i.e. retrograde contrast study
	Estimated blood loss
	Intra-operative complications, if any
	Intravesical therapy if given or planned in recovery setting

**Adapted from Mostafid et al., and Suarez-Ibarrola et al., [140, 220].*
NBI = narrow-band imaging; PDD = photodynamic diagnosis; TURBT = transurethral resection of bladder tumour.

5.15 Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	**LE**
Transurethral resection of the bladder tumour (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 under-staging (with the exception of Ta LG/G1 tumours).	2b
A second TURB can detect residual tumours and tumour under-staging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2
Photodynamic diagnosis has been shown to improve the detection of bladder cancer, especially CIS.	1a

Recommendations	Strength rating
In patients suspected of having bladder cancer, perform a transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia before starting the procedure and at the end; • 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 including visual impression of grade/stage; • precise description of the specimen(s) for pathology evaluation.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium.	Strong
Take multiple biopsies (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) or perform photodynamic diagnosis (PDD) guided biopsies, in case of normal looking urothelium and positive urine cytology.	Strong
Take a sample of the prostatic urethra if there is positive urine cytology without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible (see section 5.11.2).	Strong
Take a sample biopsy of the prostatic urethra in cases of bladder neck tumour, suspicion of bladder CIS and/or T1 disease. If a sample was not taken during the initial procedure, it should be performed at the time of second resection, if the latter is needed (see section 5.11.2).	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. Submit the tumour base separately especially in large and multifocal tumours or when *en-bloc* resection is not feasible.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, extent, macroscopic completeness of resection as well as any complications.	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: • after incomplete initial TURB, or in case of doubt about completeness of a TURB; • if there is no detrusor muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within 2–6 weeks after the initial resection. This second TURB should include resection of the primary tumour site.	Weak
Record the pathology results of the 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, subtypes of urothelial carcinoma, presence of CIS and detrusor muscle.	Strong

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

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

*6.1.1 **Scoring models using the WHO 1973 classification system***

6.1.1.1 The 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model

To be able to predict both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group (GUCG) published a scoring system and risk tables based on the WHO 1973 classification in 2006 [221]. The scoring system is based on the 6 most significant clinical and pathological factors in patients mainly treated by intravesical chemotherapy:

- number of tumours;
- tumour diameter;
- prior recurrence rate;
- T category;
- concurrent CIS;
- WHO 1973 tumour grade.

Using the 2006 EORTC scoring model, individual probabilities of recurrence and progression at 1 and 5 years may be calculated (https://www.omnicalculator.com/health/eortc-bladder-cancer).

6.1.1.2 The model for patients with Ta G1/G2 (WHO 1973) tumours treated with chemotherapy

Patients with Ta G1/G2 tumours receiving chemotherapy were stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy [222].

6.1.1.3 Club Urologico Español de Tratamiento Oncologico (CUETO) scoring model for BCG-treated patients

A model that predicts the risk of recurrence and progression, based on 12 doses of intravesical BCG over a 5 to 6 months period following TURB, has been published by the CUETO (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from 4 CUETO trials that compared different intravesical BCG treatments. 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;
- WHO 1973 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 [223] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this study. The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG [224] and by long-term follow-up in another patient population [225].

6.1.1.4 The 2016 EORTC scoring model for patients treated with maintenance BCG

In 1,812 intermediate- and high-risk patients without CIS treated with 1 to 3 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 WHO 1973 grade for disease progression and disease- specific survival, while age and WHO 1973 grade were the most important prognostic factors for OS. T1 G3 patients did poorly, with 1- and 5-year disease-progression rates of 11.4% and 19.8%, respectively. Using these data, EORTC risk groups and nomograms for BCG-treated patients were developed [226].

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

6.1.2.1 EAU NMIBC 2021 scoring model

To update the risk of disease progression and create new prognostic factor risk groups using both the WHO 1973 and WHO 2004/2016 classification systems (without central pathology review), individual patient data from 3,401 primary patients treated from 1990 to 2018 were used [227] (see Section 4.5). Only patients treated with TURB ± intravesical chemotherapy were included, those treated with adjuvant intravesical BCG were excluded because BCG may reduce the risk of disease progression. From the multivariate analyses, tumour stage, WHO 1973 grade, WHO 2004/2022 grade, concomitant CIS, number of tumours, tumour size and age were independent predictors of disease progression [227].

This is the only available model where the WHO 2004/2022 classification system is included as one of the parameters to calculate an individual patient's risk group and probability of progression. As the WHO 2004/2022 classification system is the main grading classification system used by pathologists, the Guidelines Panel recommends to use the 2021 EAU NMIBC scoring model for risk groups definition (see Section 6.3).

The 2021 EAU NMIBC scoring model determines the risk of tumour progression, but not recurrence; therefore any of the models mentioned in Section 6.1.1 may be used for calculation of an individual's risk of disease recurrence.

*6.1.3 **Further prognostic factors***

Further prognostic factors have been described in selected patient populations:

- In T1 HG/G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with an induction course only) [177, 228].
- Attention must be given to patients with T1 HG/G3 tumours in bladder diverticulum because of the absence of muscle layer in the diverticular wall [229].
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [212-214].
- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [230].
- 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 [225, 231].

6.2 Primary carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [232] (LE: 3). There are no reliable prognostic factors, but some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [233, 234], in extended CIS [235] and in CIS in the prostatic urethra [177]. The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [223, 224, 230]. Approximately 10 to 20% of complete responders eventually experience disease progression to muscle-invasive disease, compared with 66% of non- responders [236, 237].

6.3 Patient stratification into risk groups

To be able to facilitate treatment recommendations, the Guidelines Panel recommends the stratification of patients into risk groups based on their probability of progression to muscle-invasive disease. The new risk group definitions provided in these EAU Guidelines are based on an individual patient data analysis in primary patients and the calculation of their progression scores (2021 EAU NMIBC scoring model) as presented in Sections 4.5 and 6.1.2) [227].

For calculation of the risk group in individual patients, either one, or both, of the WHO 1973 and WHO 2004/2016 classification systems may be used. The probability of progression at 5 years varies from less than 1% to more than 40% between the risk groups.

For factors where individual patient data were not collected such as subtypes of UC, LVI, primary CIS and CIS in the prostatic urethra; literature data have been used to classify patients into risk groups.

The clinical compositions of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or WHO 1973 classification systems are provided in Table 6.1. Applications for the web (www.nmibc.net), iOS and Android have been developed to facilitate determining a patient's risk group in daily clinical practice. The individual probability of disease progression at 1, 5 and 10 years for the new EAU NMIBC risk groups is presented in Table 6.2. A single-centre study validated the EAU NMIBC 2021 scoring model in 529 patients who

received BCG [238]. The authors found that the progression risk for the EAU 2021 high- and very high-risk groups were significantly lower in BCG-treated patients than that in Table 6.2 [227]. These lower risks may be attributed to the use of BCG.

Table 6.1: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems [227]

- Only one of the two classification systems (WHO 1973 or WHO 2004/2016) is required to use this table.
- If both classification systems are available in an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973 as it has better prognostic value.
- The category of LG tumours (WHO 2004/2016) also includes patients with tumours classified as PUNLMP.
- Additional clinical risk factors are: age > 70; multiple papillary tumours; and tumour diameter > 3 cm.

Risk group	
Low Risk	• A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years • A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate Risk	• Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

The scoring model is based on individual patient data, but does not consider patients with primary CIS (high risk) or with recurrent tumours, as well as some pathologic parameters like subtypes of UC (see Section 4.7) and LVI. Nevertheless:

- Based on data from the literature, all patients with CIS in the prostatic urethra, with subtypes of UC (see Section 4.8) or with LVI should be included in the very high-risk group.
- Patients with recurrent tumours should be included in the intermediate-, high-, or very high-risk groups according to their other prognostic factors.

Table 6.2: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [227]*

Risk group	*Probability of Progression and 95% Confidence Interval (CI)*		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)
New Risk Groups with WHO 1973			
Low	0.12% (CI: 0.02%–0.82%)	0.57% (CI: 0.21%–1.5%)	3.0% (CI: 1.5%–6.3%)
Intermediate	0.65% (CI: 0.36%–1.2%)	3.6% (CI: 2.7%–4.9%)	7.4% (CI: 5.5%–10%)
High	3.8% (CI: 2.6%–5.7%)	11% (CI: 8.1%–14%)	14% (CI: 10%–19%)
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

WHO = World Health Organization.

**Table 6.2 does not include patients with subtypes of urothelial carcinoma (variant histologies), LVI, CIS in the prostatic urethra, primary CIS or recurrent patients.*

**Please note that these percentages refer to patients who were not (immediately) treated with adjuvant BCG instillations after their primary TUR.*

6.4 Summary of evidence and guidelines for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EAU NMIBC 2021 scoring model and risk tables predict the short- and long-term risks of disease progression in individual patients with primary NMIBC using either the WHO 1973 or the WHO 2022 classification system (see Section 6.1.2.1).	2b
The 2006 EORTC scoring model and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with NMIBC using the WHO 1973 classification system (see Section 6.1.1.1).	1b
Patients with Ta G1/G2 tumours receiving chemotherapy have been further stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy (see Section 6.1.1.2).	2b
In patients treated with 5 to 6 months of BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression using the WHO 1973 classification system (see Section 6.1.1.3).	1b
In patients receiving at least 1 year of 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 (WHO 1973) are the most important prognostic factors for OS (see Section 6.1.1.4).	1b

Recommendations	Strength rating
Stratify patients into 4 risk groups to predict progression, according to Table 6.1. A patient's risk group can be determined using the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours, not treated with bacillus Calmette-Guérin (BCG), use the data from Table 6.2.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with BCG.	Strong
Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1 to 3 years of maintenance, the CUETO model for 5 to 6 months).	Strong

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression in NMIBC patients [239-241] as well as mortality in all BC patients [242]. A subgroup analysis of 4,405 patients in a large systematic review revealed that current smokers had a significantly higher risk of recurrence compared with former smokers [241]. Patients should be counselled to stop smoking due to the general health risks associated with tobacco smoking [229, 243-245].

7.2 Office-based fulguration and laser vaporisation

In patients with a history of small Ta LG/G1 tumours, fulguration, or laser vaporisation of small papillary recurrences on an outpatient basis can reduce the therapeutic burden [246, 247]. In a prospective RCT, laser photocoagulation with intravesical lidocaine in an outpatient setting proved non inferior to standard TURB under general anaesthesia for the 4 months recurrence rate. Notably, the laser fulguration procedure resulted in only a modest pain score (2.4) and was preferred by 98% of patients [248].

7.3 Active Surveillance

With recurrence in LG(G1) Ta tumours being more likely low grade and non-invasive [249-251] the risk of progression to a higher grade or stage is infrequent to rare [252-254]. Expectant management or active surveillance (AS), offer an alternative to TURB and office-based fulguration. Observing no progression to MIBC, Soloway *et al.*, first recommended this approach in 2003 [255] and Miyake *et al.*, subsequently proposed an algorithm for AS using changes in size and multifocality as triggers for intervention [256]. However, from a review undertaken by the EAU Young Academic Urology group [257], it appears that the level of evidence in favour of AS is low, with observational studies having heterogenous selection criteria, triggers for intervention and surveillance tools. The multicentre prospective Bladder Cancer Italian Active Surveillance (BIAS) project, conversely, demonstrated that AS is feasible in selected patients [258, 259] and its success be predicted by prognostic variables associated to TaLG disease [260]. However, additional evidence from quality clinical trials is required.

7.4 Adjuvant intravesical 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 [144]. It is therefore necessary to consider adjuvant therapy in all patients.

*7.4.1 **Post-operative irrigation***

Two systematic reviews [261, 262] and one meta-analysis [263] suggest efficacy of continuous irrigation in the prevention of early recurrences. In case intravesical chemotherapy is not feasible, irrigation of the bladder might be considered. Optimal volume infused and duration of irrigation remains unknown.

*7.4.2 **Intravesical chemotherapy***

7.4.2.1 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 [264-267]. 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 [268-271]. In a systematic review and individual patient data meta-analysis of 2,278 eligible patients [268], SI reduced the 5-year recurrence rate by 14%, from 59% to 45%. Only patients with primary tumours or intermediate-risk recurrent tumours with a prior recurrence rate of < 1 recurrence/year and those with a 2006 EORTC recurrence score < 5 benefited from SI. In patients with a 2006 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 [268-271].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin [268], as well as gemcitabine [271], have all shown to lower the intravesical recurrence rate. Single instillation with gemcitabine was superior to saline in a RCT with approximately 200 patients per arm with remarkably low toxicity rates [272]. These findings are in contrast with a previous study, which, however, used a shorter instillation time [273]. 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 [273].

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 [264, 274-276]. In all SI studies, the instillation was administered within 24 hours. Two RCTs found no overall impact of SI with apaziquone, a bio reductive prodrug similar to MMC; in contrast, a *post-hoc* analysis did find a reduction of recurrence risk in patients receiving apaziquone within 90 minutes following TURB [277].

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, safety measures should be maintained (see Section 7.7) [278, 279]. To allow for optimal compliance with this Level 1 evidence, clinical teams are encouraged to explore barriers and facilitators within their practice [280].

7.4.2.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1 and 6.2), a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [268, 269]. For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1 and 6.2). 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 [281].

Repeat chemotherapy instillations vs. no adjuvant treatment

A large meta-analysis of 3,703 patients from 11 RCTs showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [282]. This corresponds to an absolute difference of 13–14% in the proportion of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may also reduce the risk of tumour progression [283, 284] (see Section 7.2.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [285-287] (see Section 7.2.2.1). However, BCG causes significantly more side effects than chemotherapy [287].

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 [288-291]. A 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 3 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 [288]. 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 [292]. The results of this study should be considered with caution since some patients did not receive adequate therapy. Another RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC patients [293].

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 [291]. A systematic review of 16 comparative studies concluded that most of the available evidence does not support the use of maintenance chemotherapy over induction only in the treatment of NMIBC [294].

7.4.2.3 Measures to improve the efficacy of intravesical chemotherapy

7.4.2.3.1 Adjustment of pH, duration of instillation, and drug concentration

Two prospective RCTs showed that optimized intravesical administration of MMC reduced recurrence rates, either by a combination of measures (higher MMC-dose, peroral sodium bicarbonate, and refraining from drinking) [295] and by adding cytosine arabinoside [296], respectively. The value of these measures in addition to alternative maintenance schedules is not known however MMC admixtures ≥ 1 mg/ml do not achieve full solubilisation which might lead to decreased drug exposure to the bladder [297]. Another trial reported that duration of a one- hour instillation of MMC was more effective compared to a 30-minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [298]. Another RCT using epirubicin has documented that concentration is more important than treatment duration [299]. In view of these data, instructions are provided (see Section 7.7).

7.4.2.3.2 Device-assisted intravesical chemotherapy

Hyperthermic intravesical chemotherapy

Different technologies which increase the temperature of instilled MMC are available. A recent systematic review and meta-analysis including four RCTs suggests similar toxicity as for BCG with maintenance schedule [300].

Microwave-induced hyperthermia effect (RITE)

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [301]. 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 [302].

Conductive chemohyperthermia

In an open-label phase II RCT including 259 patients, HIVEC chemo-hyperthermia failed to demonstrate an improvement in DFS at 24 months over standard adjuvant intravesical chemotherapy in intermediate-risk NMIBC (61% vs. 60%), with a higher risk of treatment discontinuation (59% vs. 89% of completed planned treatments) [303]. These results are in line with the multicentre HIVEC 1 phase 3 open label RCT, including 212 intermediate-risk patients, showing that four-month adjuvant hyperthermic MMC using the COMBAT system in intermediate-risk NMIBC was well tolerated, but was not superior to normothermic MMC at 24 months [304].

In a pilot phase II RCT on 50 high-risk NMIBCs, HIVEC™ MMC showed early outcomes comparable to BCG (24 months RFS, 86.5% with HIVEC™ and 71.8% with BCG, p = 0.184) [305]. These data need to be corroborated by further studies.

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 [306]. The definitive conclusion, however, needs further confirmation. For application of device-assisted instillations in patients recurring after BCG treatment, see Section 7.9.3.

7.4.2.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	**LE**
In patients with low-risk NMIBC and in those with a small Ta LG/G1 recurrence detected more than one year after previous TURB, a SI significantly reduces the recurrence rate compared to TURB alone.	1a
Single instillation might have an impact on recurrence even when further adjuvant chemotherapy instillations are given, but not in high-risk NMIBC treated with adjuvant BCG.	3
Repeat chemotherapy instillations (with or without previous SI) improve RFS in intermediate-risk patients.	2a

7.4.3 ***Intravesical bacillus Calmette-Guérin (BCG) immunotherapy***

7.4.3.1 Efficacy of BCG

7.4.3.1.1 Recurrence rate

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC [285, 307-310]. Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (INF) [311], MMC [312], or epirubicin alone [286] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting [286, 312] and was also observed in a separate analysis of patients with intermediate-risk tumours [286]. One meta-analysis [285] has evaluated the individual data from 2,820 patients enrolled in 9 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. A Cochrane systematic review confirmed that BCG is more effective in reducing the recurrence rate over MMC [313].

7.4.3.1.2 Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [283, 284, 310] (LE: 1a). A meta-analysis carried out by the EORTC 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 [284]. A 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 [286] (LE: 1b). In contrast, an individual patient data meta-analysis and Cochrane review were not able to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [285, 313].

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.

7.4.3.1.3 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 [314]. In the individual patient data 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 [285] (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 [315] (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 [316].

7.4.3.2 BCG strain

Although smaller studies without maintenance demonstrated some differences between strains [316-318], 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 [319].

Similarly, a meta-analysis of prospective RCTs [284], published data from a prospective registry [320] as well as from a *post-hoc* analysis of a large phase II prospective trial assessing BCG and INF-α in both BCG-naive and BCG-failure patients did not suggest any clear difference in efficacy between the different BCG strains [321]. The quality of data, however, does not allow definitive conclusions.

7.4.3.3 BCG toxicity

Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [284, 313]. However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [322]. The incidence of BCG infections after BCG instillations was 1% in a registry-based cohort analysis [323]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [322]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [324]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [325]. No significant difference in toxicity between different BCG strains was demonstrated [320]. 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 albeit delayed hypersensitivity to BCG may rarely present even years after completion of treatment [326].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.9). 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 [131, 327] (LE: 3). Three RCTs showed reduced side effects by administering different quinolones in conjunction with the BCG-instillations [328-330]. The latter, by using two doses of levofloxacin (at 6 and 12 hours after first voiding) in conjunction with each BCG-instillation, reduced the proportion of patients with high-grade side effects, both local (pollakisuria) and systemic (fever), without improving the completion rate of the maintenance regimen or the risk of severe BCG related adverse events [330].

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients. Immunosuppression, for example human immunodeficiency virus (HIV) infection, poses relative contraindications [331], 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 [332-334]. Kidney transplant recipients can be safely treated with BCG [335].

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 [336, 337] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [337-340]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs).
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation. b. Perform a urine culture. c. Start empirical antibiotic treatment.
	If symptoms persist even with antibiotic treatment: a. With positive culture: adjust antibiotic treatment according to sensitivity. b. With negative culture: quinolones* and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [338].
	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 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis [339]	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.
	Reactive arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs [340].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin, and ethambutol 1.2 g daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. • Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or *Enterococcus.*

Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

** Persistent severe cystitis symptoms associated with BCG use have a high risk to underlie a complicated UTI (even in the absence of a positive culture) and thus no restriction applies to the empirical use of quinolones by the Pharmacovigilance Risk Assessment Committee of the EMA (see also Section 3.7 Complicated UTI and 3.7.4.1- Choice of antimicrobials of the EAU Guidelines on Urological Infection 2022) [341, 342].*

7.4.3.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales *et al.*, [343]. For optimal efficacy, BCG must be given in a maintenance schedule [283-285, 310]. Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 to 27 weeks over 3 years [344]. The optimal 3-years maintenance schedule is outlined in recommendation table 7.10.

7.4.3.4.1 Optimal number of induction instillations and frequency of instillations during maintenance

The optimal number of induction instillations and frequency of maintenance instillations were evaluated by NIMBUS, a prospective phase III RCT. Safety analysis after 345 randomised patients demonstrated that a reduced number of instillations (3 instillations in induction and 2 instillations at 3, 6 and 12 months) proved inferior to the standard schedule (6 instillation in induction and 3 instillations at 3, 6 and 12 months) regarding the time to first recurrence [345]. In a RCT including 397 patients CUETO showed that in high-risk tumours a maintenance schedule with only one instillation every 3 months for 3 years was not superior to induction therapy only, which suggested that one instillation may be suboptimal to 3 instillations in each maintenance cycle [346].

7.4.3.4.2 Optimal length of maintenance

In their meta-analysis, Böhle *et al.*, concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [283].

In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, 3 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 [347]. The main reason why these patients stopped treatment was treatment inefficacy, not toxicity.

7.4.3.5 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 [348, 349]. 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 [350]. 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 [324, 347]. In a recent meta-analysis of 9 RCTs, patients who received less than half of the standard BCG dose experienced less adverse events as compared to patients receiving the full dose, but faced more unfavourable outcomes such as higher rates of disease recurrences [351].

7.4.3.6 BCG shortage

A statement by the Panel on BCG shortage can be accessed online:
https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/publications-appendices.

7.4.3.7 Summary of evidence - BCG treatment

Summary of evidence	**LE**
In patients with intermediate- and high-risk tumours, intravesical 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. A complete BCG schedule comprises an induction phase of 6-weekly instillations, followed by a maintenance phase of three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months, respectively.	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

*7.4.4 **Combination therapy***

7.4.4.1 Intravesical BCG plus chemotherapy versus BCG alone

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing the risk of disease recurrence while increasing toxicity compared to BCG monotherapy. Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by an added MMC instillation [352]. In a 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 [306, 353]. Two meta-analyses demonstrated improved disease-free survival (DFS), but no benefit in PFS in patients treated with combination treatment comparing to BCG monotherapy [353, 354].

7.4.4.2 Combination treatment using interferon

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2α did not show a clear difference in recurrence and progression over BCG alone [355]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2α showed a higher probability of recurrence compared to MMC followed by BCG alone [356]. Additionally, a 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 [357].

7.4.4.3 Sequential chemotherapy instillations

Preclinical data suggest that the efficacy of intravesical chemotherapy instillations can be improved by combinations compared to the administration of single agents only [358]. Sequential (immediate) instillations of gemcitabine and docetaxel was initially reported in 2015 in the wake of BCG-shortage but also at times of limited access to mitomycin [359]. Subsequently other sequential chemotherapy combinations such as valrubicin and docetaxel have been suggested [360]. Over time, additional retrospective data have accumulated where sequential gemcitabine and docetaxel instillations were used in patients recurring after induction BCG and BCG-unresponsive disease [361]; in patients with recurrence after BCG-induction but not fulfilling the criteria for BCG-unresponsive disease [362]; and also in BCG-naïve high-risk patients [363]. Thus, in patients with BCG-unresponsive disease when the treatment standard (radical cystectomy) is not feasible due to age and/or comorbidity or when patients are unwilling to accept radical surgery, sequential instillations with gemcitabine and docetaxel is an emerging treatment concept awaiting further prospective scientific evaluation.

*7.4.5 **Specific aspects of treatment of carcinoma in situ***

7.4.5.1 Treatment strategy

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [221, 223]. In this case further treatment according to the criteria summarised in Sections 7.4.2, 7.4.3 and 7.9 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. Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [232].

7.4.5.2 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 [232-235, 356]. Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [235, 276, 344, 364].

7.4.5.3 Prospective randomised trials on intravesical BCG or chemotherapy

Unfortunately, there have been few RCTs 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 [365].

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 immunotherapy [284]. The combination of BCG and MMC was not superior to BCG alone [366]. 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.

7.4.5.4 Treatment of CIS in the 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 [367]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [367]. In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [368]. 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 [137, 369]. 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 [369, 370].

7.4.5.5 Summary of evidence - treatment of carcinoma in situ

Summary of evidence	**LE**
Carcinoma *in situ* cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, intravesical BCG maintenance instillations increase the complete response rate, the overall percentage of patients who remain disease free, and reduce the risk of tumour progression.	1b

7.5 Intravesical chemoablation and neoadjuvant treatment

Two different modalities of administering chemotherapy as first-line approach for a presumed NMIBC have been reported: neoadjuvant intravesical chemotherapy before TURB or chemoresection of the tumour as a replacement of TURB.

Neoadjuvant

Hypothesis-generating findings from an older RCT comparing immediate pre-operative device-assisted (EMDA) MMC with post-operative SI with MMC and TURB only, showed improved long-term RFS among patients treated prior to TURB [371], and thus even suggest a long-term effect after neoadjuvant instillations. While this has not been reproduced by other groups, two recent small neoadjuvant RCTs have reported conflicting results on the ability of neoadjuvant administration of MMC to improve outcomes over the standard approach [372, 373].

Chemoablation

Older marker lesion studies have shown that chemoablation with a single intravesical chemotherapy instillation can achieve a complete response in a proportion of patients [374]; therefore, making it possible to avoid TURB. In recurrent low-grade [375] and recurrent Ta tumours [376], 4 and 6 intravesical MMC instillations achieved complete response in 37% and 57% of the patients, respectively. In an update of the DaBlaCa-13 RCT evaluating chemoablation with 40 mg/40 mL of intravesical MMC three times a week for 2 weeks without preceding biopsy to standard TURB, the 12-month RFS was 36% in the chemoablation group vs. 43% in the TURB group, with no statistical significant difference [376]. Despite the lack of long-term outcomes, chemoablation appears to be a promising treatment option for well-selected NMIBC patients and can potentially help avoid unnecessary TURB, specifically in some elderly patients with intermediate-risk NMIBC [377].

7.6 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 [180, 378-382].
- 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 [383, 384].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life (QoL) 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 very high risk of disease progression (see Section 6.3 and Tables 6.1 and 6.2) [73, 177, 221, 223, 385].

Early RC is strongly recommended in patients with BCG-unresponsive tumours and should be considered in BCG relapsing HG tumours as mentioned in Section 7.9 and Table 7.3. A delay in RC may lead to decreased disease-specific survival [386].

In patients in whom RC is performed before progression to MIBC, the 5-year DFS rate exceeds 80% [387-389].

7.7 Primary treatment by disease type

The type of further therapy after TURB should be based on the risk groups shown in Section 6.3 and Table 6.1. The stratification and treatment recommendations are primarily based on the risk of disease progression (Table 6.2). In some instances, mainly in intermediate-risk tumours, the 2006 EORTC scoring model is useful (Section 6.1.1.1) to determine a patient's individual risk of disease recurrence as the basis to decide further treatment on.

- Treatment of low-risk disease
  Patients in the low-risk group have a negligible risk of disease progression. The single post-operative instillation of chemotherapy reduces the risk of recurrence and is considered as sufficient treatment in these patients.

- Treatment of intermediate-risk disease
  Patients in the intermediate-risk group have a relatively low risk of disease progression (7.4 and 8.5% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients induction chemotherapy with or without maintenance for a maximum of one year is a reasonable first-line option in the majority of patients. One-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), is an alternative option. 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.

- Treatment of high-risk disease
  Patients in the high-risk group have a high risk of disease progression (14% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients full-dose intravesical BCG for one to 3 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 associated with BCG shortage. Because of the high risk of progression, immediate RC may also be discussed with the patient. Radical cystectomy is the safest approach from an oncological point of view, it is, however, associated with the risk of complications and QoL impairment and represents over-treatment in some patients.

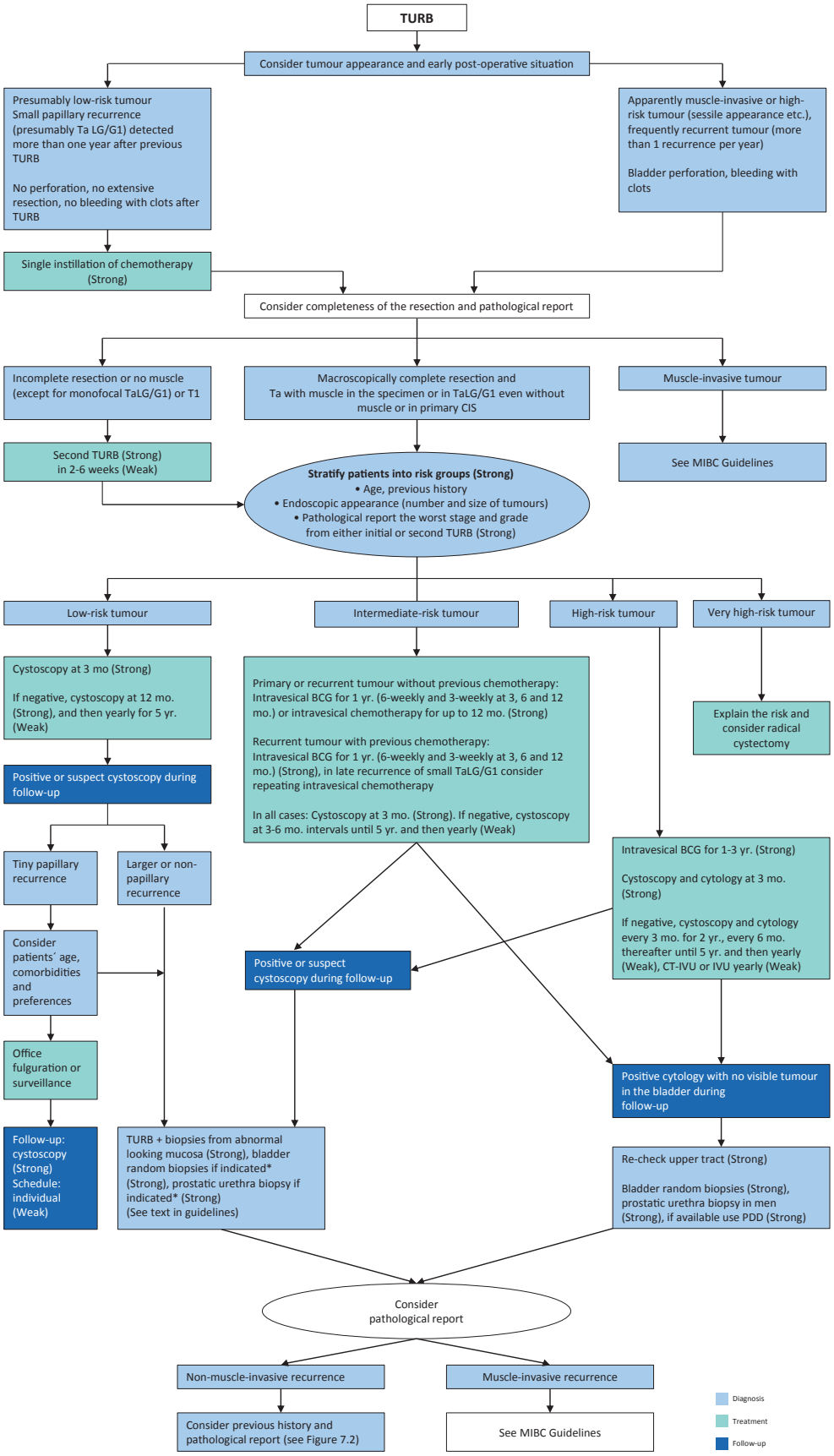
- Treatment of very high-risk disease
  Patients in the very high-risk group have an extremely high risk of tumour progression (53.1 and 58.6% after 10 years according to the 2021 EAU NMIBC scoring model). Immediate RC should be discussed with these patients. In case RC is not feasible or refused by the patient, full-dose intravesical BCG for one to 3 years should be offered.

- Treatment of carcinoma *in situ*
  Patients with carcinoma *in situ* cannot be managed by an endoscopic procedure alone and should be offered either intravesical BCG instillations or RC. 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. In comparison, immediate RC for CIS results in excellent tumour-specific survival rates although a large proportion of patients might be over-treated [232].

7.8 Multidisciplinary tumour board

A multidisciplinary tumour board (MDT) approach including reassessment of radiology and pathology is associated with a changed treatment plan in up to 44% of BC patients [390-393], such as refraining from or recommending cystectomy in 7% of stage T1 patients [391-393], often as a result of the pathologic review [68, 392]. Thus, patients with high-risk and very high-risk NMIBC will especially benefit from MDT discussion and such an approach is recommended for these patients. Figure 7.1 presents a treatment flow chart based on risk category, which may guide management of an individual patient.

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; CT = computed tomography; IVU = intravenous urography; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.9 Treatment of failure of intravesical therapy

7.9.1 Recurrence during or after intravesical chemotherapy

Patients with NMIBC recurrence during or after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillations [285].

7.9.2 Treatment failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any HG disease occurring during or after BCG therapy, have been proposed (see Table 7.2). Non-muscle-invasive BC may not respond at all (BCG refractory) or may relapse after initial response (BCG relapsing). Some evidence suggests that patients with BCG relapse have better outcomes than BCG refractory patients [394].

To be able to specify the subgroup of patients where additional BCG is unlikely to provide benefit, the category of **BCG-unresponsive** tumour was defined. Further BCG instillations in these patients are associated with an increased risk of progression [236, 395]. The category of BCG-unresponsive tumours comprises BCG-refractory and some of BCG-relapsing tumours (see Table 7.2) [396]. The definition was developed in consultation with the U.S. Food and Drug Administration (FDA), in particular to promote single-arm trials to provide primary evidence of effectiveness in this setting [397]. Patients who experience recurrence with high-grade NMIBC after BCG without meeting BCG-unresponsive criteria may benefit from additional BCG therapy. This category of high risk patients that lies between BCG-naïve and BCG-unresponsive NMIBC is termed **BCG-exposed** [398, 399], and includes:

1. BCG-resistant: persistent or recurrent Ta HG and/or CIS disease at three months following at least five of six doses of induction BCG. According to the definition of adequate BCG (table 7.2), these patients have received inadequate BCG.
2. Delayed relapse after inadequate BCG: to indicate Ta/T1 HG or CIS patients found disease free at the three-months evaluation that recur in between 6 and 24 months without receiving more than an induction course.
3. Delayed relapse after adequate BCG: to indicate patients that are disease free after adequate BCG, but subsequently experience a high-grade recurrence outside of the BCG-unresponsive window (>6 mo for Ta/T1 and >12 mo for CIS), up to 24 months.

Non-HG recurrence after BCG is not considered as BCG failure.

Table 7.2: Categories of high-grade recurrence during or after BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1 HG/G3 tumour is present at 3 months [236, 395, 400]. 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [368]. 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 [65, 364, 368]. 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of HG/G3) tumour after completion of BCG maintenance, despite an initial response [401].
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [396].
BCG-exposed tumour [398, 399]
1. If Ta HG/G3 or CIS is present at three months evaluation after induction BCG only 2. delayed relapse after adequate or inadequate BCG
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [337].

** Patients with LG 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.*

7.9.3 ***Treatment of BCG-unresponsive tumours, BCG-exposed tumours, BCG relapses and LG recurrences after BCG treatment***

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Currently, several bladder preservation strategies are being investigated such as cytotoxic intravesical therapies [402-405], device assisted instillations [406-408], intravesical immunotherapy [409, 410], combination therapies (mainly sequential chemotherapies see section 7.4.4.3), systemic immunotherapy [411] or gene therapy [412-414].

A phase III RCT including predominantly high-risk NMIBC patients failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia provided 35% overall DFS at 2 years as compared to 41% in the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at the discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave- induced thermotherapy showed lower response rates in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [408].

Promising data on BCG-unresponsive cohorts of patients with CIS alone or concomitant to papillary tumours were recently reported following new immunotherapies. Systemic pembrolizumab achieved a 40% complete response rate in a prospective phase II study which was maintained in 48% of patients for up to 12 months (n = 101), resulting in FDA approval of the study drug for this patient population [415]. Promising data from a phase III multicentre RCT with intravesical nadofaragene firadenovec showed a complete response in 53.4% of patients with BCG-unresponsive CIS which was maintained in 45% at one year in those who initially responded [416]. A secondary analysis indicates that a combination of post- treatment titres of serum anti–human adenovirus type-5 antibody and fold change from baseline can predict treatment efficacy [417]. Additional ongoing studies are addressing combination of intravesical or systemic immunotherapy [418, 419].

A systematic review and meta-analysis including 4 RCTs and 24 single-arm studies (all currently available prospective studies) assessed bladder-sparing treatments following BCG failure [420]. The significant heterogeneity of both trial designs and patient characteristics included in these studies, the different definitions of BCG failures used, and missing information on prior BCG courses may account for the variability in efficacy for the different compounds assessed across different trials. A higher number of previous BCG courses, BCG refractory/unresponsive or CIS predicted lower response rates. The pooled 12-month response rates were 24% for trials with > 2 prior BCG courses and 36% for those with > 1 BCG courses. Initial response rate did not predict durable responses highlighting the need for longer-term follow-up. More recently, a systematic review assessing 42 prospective trials on bladder-preserving treatments after BCG showed that patients with papillary-only recurrences appeared more effectively treated (median recurrence free rate of 44% at 1 year, median progression-free rate of 89% at a median follow-up of 19 months) than CIS-containing tumours (median complete response rate of 17% at 1 year with a median progression-free rate of 95% at a median follow-up of 12 months), highlighting potential biological differences between these two tumour entities which should be analysed separately when reporting results of clinical trials [421].

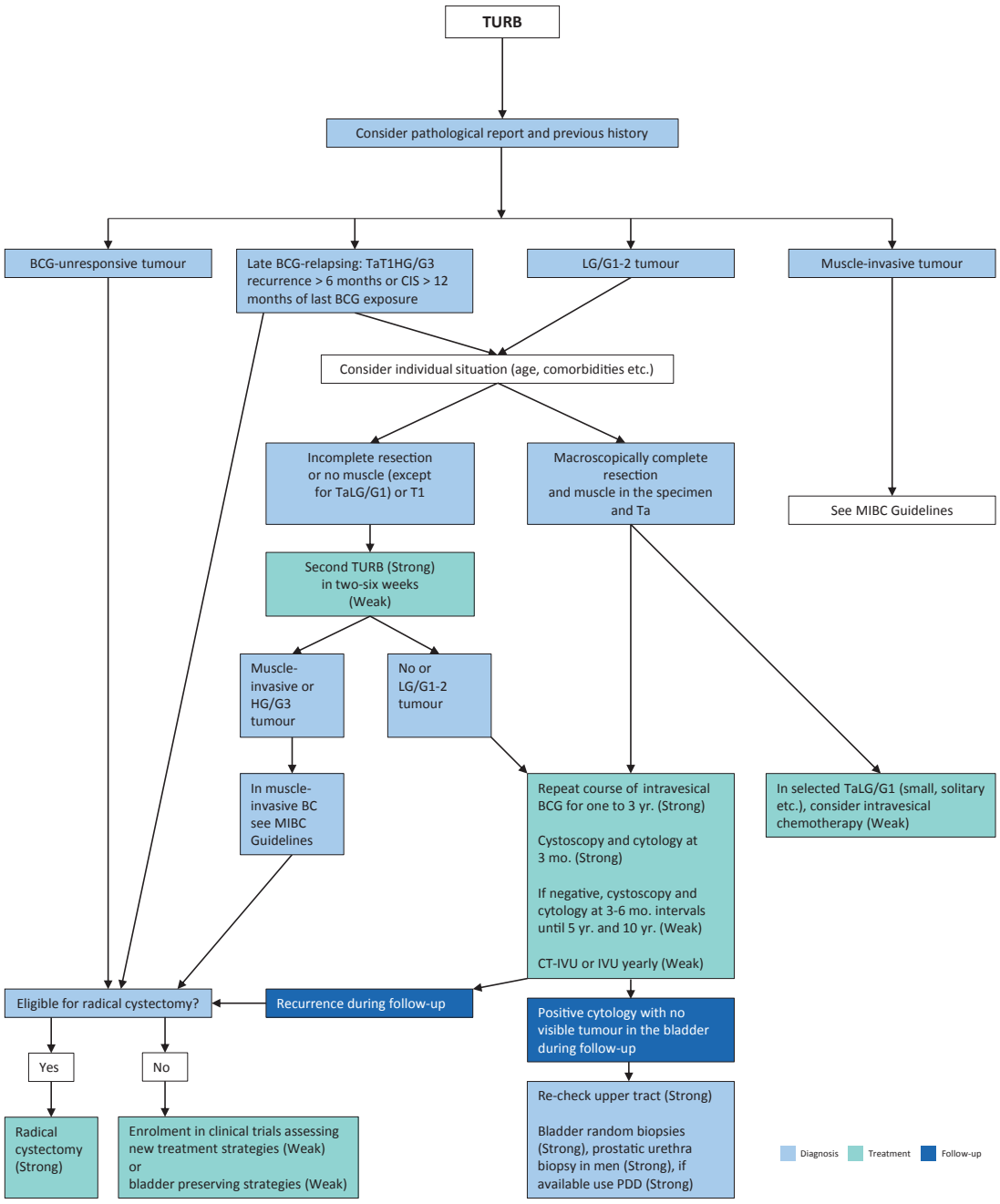
At the present time, treatments other than RC are considered oncologically inferior in patients with BCG-unresponsive disease [236, 395, 400]. Various studies suggest that repeat-BCG therapy is appropriate for non-HG and even for some HG recurrent tumours; namely those relapsing beyond one year after BCG exposure (cases which do not meet the criteria of BCG-unresponsive disease) [399, 422]. BCG exposed patients and late BCG relapses (beyond 24 months) are likely to benefit from further BCG [398, 399].

Treatment decisions in LG recurrences after BCG (which are not considered as any category of BCG failure) should be individualised according to tumour characteristics. Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

7.9.4 ***Summary of evidence - treatment failure of intravesical therapy***

Summary of evidence	**LE**
Prior intravesical chemotherapy has no impact on the effect of BCG instillation.	1a
Treatments other than RC 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.

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

General recommendations	Strength rating
Counsel smokers 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 Section 6.3 and Table 6.1. For determination of a patient's risk group use the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, offer one immediate single chemotherapy instillation.	Strong
Offer post-operative saline or water continuous irrigation of the bladder to patients who cannot receive a single instillation of chemotherapy.	Strong
Patients with small recurrent low-grade Ta tumours can be effectively and safely offered office fulguration.	Strong
Only offer active surveillance to selected patients with presumed low-grade tumours not amendable to endoscopic ablation.	Weak
In patients with intermediate-risk tumours (with or without immediate instillation), offer instillations of chemotherapy (the optimal schedule is not known) or one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months). Chemotherapy is a reasonable first option in the majority of cases; however, the final choice should be made in a shared decision-making process with the patient, reflecting his/her risk of recurrence and progression, as well as the efficacy and side effects of each treatment modality.	Strong
Administer a full-dose intravesical bacillus Calmette-Guérin (BCG) for one to three years in patients with high-risk tumours (a complete BCG schedule comprises an induction phase of six-weekly instillations, followed by a maintenance phase of three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months, respectively). The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and access to BCG. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
Discuss immediate RC in patients with very high-risk tumours. Intravesical full-dose BCG instillations for one to three years remains an option for selected patients, particularly those who decline or are unfit for RC.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra if a bladder sparing strategy is considered.	Weak
Cautiously offer quinolones to treat BCG-related side effects*.	Weak
The definition of 'BCG-unresponsive' should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations.	Strong
Offer a RC to patients with BCG-unresponsive tumours.	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
Discuss high-risk and very high-risk patients within a multidisciplinary board, when possible.	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

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 a minimum of one, and up to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

**The side-effect profile of quinolones and fluoroquinolones resulted in the adoption of European regulation restricting their use [341].*

7.11 Guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification

Recommendations	Strength rating
EAU risk group: Low	
Offer one immediate instillation of intravesical chemotherapy after transurethral resection of the bladder (TURB).	Strong
EAU Risk Group: Intermediate	
In general, chemotherapy (the optimal schedule is unknown) is a reasonable first-line option in the majority of patients. One-year full-dose BCG treatment (induction plus three-weekly instillations at 3, 6 and 12 months), is an alternative option. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than one year after previous TURB.	Strong
EAU risk group: High	
Offer intravesical full-dose BCG instillations for one to three years but discuss immediate radical cystectomy (RC).	Strong
EAU risk group: Very High	
Offer RC or intravesical full-dose BCG instillations for one to three years, particularly to those who decline or are unfit for RC.	Strong

Table 7.3: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC). 2. Enrolment in clinical trials assessing new treatment strategies. 3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG relapsing: TaT1 HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to a patient's individual situation. 2. Bladder-preserving strategies. 3. Enrolment in clinical trials assessing new treatment strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy. 2. Enrolment in clinical trials assessing new treatment strategies.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

Due to the risk of recurrence and progression, patients with NMIBC need follow-up after treatment. The first cystoscopy after TURB at 3 months is an important prognostic indicator for recurrence and progression [230, 235, 250, 253, 423]. Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with TaT1 tumours and CIS. The subsequent frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk. This can be defined by using the EAU NMIBC prognostic factor risk groups (section 6.3, Tables 6.1 and 6.2) or further prognostic models for specific patient populations (section 6) which predict, the short- and long- term risks of recurrence and progression in individual patients (section 8.1) [221, 223]. However, recommendations for follow-up are mainly based on retrospective data and there is a lack of RCTs investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

8.1 Intravesical surveillance during follow-up

*8.1.1 **Follow-up of low-risk NMIBC***

Low-risk group is nearly always low stage and LG/G1. Small, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [252, 424]. In addition, recurrence after 5 recurrence-free years is low [253] (LE: 3). Therefore, in low-risk tumours, after 5 years of follow-up, discontinuation of cystoscopy or its replacement with less invasive methods should be considered [423].

*8.1.2 **Follow-up of intermediate-risk NMIBC***

Patients in the intermediate-risk group carry a risk of progression somewhere in between the low and high risk categories [227]; therefore, the intensity of any follow-up scheme could be adapted in line with this. Based on the safety of a reduced intensity follow-up scheme compared to high-risk NMIBC, in a small RCT on multiple and/or recurrent low grade tumours [425], low-grade intermediate-risk NMIBC can be safely followed-up with a cystoscopy at 3 months and, if negative, with 6 monthly cystoscopies for 2 years followed by yearly cystoscopies up to 10 years. This surveillance scheme for this disease category has already been adopted by the Scottish Access Collaborative Workstream [426]. Due to lack of data supporting the safety of a reduced scheme in the subgroup of high-grade intermediate-risk NMIBC the panel recommend this group be followed-up in the same way of high-risk NMIBC.

*8.1.3 **Follow-up of high- and very high-risk NMIBC***

In tumours originally, high risk, or very high risk treated conservatively the prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial and the percentage of tumours missed should be as low as possible because a delay in diagnosis and therapy can be life-threatening. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology. Recurrences after ten years tumour-free are not unusual [427]. Therefore, the optimal surveillance strategy for these patients includes initial frequent cystoscopy and cytology and life-long follow-up [423].

*8.1.4 **Follow-up of extravesical sites urothelium***

The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders). This risk becomes significant for both sites in high-risk tumours [94], with 10 year tumour rates in UUT varing between 2.8% in CIS [428] and 25% in patients with multiple and recurrent high risk NMIBC [429]. Urine cytology, cystoscopy and CT urography are key investigations for early detection of extravesical recurrence.

*8.1.5 **Aids for tumour detection during follow-up***

8.1.5.1 Enhanced visualisation

There may be a role for newer methods of tumour visualisation in follow-up cystoscopy. In two prospective studies of blue light flexible cystoscopy (BLFC) for surveillance of NMIBC, BLFC allowed identification of 4 to 5.7% of recurrences that would have been missed in case of WL cystoscopy alone [430, 431]. On the other hand, a prospective study of NBI for NMIBC surveillance failed to show any benefit for NBI over WL cystoscopy alone [432].

8.1.5.2 Ultrasound

In patients initially diagnosed with Ta LG/G1–2 BC, US of the bladder and/or a urinary marker may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [133, 433, 434].

8.1.5.3 Urinary molecular markers and urine cytology

Non-invasive follow-up strategies include urine cytology and urinary molecular marker tests as adjunct (or companion) tests to improve detection at the time of flexible cystoscopy or as replacement tests to reduce the number of flexible cystoscopies. Research has been carried out into the usefulness of urinary cytology vs. urinary molecular markers in the follow-up of NMIBC [112, 115, 120, 130, 433, 435]. In order to reduce or replace cystoscopy altogether, urinary markers should be able to detect recurrence in all risk groups. However, the reported low sensitivity for LG recurrences limits their utility in this group [130, 436] although more recent studies have shown reasonable sensitivity in low grade recurrences sensitivity of 40–65% [118, 437]. According to current knowledge, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion. Nonetheless, some urinary markers have shown fairly high sensitivities to detect tumour recurrence, particularly in HG disease, along with very high NPVs to make the premises for their future implementation in follow-up [117, 437-439] (Table 8.1).

Table 8.1: Urinary markers in the surveillance setting*

Marker	Sensitivity overall	HG	Specificity overall	HG	PPV overall	HG	NPV overall	HG	N studies/ patients
XPERT BC® MONITOR	0.72	0.88	0.76	0.75	0.43	0.18	0.92	0.99	10/> 2000
EpiCheck™	0.74	0.91	0.84	0.81	0.48	0.43	0.94	0.98	5/1600
ADX Bladder™	0.57	0.71	0.62	0.76	0.29	0.37	0.82	0.93	3/1600
CX BLADDER	0.91	-	0.61	-	0.16	-	0.98	-	2/1000
FDFGR3+TERT	0.93	-	0.79	-	0.67	-	0.96	-	2/250

**Data extracted from a pooled analyses of systematic review [435].*
HG = high grade; NMIBC = non-muscle-invasive bladder cancer; PPV = positive predictive value; NPV = negative predictive value; n = number.

Table 8.2: Proposed follow-up schedule based on patient's risk category

Risk group	Cytology*	Cystoscopy	Imaging	Duration of follow-up
Low	No	At 3 and 12 months Then annually	Not systematic	5 years
Intermediate (not including HG/G3 subgroup)*	No	At 3 months Then every 6 months for 2 years Then annually	Not systematic	10 years
High and Very High	Yes**	Every 3 months for 2 years Then every 6 months up to 5 years Then annually	CT annually up to 5 years Then CT every 2 years up to 10 years	Life long

**Intermediate-risk HG/G3 subgroup should be followed-up as high-risk*
*** At the same intervals as cystoscopy*

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

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

Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (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 and those with very high-risk tumours treated conservatively 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 annually lifelong.	Weak
Perform cystoscopy at three months for patients with intermediate-risk Ta low-grade tumours. If negative, subsequent cystoscopy can be repeated every six months for two years, and then annually for ten years. The subgroup of intermediate-risk that are high grade should be followed up as high-risk.	Weak
Take regular and long-term upper tract imaging (computed tomography urography) for high-risk and very high-risk tumours.	Weak
Perform endoscopy under anaesthesia and bladder biopsies 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

9. PATIENT REPORTED OUTCOME MEASURES AND QUALITY INDICATORS FOR NMIBC

9.1 PROMS and PREMS in NMIBC

As NMIBC is associated with a significant number of hospital visits and interventions (TURBT, re-TURBT, surveillance cystoscopy, intravesical instillations) survivorship has a significant effect on patient QoL [440, 441]. Several Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) have been developed to gauge the impact of treatment and surveillance on patients with a view to improving quality of care; however, due to lack of standardisation and heterogeneity none of them can currently be recommended for use in clinical practice [442]. Regardless, in order to provide the best possible care, clinicians should always be cognisant of the impact of disease and treatment (including surveillance) on their patients' QoL. The use of PROMs is an important endpoint for quality metrics and RCTs should systematically incorporate PROs for patient-centred research design.

9.2 Quality Indicators (QI) in Bladder Cancer

Evidence based Quality Indicators (QIs) and Quality Performance Indicators (QPIs) are designed to be surrogates of good practice and consequently, outcomes. They allow for the gap between efficacy and effectiveness to be narrowed, i.e. being able to bring research evidence and guideline recommendations into real world practice by improving compliance to them [443]. They also permit objective monitoring of the quality of care and thus facilitate quality control as well as service and process improvements.

Several QIs for bladder cancer have been suggested [444-447]. The table below represents the general and NMIBC related QIs adapted from Leow *et al.*, [446] and the Scottish Quality Performance Indicator (QPI) programme [447]. Quality indicators and QPIs should be SMART (Specific, Measurable, Achievable, Relevant, Trainable) [443]. Scotland introduced such a programme for Bladder Cancer in 2014 [447], and have been an exemplar by being able to demonstrate high levels of compliance to QPIs while reducing practice variation across country whilst also demonstrating the clinical value of such a programme [161], including development of prognostic models [426].

Successful implementation of a QI programme has the potential to inspire and catalyse clinical excellence in contemporary Bladder Cancer practice [443].

Table 9.1: Quality Indicators for general aspects of bladder cancer and NMIBC care adapted from [446, 447].

General aspects of bladder cancer care	Recommended Quality Indicators
Appropriate imaging for patients newly diagnosed with bladder cancer	Newly diagnosed bladder cancer patients who have cross-sectional imaging of upper urinary tract (eg, CT, MRI, or US) - as recommended in section 5.4
Participation in clinical trials	Availability of clinical trials to bladder cancer patients who are treated at a particular health care facility.
Aspects of NMIBC care	**Recommended Quality Indicators**
Pre-operative:	
Counselling	At the time of diagnosis, patients should be counselled to discontinue tobacco smoking.
Intra-operative:	
Tumour/patient history	Use of an Intra-operative checklist (as recommended in Table 5.1)
Conduct of TURBT	Patients with muscle present in specimen from initial TURBT (excluding TaLG disease).
	Use of a Bladder Diagram (as per Figure 5.1)
Re-staging TURBT	Restaging TURBT should be performed within 2–6 wk of the initial TURBT and include resection of the primary tumour site as per recommendations in section 5.13.
Post-operative:	
Risk stratification and surveillance counselling for patients with NMIBC	Use the EAU 2021 Risk Stratification for progression and the 2006 EORTC scoring model for recurrence to counsel patients with NMIBC on treatment and surveillance.
Intravesical therapy	Patients who received immediate post-TURBT instillation of intravesical chemotherapy, excluding those with contraindications (eg, incomplete resection, suspected perforation, significant haematuria).
	Intermediate- and high-risk NMIBC patients who were counselled and subsequently initiated adjuvant intravesical chemotherapy or BCG, respectively.
Multidisciplinary Team management	Patients with high risk and very high risk NMIBC should be discussed in a multi-disciplinary meeting to ensure comprehensive review and options.
Appropriate frequency of surveillance based on stage/grade of bladder cancer	Appropriate intervals between cystoscopic surveillance as per Table 8.2.
	Appropriate assessment of the upper urinary tract in high-risk patients.

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11. 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 open access available on the European Association of Urology website: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/panel.

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

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