EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

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TABLE OF CONTENTS PAGE

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). Unless specified otherwise, the information presented is limited to urothelial carcinoma (UC). 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 (PUC) [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

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

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available online and in print. This reference document is an abridged version that may require consultation together with the full text version. All documents are accessible on the EAU website: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer. An EAU Guidelines App is also available for iOS and Android devices containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, guidelines cheat sheets and links to the extended guidelines.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU Guidelines on NMIBC 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 These 2026 NMIBC Guidelines present a complete update of the 2025 publication.

1.4.2 Summary of changes

For the 2026 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 64 updated studies across the Guidelines. Key changes include:

- Update of Figure 4.1: Schematic representation of tumours according to the WHO 1973, WHO 2004/2022 grading systems and a three-tier and four-tier hybrid combination of the two systems.
- Update of the levels of evidence and recommendations in Section 4.10: Summary of evidence and recommendations for bladder cancer classification
- Update of the summary of evidence and recommendation on cystoscopy in Section 5.9: Summary of evidence and recommendations for the primary assessment of non-muscle invasive bladder cancer.
- Removal and adaption of recommendations in section 5.15: Summary of evidence and recommendations for TURB, biopsies and pathology report.
- Removal and adaption of the summary of evidence and recommendations in section 6.5: Summary of evidence and recommendations for stratification of NMIBC.
- Addition of two new tables summarising the treatment options for BCG-unresponsive tumours. Table 7.3 Papillary Ta/T1 and Table 7.4 Carcinoma *in situ* ± papillary.
- Addition of a new recommendation relating to the addition of sasanlimab and durvalumab to Bacillus Calmette-Guérin (BCG) with maintenance in selected BCG-naive patients with high and very high-risk NMIBC in Section 7.10: Recommendations for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*.
- Update of Table 7.5: Treatment options for the various categories of BCG failure.
- Removal and adaption of the recommendations in Section 8.2: Summary of evidence and recommendations for follow-up of patients after TURB for NMIBC.

2. METHODS

2.1 Data identification

For the 2026 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 carried out. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between 1 May 2024 and 1 May 2025. A total of 773 unique records were identified, retrieved and screened for relevance. To ensure completeness, a number of key studies published after the predefined search cut-off date were also included. A total of 64 new references were added to the 2026 NMIBC Guidelines. A detailed search strategy is available online: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/publications-appendices.

The references used in Chapters 3 through 6 have been assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [4]. For Chapters 7, 'Disease management,' and 8, 'Follow-up of patients with NMIBC,' a system modified from the 2009 CEBM levels of evidence has been used [4].

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 that accompany each guidelines recommendation, addresses a number of key elements:

1. the overall quality of the evidence that exists for the recommendation [4];
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; and
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 [5].

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

2.2 Review

The 2026 publication was peer reviewed prior to publication..

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Bladder cancer is the sixth most commonly diagnosed cancer in the male population worldwide, and it is the ninth when both sexes are considered [6]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.3 in males and 2.4 in females [6]. In the European Union, the age-standardised incidence rate is 23.2 in males and 5.9 in females [6]. Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) is 3.1 for males versus 0.80 for females [6]. 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 [7]. The incidence and mortality of BC has decreased in countries across Asia, Oceania, and the Americas, possibly reflecting the decreased impact of causative factors [8].

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 [9]. 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 [6, 7].

3.2 Aetiology

*3.2.1 **Main risk factors***

3.2.1.a Tobacco

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [7, 8, 10, 11]. 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 (risk ratio [RR]: 2.52; 95% confidence interval [CI]: 2.41-2.64 for ten cigarettes per day; and RR: 3.27; 95% CI: 3.16-3.38 for 20 cigarettes per day) [12]. 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]. Passive exposure to tobacco smoke is also associated with an increased risk of BC [7]. A genome-wide association study reported smoking as a modifiable risk factor for BC [15].

3.2.1.b Occupational exposure

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for approximately 10% of all cases. This type of occupational exposure occurs mainly in industrial plants that process paint, dye, metal, and petroleum products [7, 8, 16, 17]. In developed industrial settings these risks have been reduced by work-safety guidelines. Chemical workers therefore no longer have a higher incidence of BC compared to the general population [7, 16, 17]. Recently, greater occupational exposure to diesel exhaust has been suggested as a significant risk factor (odds ratio [OR]: 1.61; 95% CI: 1.08-2.40) [18]. 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 (a centre for petrochemical industry) had a significantly higher incidence of several cancers, including BC (hazard ratio [HR] 1.11; 95% CI: 1.01-1.23), compared with non-residents [19].

*3.2.2 **Genetic***

Family history appears to have little impact [20]; however, a history of smoking and alcohol consumption seem to significantly increase the risk of BC in patients with a family history of the disease [21]. Lynch syndrome carriers appear to have a higher relative risk of developing BC [22]. A genome-wide association study combining data from three large European cohorts (United Kingdom [UK] Biobank, FinnGen and SIMPLER), including 6,984 BC cases and 708,432 controls, identified 17 susceptibility loci. The study highlighted the key role of detoxification pathways, mainly glutathione S-transferase 1 (GSTM1), in BC aetiology [15]. 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) [7, 23-28], that has been confirmed more recently [29]. A study identified three single nucleotide polymorphisms related to the development of aggressive NMIBC [30]. Currently, there is insufficient evidence to support genetic screening for BC.

*3.2.3 **Dietary habits***

Dietary habits appear to have limited impact on the risk of developing BC. A protective impact for flavonoids has been suggested [31]. 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) [32-36]. A Western diet (high in saturated fats) and consumption of organ meat have been shown to increase the risk of BC in a recent meta-analysis [37, 38]. Increased consumption of fruits has been suggested to reduce the risk of BC. This effect has been shown to be significant only in females (HR: 0.92; 95% CI: 0.85-0.99) [39]. This gender discrepancy was also evident in the BLEND study which showed that in males, 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 females, 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 [40]. In a large multi-ethnic cohort of nearly 186,979 participants with nearly two decades of follow-up, females adhering to higher quality diets, as defined by established dietary indices, had a lower risk of invasive BC [41]. This association was not observed in males. One possible explanation for this gender discrepancy is the difference in the main source of vitamin intake among study participants, being meat in males and fruits/vegetables in females. Other potential reasons include the greater influence of occupational and environmental exposures in males that may outweigh dietary benefits.

In addition, higher consumption of tea has also been associated with a reduction in risk of BC in males but through an interaction with tobacco smoking; therefore, making the protective effect of this compound questionable [42]. At present, no supplement has been found to be associated with BC prevention; however, vitamin E supplementation has been associated with an increased risk of recurrence [43]. Considering patients with previous history of BC, preliminary results suggest that a dietary intervention based on cruciferous vegetables, leading to an increased level of isothiocyanates, might be beneficial in reducing the risk of recurrence and progression [44]. At present, there is no definitive evidence for the impact of diet on BC development or prevention.

*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 [45]. Additionally, exposure to arsenic in drinking water has been suggested to increase the risk of BC [7, 46]. Arsenic intake and smoking have a combined effect [47]. Conversely, chronic exposure to nitrate in drinking water does not appear to be associated with increased risk of BC [48].

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 [7], but a large prospective cohort study could not identify an association between hair dye and risk of cancer and cancer-related mortality [49].

*3.2.5 **Pelvic radiation***

Exposure to pelvic ionising radiation is associated with an increased risk of BC [50, 51]. 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 (HR: 1.35; OR: 1.18-1.55) [50]. 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 [51].

*3.2.6 **Other***

The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol and triglycerides) remains uncertain [52]. A genome-wide association study reported abdominal obesity (waist-to-hip ratio) as a modifiable risk factor for BC [15]. Whereas other data suggest that high circulating levels of vitamin D and physical exercise are associated with a reduction in the risk of BC [15, 53, 54]. Schistosomiasis, an infection caused by a parasitic trematode, can lead to BC [7]. A weak association was also suggested for cyclophosphamide and pioglitazone [7, 46, 55].

Table 3.1: Risk factors for bladder cancer

Nature of Risk Factor	Risk Factors	Causality vs. Association
Modifiable	Tobacco smoking, including passive smoking	Causality established
	Occupational exposure: Aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons for e.g. industrial plants which process paint, dye, metal, and petroleum products	
	Diet: • Protective: Flavonoids, mediterranean diet, cruciferous vegetables, fruits*, vitamin B*, high quality diet defined by established dietary indices* • Increased recurrence risk: Vitamin E	Association
	Exercise	
	Obesity (waist-to-hip ratio)	
Non-modifiable	Genetics • 17 susceptibility loci • Detoxification pathways, mainly glutathione S-transferase 1 (GSTM1)	Association

Partly Modifiable	Schistosomiasis	Causality established
	Environmental factors: Chlorination and arsenic exposure to drinking water	Association
	Pelvic radiation	
	Drugs: • Cyclophosphamide • Pioglitazone	

Table 3.1 summarises the main bladder cancer risk factors stratified into modifiable, non-modifiable, and partly modifiable risk categorised according to the existence of an established causality or a mere association with the disease.
** Reported to be protective only in females.*

3.3 Summary of evidence for epidemiology and aetiology

Summary of evidence	LE
Worldwide, BC is the ninth 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 [56]. 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 tumour (TURBT), eventually in combination with intravesical instillations, and are therefore grouped under the heading of NMIBC for therapeutic purposes. The term 'non-muscle-invasive bladder cancer' 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, because it is incorrect.

4.2 Tumour, Node, Metastasis classification

The guidelines refer to the latest TNM classification approved by the Union International Contre le Cancer (UICC) 9th Edn. (Table 4.1) [57].

Table 4.1: 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 [56, 58]. Its use is advised by the most recent 2022 World Health Organization (WHO) classification [59, 60]. 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 [61, 62].

4.4 Lymphovascular invasion

The presence of lymphovascular invasion (LVI) in TURBT specimens is associated with an increased risk of pathological upstaging and worse prognosis [63-67]. Immunohistochemistry for confirmation is not mandatory [59].

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 incorporated into the updated 2016/2022 WHO classifications [59, 60]. The system 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 [61, 68].

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) [69, 70]. According to a multi-institutional individual patient data (IPD) analysis, the proportion of tumours classified as PUNLMP (WHO 2004/2016) has decreased to very low levels in the last decade [71].

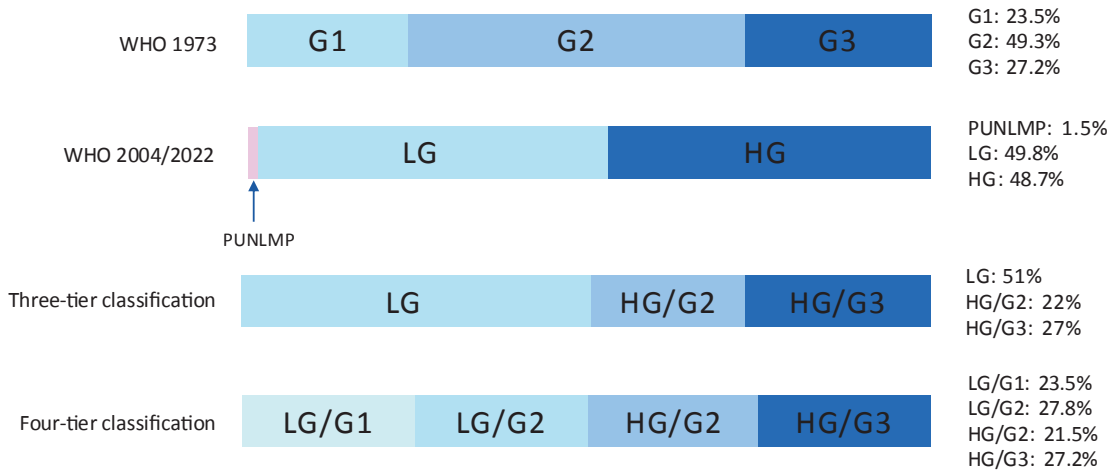
4.5.2 Prognostic value of histological grading

A systematic review and meta-analysis did not show that the 2004/2016 WHO classification outperforms the 1973 classification in prediction of recurrence and progression [69]. To compare the prognostic value of both WHO classifications, an IPD analysis of 5,145 primary TaT1 NMIBC patients from 16 centres throughout Europe and one in Canada was conducted. Patients had a 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 three-tier (LG/G1-G2, HG/G2 & HG/G3) hybrid combination [72] of both classification systems separating HG into HG/G2 and HG/G3 or a four-tier (LG/G1, LG/G2, HG/G2 and HG/G3) classification systems [73] that divides the large group of G2 patients into two subgroups (LG/HG) proved to be superior to either classification system alone (Figure 4.1) [74]. In a subgroup of 3,311 patients with primary Ta bladder tumours, a similar prognosis was found for PUNLMP and Ta LG carcinomas [71].

4.5.3 *Clinical application of histological grading systems*

- The WHO currently supports the WHO 2004/2022 classification system for clinical application. Nevertheless, the WHO 1973 is still being used.
- The most important parameters that must be considered for clinical application of any grading system are the classification system's 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 the WHO 1973, WHO 2004/2022 grading systems and a three-tier and four-tier hybrid combination of the two systems



The percentages refer to the rate of each grade for the WHO 1973, the WHO 2004/2022 and the corresponding calculated three-tier and four-tier systems in a multicentre cohort of 5,145 primary Ta, T1 NMIBC patients.
G = grade; HG = high-grade; LG = low-grade; PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organization.

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, prostatic ducts and urethra [75].

From a clinical point of view, CIS can be classified as [76]:

- 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

Significant variability exists among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70-78% of cases [77]. Inter-observer variability is also seen in the classification of stage T1 versus Ta tumours and tumour grading in both the 1973 and 2022 WHO classifications. The general conformity between pathologists in staging and grading is 50-60% [78-81]. The 2004/2022 WHO classification provides slightly better reproducibility than the 1973 classification [69].

4.8 Subtypes of urothelial carcinoma

The following differentiations of UC are currently used [82, 83]:

- Pure UC (more than 90% of all cases)
- UC with partial (squamous-glandular or trophoblastic) divergent differentiation
- UC with micropapillary differentiation
- UC with nested/microcystic differentiation
- UC with microtubular differentiation
- UC with large, nested differentiation
- UC with plasmacytoid differentiation
- UC with lymphoepithelioma-like differentiation
- UC with giant cell, diffuse, undifferentiated differentiation
- UC with sarcomatoid differentiation

- Some UCs with other rare differentiations, for example, clear cell differentiation
- UCs with partial neuroendocrine (NE) (NE differentiation, % to be given)
- Pure NE carcinoma (including small and large cell NE carcinomas)

In the new 2022 WHO classification, all subtypes are considered HG [60]. Up to 14.6% of NMIBC may harbour a urothelial subtype [84]. The percentage of subtype in the specimen should be reported since it has been shown to be of prognostic value [85]. The 2022 WHO classification considers all subtypes UC (LG and HG) with more than 5% of HG as a HG tumour [2, 85-92]. Clinical implications of urothelial subtypes are discussed in Section 6.3.

4.9 Tumour markers and molecular classification

Tumour markers and their prognostic role have been investigated [93-97]. 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 [62, 98, 99].

4.10 Summary of evidence and recommendations for bladder cancer classification

Summary of evidence	LE
The depth of invasion (staging) is classified according to the TNM classification.	2b
Tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, HG tumours that are confined to the mucosa are classified as CIS (Tis).	2b
Histological grading of urothelial NMIBC is classified according to the 2004/2016/2022 WHO (PUNLMP, LG/HG) systems and/or 1973 WHO (G1-G3).	2b
The 2004/2016/2022 WHO classification provides slightly better reproducibility than the 1973 classification.	3
Both the 1973 WHO and the 2004/2016/2022 WHO classification systems are prognostic for progression, but not for recurrence.	3
The 1973 WHO is a stronger prognosticator of progression in TaT1 NMIBC than the 2004/2016 WHO. However, a three-tier hybrid (LG/G1-G2, HG/G2 and HG/G3) or a four-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.	3

Recommendations	Strength rating
Use the 2025 Tumour, Node, Metastasis system for classification of the depth of tumour invasion (staging).	Strong
Use the 2004/2022 World Health Organization grading classification systems. If available, use a hybrid system based on both the 1973 and 2004/2022 WHO grading classification systems.	Strong
Do not use the term ‘superficial’ bladder cancer.	Strong

5. DIAGNOSIS

5.1 Patient history

A focused patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher stage at diagnosis disease compared to nonvisible haematuria [100]. 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 [101, 102].

Intravenous urography (IVU) is an alternative if CT is not available [103], but CT urography provides more information particularly in muscle-invasive tumours of the bladder and in UTUCs (including status of lymph nodes and tumour involvement of 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 that can be obtained [104-106]. The incidence of UTUCs is low (1.8%) but increases to 7.5% in tumours located in the trigone [105]. The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [107].

*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. Ultrasound 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 [108, 109]. It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

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

Multi-parametric magnetic resonance imaging (mpMRI) might provide additional information regarding the local staging of BC. A standardised methodology of magnetic resonance imaging (MRI) reporting (Vesical Imaging-Reporting and Data System [VI-RADS]) in patients with BC has been developed [110]. A systematic review showed that a VI-RADS score of ≥ 4 had a pooled weighted sensitivity of 0.78 and specificity of 0.94 in predicting MIBC, with high reliability across different centres with varying experience [111]. A diagnosis of CIS cannot be made using imaging methods alone (CT urography, IVU, US), including mpMRI [112].

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG/G3 tumours (84%), but low sensitivity in LG/G1 tumours (16%) [113]. The sensitivity in CIS detection is 28-100% [114]. A recent report applying the Paris system found a sensitivity of 46% for HG disease [115]. 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; however, negative cytology does not exclude its presence.

Cytological interpretation is user-dependent [116, 117] and evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations; although in experienced hands specificity exceeds 90% [118]. Artificial intelligence (AI) algorithms combined with digital image processing (VisioCyt test) improved the sensitivity of cytology for HG tumours by up to 92% [119].

A standardised reporting system known as The Paris System, published in 2022 (2nd Edn.), redefined urinary cytology diagnostic categories and full category names should always be cited [120]:

- 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 underscore 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 [121, 122]. A prospective study suggests that voided urine cytology can be used to risk-stratify patients with NMIBC prior to TURBT, i.e. voided urine cytology negative for HG exhibits high specificity for LG disease (93%) while a positive result for HG predicts HG disease with a 92% specificity and 91% positive predictive value (PPV) [123].

Urine collection should respect the recommendations provided in Section 5.9. One cytospin slide from the sample is usually sufficient [120]. In patients with suspicious cytology, repeat investigation is advised because the underlying risk of a HG lesion is between 24 and 53% [124].

5.6 Urinary molecular marker tests

The implementation of the Paris System when reporting urinary tract cytology has improved detection of HG tumours and therefore its utility in these patients. Numerous urinary molecular marker tests have been developed [125, 126]; however, none of these markers have been accepted in routine practice by any clinical guidelines for diagnosis (see Section 5.7). For follow-up, two randomised controlled trials (RCTs) have suggested a role for urinary marker tests in patients (see Chapter 8) [127, 128].

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

- Sensitivity is usually higher at the cost of lower specificity compared to urine cytology [120].
- Benign conditions and previous Bacillus Calmette-Guérin (BCG) instillations may influence the results of many urinary marker tests [129].
- Requirements for sensitivity and specificity of a urinary marker test depend largely on the clinical context of the patient (screening, primary detection, follow-up [high-risk, low/intermediate-risk]) [120].
- Several commercially available urinary biomarkers, assessing multiple targets to increase sensitivity, have been tested in prospective multicentre studies [130-134].
- 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®, mutations in Fibroblast Growth Factor Receptor 3 (*FGFR3*) or Telomerase Reverse Transcriptase promotor (*TERT*) gene and microsatellite analysis may identify patients more likely to experience disease recurrence and possibly progression [135-142].
- Practical and cost-effectiveness dimensions and certification of *in vitro* diagnostics (CE-IVD) should be considered before clinical implementation of urinary molecular marker tests [143].

5.7 Potential application of urinary cytology and markers

The following sections indicate the clinical contexts in which urine cytology and/or other urinary markers have been assessed.

5.7.1 Screening of the population at risk of bladder cancer

The application of haematuria dipstick, followed by assessment of several urine markers (a reflex-test assessing *FGFR3*-mutations, microsatellite analysis, (NMP)22®, and multiplex ligation probe amplification methylation detection in urine) in case of positive dipstick has been reported in BC screening in high-risk populations [144]. However, the low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness of BC screening [138, 144]. Therefore, routine screening for BC is not recommended [138, 144, 145].

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 [146]. In addition, Xpert Bladder® had higher

sensitivity and negative-predictive value than either cytology or UroVysion™ for the detection of BC in patients with haematuria [147]. A randomised trial showed that in patients presenting with lower risk micro-haematuria (defined as 3 to 29 RBC/hpf and minimal smoking history), the use of Cxbladder Triage showed a 90% sensitivity compared to cystoscopy and resulted in a 59% reduction in cystoscopy use [148]. However, this study is limited by the lack of a confirmatory cystoscopy examination in 57% of the patients and the low specificity of the marker (56%).

*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 NMIBC is discussed in Chapter 8.

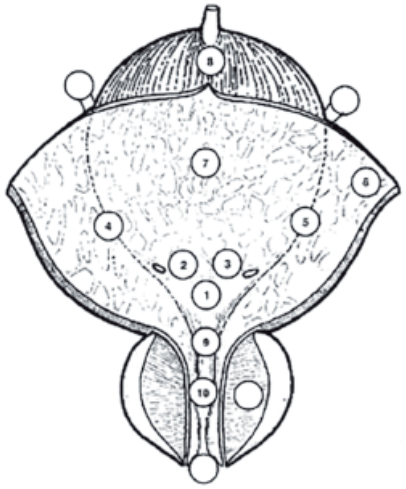
5.8 Cystoscopy

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 based on cystoscopy and urine cytology and confirmed by histological evaluation of multiple bladder biopsies [149].

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 male patients [150, 151]. Tissue sampling can be obtained using biopsy forceps introduced via a flexible cystoscope [152].

Two randomised trials, both including male patients only, showed that the irrigation 'bag squeeze' technique (applying pressure to open the urethral sphincter to gain access to the bladder) could significantly reduce pain during the flexible cystoscopy procedure [153, 154]. Moreover, several randomised trials and a meta-analysis have shown that listening to music during cystoscopy reduces procedural pain and anxiety [155-157].

Figure 5.1: Bladder diagram



1 =Trigone	6 = Anterior wall
2 = Right ureteral orifice	7 = Posterior wall
3 = Left ureteral orifice	8 = Dome
4 = Right wall	9 = Neck
5 = Left wall	10 = Prostatic urethra

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

Summary of evidence	LE
Cystoscopy with or without biopsy confirmation is necessary for the diagnosis of BC.	1
Urinary cytology has high sensitivity in HG tumours, including CIS.	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 (CT) urography during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g. tumours located in the trigone, or multiple- or high-risk tumours).	Strong

If a magnetic resonance imaging (MRI) is performed for local staging of bladder cancer (BC), it should be done before transurethral resection of bladder tumour (TURBT).	Strong
Perform cystoscopy with or without biopsy confirmation in patients with symptoms suggestive of BC. It cannot be replaced by cytology or by any other non-invasive test.	Strong
Use a flexible cystoscope, if available, in both males and females. In male patients, 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 (see 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 due to 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 TURBT 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 (see Section 5.14) [158, 159].

The operative steps necessary to achieve a successful TURBT 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) [158, 160]. Bi-manual examination may provide critical information on bladder mobility and potential infiltration of adjacent structures, such as the rectal wall in males or the vagina and urethra in females. In a single centre prospective study, bi-manual examination correctly predicted final ypT stage in 80% of the cases and provided prognostic information on surgical margin status [161].

Documentation of cystoscopic tumour characteristics and consequent clinically predicted tumour grade and stage can help assign patients to post-TURBT single instillation (SI) of chemotherapy (LG non-invasive) and muscle-invasive cancers to be fast tracked to definitive treatment [162]. To measure the size of the largest tumour, the end of the cutting loop, which is approximately 1 cm wide, can be used as a reference. Tumour architecture can be sessile, nodular, papillary, mixed papillary/solid or flat. Documentation of the severity of complications, such as bladder perforation using a standardised approach, may allow for better comparison between surgical techniques and quality control [163].

*5.10.2 **Surgical and technical aspects of tumour resection***

5.10.2.a 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 [159, 164]. The following subsections describe each of these techniques.

Piecemeal resection

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 [165]. To facilitate better pathological assessment of detrusor muscle, it is ideal for the tumour base to be sent separately.

***En-bloc* resection**

En-bloc resection using monopolar or bipolar current or lasers is feasible in selected exophytic tumours, particularly those with tumour size of ≤ 3cm [166]. This procedure aims to uphold basic oncological principles by avoiding tumour fragmentation and ensuring complete tumour resection with clear margins [167]. *En-bloc* resection also aims to provide high-quality resected specimens with the presence of detrusor muscle [159, 168-175]; however, its superiority over conventional TURBT remains debatable [176, 177]. Detrusor muscle sampling rates were no different between these techniques in a systematic review of 1,142 patients [178], and in a single centre RCT showing similar detrusor muscle sampling rates of 95% between conventional TURBT and *en-bloc* resection [176]. Conversely, two systematic reviews of 4,484 and 2,097 patients, respectively, revealed higher detrusor muscle sampling rates in favour of *en-bloc* resection [168, 179]. A further *post-hoc* analysis of

this RCT showed that the combination of an *en-bloc* resection plus BCG was associated with lower one year recurrence rates over conventional TURBT plus BCG (5%; 95% CI: 0-14% vs. 26%; 95% CI: 5.8-42%; p = 0.056) [180], suggesting that good-quality surgery plus good adjuvant therapy (see Section 7.4) are both important in optimising the oncological outcomes of NMIBC.

Respect for tumour architecture increases the accuracy of T1 staging and the possibility of sub-staging while potentially reducing the risk of bladder perforation [168, 173-176]. With regard to oncological outcomes, two RCTs did not reveal a difference in time to recurrence between *en-bloc* resection and conventional TURBT [176, 177]. This has also been shown in two systematic reviews [168, 178]. However, in an RCT comparing *en-bloc* resection and conventional TURBT in patients with tumours ≤ 3 cm, *en-bloc* resection resulted in a significant reduction in one-year recurrence rate (38.1% to 28.5%). Upon subgroup analysis, patients with 1-3 cm bladder tumour, single tumour, Ta disease or intermediate-risk NMIBC had a significant benefit from *en-bloc* resection. There were no apparent differences in rates of progression nor complications [181].

The technique selected depends on the size and location of the tumour, and the 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 3 cm [166]. 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.b 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 [182]. The presence of detrusor muscle in the specimen is considered as a surrogate criterion of the resection quality [182] and is required (except in Ta LG/G1 tumours). Surgical checklists and quality performance indicator (QPI) programmes have been shown to increase surgical quality (accurate documentation of factors required to assign risk and sample detrusor muscle) and decrease recurrence rates [158, 160, 183-185]. More recently, it has been shown that achieving quality benchmarks for sampling detrusor muscle and single post-TURBT instillation of Mitomycin-C in 2,688 patients were associated with lower recurrence and progression rates when compared to not achieving these benchmarks [186]. The Panel have included a sample TURBT checklist in Table 5.1 and reported quality indicators (QIs) for the procedure in Table 9.1.

It has been shown that surgical experience can improve TURBT results, which supports the role of teaching programmes [182, 187]. Virtual training on simulators is an emerging approach [188]. Its role in the teaching process still needs to be established [158]. Surgical experience and/or volume has been associated with risk of complications [189], recurrence [190] and survival [191] in retrospective studies. Despite a relatively low overall rate of detrusor muscle 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%) versus 'experts' (50.6%) whose utilisation of checklists was lower [158, 185].

5.10.2.c 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 [192-194], with significant inherent limitations due to selection bias, heterogeneity of surgical approach, or inability to qualify surgeon experience. A systematic review of 13 RCTs (n = 2,379) showed no benefit of bipolar versus monopolar TURBT for efficacy and safety [194] while one meta-analysis of RCTs (n = 2,099) suggests a lower fall in haemoglobin and shorter hospital stay with bipolar resections [192] and another systematic review of RCTs and observational studies (n = 19,927) suggests lesser thermal artifacts in the specimen [193]. A single centre randomised trial revealed a higher detrusor sampling rate in bipolar compared with monopolar TURBT, but with no difference in longer term recurrence rate [195, 196].

5.10.2.d Resection of small papillary bladder tumours at the time of transurethral resection of the prostate

It is not uncommon to incidentally detect bladder tumours during transurethral resection of the prostate (TURP) in males with benign prostatic hyperplasia. Resecting these tumours and continuing with the resection of the prostate appears feasible, provided these tumours are papillary, rather small, and not extensively multifocal [197, 198]. Simultaneous TURBT and TURP does not appear to lead to any increased risk of tumour recurrence or progression [199]. Whilst most reports have suggested surgeons prefer to undertake saline irrigation following the combined TURBT and TURP, postoperative SI of chemotherapy also appears to be feasible and safe, provided there is no capsular or bladder perforation [200].

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 [201, 202]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [201, 202]. 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 males with NMIBC has been reported. The incidence of CIS in the prostatic urethra was shown to be 11.7% in 128 males with T1 G3 UC [203]. 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 with multiple tumours [204]. Based on this observation, a biopsy from the prostatic urethra is necessary in some cases [203, 205, 206]. Biopsies should preferably be from the pre-collicular area (between the 5 and 7 o'clock position next to the verumontanum) using a resection loop.

5.12 New methods of tumour visualisation

As a standard procedure, cystoscopy and TURBT 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 (5-ALA) or hexaminolaevulinic acid (HAL).

5.12.1.a 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 [207, 208]. In a systematic review and meta-analysis, PDD had higher sensitivity than WL endoscopy in the pooled estimates of analyses at both patient (92% vs. 71%) and biopsy-level (93% vs. 65%) [208]. A prospective RCT did not confirm a higher detection rate in patients with known positive cytology before TURBT [209].

Photodynamic diagnosis had lower specificity than WL endoscopy (63% vs. 81%) and it does not help to rule out prostatic involvement [208]. False-positivity can be induced by inflammation or recent TURBT and during the first three months after BCG instillation [210, 211].

5.12.1.b Impact on bladder cancer recurrence

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURBT was evaluated. A systematic review and meta-analysis of 14 RCTs including 2,906 patients, six using 5-ALA and 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 inconsistencies between trials and potential susceptibility to performance and publication bias [212]. Another systematic review and meta-analysis of 12 RCTs (n = 2,288) revealed, with moderate certainty, that PDD is associated with lower risk of recurrence and improved time to recurrence (at least in the first two years and possibly up to five years) [213]. The most recent Cochrane systematic review and meta-analysis of 16 RCTs (n = 4,325) suggested a favourable impact of PDD-assisted TURBT on the risk of recurrence and progression, albeit with low certainty of evidence [214]. These findings are consistent with a systematic review and meta-analysis of 12 RCTs involving 2,775 patients that confirmed a reduced risk of recurrence and progression, but no significant difference in time to first recurrence and residual tumour rate [215].

Contrary to previous evidence, a multicentre RCT from the UK showed that PDD-guided TURBT did not reduce recurrence rates, nor was it cost-effective compared with WL cystoscopy at three years [216].

In conclusion the abovementioned studies highlight the need for further investigation to better elucidate the impact of PDD on recurrence. Further studies should also consider that long-term recurrence rates are influenced by adjuvant treatment and not solely by the initial surgery.

*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 means of NBI-flexible cystoscopy and NBI-guided biopsies and resection [217-220]. Two RCTs assessed the reduction of recurrence rates if NBI is used during TURBT [220, 221]. Although the overall results were negative, a benefit after three and 12 months was observed for low-risk tumours (pTa LG, < 30 mm; no CIS) [221].

A systematic review and meta-analysis including 17 RCTs and non-RCTs demonstrated improved detection (diagnostic accuracy) of bladder tumours with either PDD or NBI over WL cystoscopy [222], while another study (n = 5,217) showed improved recurrence-free survival (RFS) with either enhancement technique [223]. Conversely, a systematic review and network meta-analysis that took into account the use of single postoperative instillation of chemotherapy, concluded that there was a lower likelihood of recurrence at one year only following PDD-guided TURBT (with or without SI) but not with NBI-guided surgery [224].

*5.12.3 **IMAGE1 S™, and other technologies***

IMAGE1 S™ (formerly named SPIES) is an image enhancement system based on computerised processing of different colour components using specific light filters. Thus far, limited evidence has been produced to validate the four different light spectra modalities, suggesting an improvement in the diagnostic accuracy of WL [225, 226]. Early follow-up data of RCTs failed to show an advantage in recurrence rate for the IMAGE1 S™ arm over WL, except in a subgroup of primary low- and intermediate-risk NMIBCs at 12 and 18 months, respectively [227, 228].

Confocal laser micro-endoscopy is a high-resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [229].

5.13 Second resection (second TURBT)

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

The significant risk of residual tumour after initial TURBT of TaT1 lesions has been demonstrated [164]. This residual cancer has the potential to worsen oncological outcomes and therefore further emphasises the importance of an effective initial TURBT. As patients with an initial incomplete TURBT (either from extensive tumour or intra-operative complications) will require a second complete resection, documentation of resection completeness at the time of the initial TURBT is essential.

The main purposes of a second TURBT 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 [230]. Conversely, a more contemporary systematic review and meta-analysis including 81 studies showed that, in patients with T1 disease, the pooled rates of any residual disease and upstaging were lower (particularly in cohorts from the 2010s) at 31.4% and 2.8%, respectively. *En-bloc* resection and visually-enhanced TURBT significantly improved residual tumour rates at repeat TURBT [231].

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 TURBT remained high even in a subgroup with detrusor muscle sampled at the initial TURBT. In a subgroup of 1,565 patients with T1 tumours with detrusor muscle present, persistent tumour was found in 58% and under-staging occurred in 11% of cases [232].

Prospective trials suggest that postoperative positive urine cytology [233] and Xpert Bladder® (urine messenger ribonucleic acid test) [234] are independently associated with residual disease at second resection and risk of future recurrences, respectively. However, these data need to be confirmed in further studies. Currently, MRI cannot replace re-TURBT (see Section 5.4.3) [112].

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

A second TURBT can increase RFS [235-237], improve outcomes after BCG treatment [238] and provide prognostic information [239-242].

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 [243]. 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 cancer-specific survival [CSS]) was better in patients who underwent second resection [191]. 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 RFS and PFS survival benefit in 104 out of 209 HG Ta patients who underwent a second TURBT, only one case was upstaged to T1 disease, and none to T2 or more [244]. From a contemporary systematic review and meta-analysis of 81 studies, patients undergoing repeat TURBT had better RFS (HR: 0.78; 95% CI: 0.62-0.97) and OS (HR: 0.86; 95% CI: 0.81-0.93). However, there was no difference in PFS and CSS [231]. Based on the available retrospective evidence, the Panel advises that after a macroscopically complete initial TURBT, a second resection should be performed in any T1 disease and in Ta HG disease where muscle is absent from the primary specimen (see recommendations in Section 5.15). Of note, Ta HG-patients undergoing re-TURBT based on EAU Guidelines recommendations demonstrated significantly lower RFS and PFS compared with those who did not [244].

*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 [245]. Based on this currently available evidence, a second TURBT, when indicated, is recommended within a pragmatic time period of two to six weeks after initial resection [245] (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 TURBT. Since the goal is to improve the quality of the initial TURBT, the results of the second resection should be recorded.

5.14 Pathology report

Pathological investigation of the specimen(s) obtained by TURBT and biopsies is an essential step in the decision-making process for BC [246]. Close cooperation between urologists and pathologists is required. Clinical information and high quality of resected and submitted tissue are essential for correct pathological assessment. To obtain all relevant information, the specimen collection, handling and evaluation should respect the recommendations provided below (see Section 5.15) [247]. In stage T1 and higher or for difficult cases, an additional review by an experienced genitourinary pathologist can be considered [79, 248, 249].

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 required
Decide irrigation fluid	Saline, glycine, water
Disease characteristics checklist	History of BC, tumour characteristics at cystoscopy if any, imaging results if any, first or second look, visual optimisation planned, risk classification
Cystoscopy/TURB	
Cystoscopy	Urethra/prostate (males)
	Ureteral orifices
	Diverticula
	Tumour location, number, size, appearance (papillary/sessile), CIS (yes/no)
	Tumour visualisation methods, if used
	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 (based on blood count results, if required)
	Intra-operative complications, if any
	Intravesical therapy, if given or planned in recovery setting

**Adapted with permission from Mostafid et al. and Suarez-Ibarrola et al. [158, 250].*
BC = bladder cancer; CIS = carcinoma in situ; TURBT = transurethral resection of the bladder tumour.

5.15 Summary of evidence and recommendations for TURBT, biopsies and pathology report

Summary of evidence	**LE**
Transurethral resection of the bladder tumour 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 TURBT can detect residual tumours and tumour under-staging, increase RFS, improve outcomes after BCG treatment and provide prognostic information.	2
Photodynamic diagnosis has been shown to improve the detection of BC, especially CIS.	1a

Recommendations	**Strength rating**
Perform a transurethral resection of the bladder tumour (TURBT) followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step in patients suspected of having bladder cancer (BC).	Strong
Perform TURBT 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; • thorough 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; and • precise description of the specimen(s) for pathology evaluation.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions.	Strong
Avoid cauterisation as much as possible during TURBT 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 fluorescence-guided (photodynamic diagnosis [PDD]) biopsies, in case of normal upper tract on contrast computed tomography, normal-looking urothelium at cystoscopy, 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 carcinoma *in situ* (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 during TURBT, 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 TURBT 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 TURBT in the following situations: • after incomplete initial TURBT, or in case of doubt about completeness of a TURBT; • if there is no detrusor muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS; or • in T1 tumours.	Strong
If indicated, perform a second TURBT within two to six weeks after the initial resection. This second TURBT should include resection of the primary tumour site.	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 the patient's risk of recurrence and prognosis. 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 1973 WHO classification system

6.1.1.a The 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model

In 2006, the EORTC Genito-Urinary Cancer Group (GUCG) published a scoring system and risk tables, based on the 1973 WHO classification, to be able to predict both the short- and long-term risks of disease recurrence and progression in individual patients [251]. This scoring system is based on the six most significant clinical and pathological factors in patients mainly treated by intravesical chemotherapy, which are:

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

Individual probabilities of recurrence and progression at one and five years may be calculated using the 2006 EORTC scoring model (https://www.omnicalculator.com/health/eortc-bladder-cancer).

6.1.1.b Prediction model for patients with Ta G1/G2 (1973 WHO) tumours treated with chemotherapy

Patients with Ta G1/G2 tumours receiving chemotherapy were stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (1973 WHO), number of tumours and adjuvant chemotherapy [252].

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

The Spanish Urological Oncology Group, CUETO, published a model that predicts the risk of recurrence and progression based on 12 doses of intravesical BCG over a five- to six-month period following TURBT. The model is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. No immediate postoperative instillation or second TURBT was performed in these patients. The scoring system is based on the evaluation of the following seven prognostic factors:

- gender
- age
- prior recurrence status
- number of tumours
- T category
- associated CIS
- 1973 WHO 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 [253]. 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 [254] and by long-term follow-up in another patient population [255].

6.1.1.d The 2016 EORTC scoring model for patients treated with maintenance BCG

In 1,812 intermediate- and high-risk patients without CIS treated with one to three years of maintenance BCG, the EORTC found that the prior disease-recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and 1973 WHO grade for disease progression and disease-specific survival, while age and 1973 WHO grade were the most important prognostic factors for OS. T1 G3 patients did poorly, with one- and five-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 [256].

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

6.1.2.a EAU NMIBC 2021 scoring model

To update the risk of disease progression and create new prognostic factor risk groups using both the 1973 and 2004/2016 WHO classification systems, IPD from 3,401 primary patients treated from 1990 to 2018 were used [257] (see Section 4.5). Only patients treated with TURBT ± 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, 1973 WHO grade, 2004/2022 WHO grade, concomitant CIS, number of tumours, tumour size and age were independent predictors of disease progression [257].

This is the only available model where the 2004/2022 WHO classification system is included as one of the parameters to calculate an individual patient's risk group and probability of progression. As the 2004/2022 WHO classification system is the main grading classification system used by pathologists, the Guidelines Panel recommends using the 2021 EAU NMIBC scoring model for risk groups definition (see Section 6.4).

The 2021 EAU NMIBC scoring model determines the risk of tumour progression (in a non-BCG treated cohort, thus reflecting the natural history of the disease), but not recurrence; therefore, any of the models mentioned in Section 6.1.1 may be used to calculate an individual's risk of disease recurrence.

6.1.3 Further prognostic factors

Additional 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 male patients treated with an induction course of BCG, age, tumour size, and concurrent CIS in BCG-treated patients (62% with an induction course only) [203, 258].
- 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 [259].
- In patients with T1 tumours, the finding of residual T1 disease at second TURBT is an unfavourable prognostic factor [240-242].
- 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 [255, 260].

6.2 Primary carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [261]. No reliable prognostic factors are available, but some studies reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [262, 263], in extended CIS [264] and in CIS in the prostatic urethra [203]. The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [253, 254, 265].

6.3 Histological subtypes

Bladder cancer is primarily composed of UC, but various histological subtypes exist, each carrying unique prognostic implications (see Section 4.8) [266]. Understanding the differences between these subtypes is critical for risk stratification, as their biological behaviour can differ significantly from conventional UC.

While most UC cases exhibit typical papillary architecture, certain subtypes, such as micropapillary, plasmacytoid, sarcomatoid, and NE subtypes, are associated with a higher risk of progression and recurrence [267, 268]. Literature on these subtypes remains limited; however, retrospective studies suggest that their aggressive behaviour correlates with a more rapid progression to MIBC.

Certain pathological features further influence the prognosis of NMIBC, especially in the presence of specific histological subtypes [269, 270]. Identifying favourable and unfavourable prognostic factors can assist in tailoring patient management. The following table highlights key factors influencing prognosis based on subtype.

Table 6.1: Key factors influencing prognosis based on histological subtypes [60]

Prognostic factors in subtypes	Risk of progression
Highly aggressive	
High percentage of subtype(s)	Very high risk of progression
Presence of CIS	
Lymphovascular invasion	
Pure micropapillary, sarcomatoid, nested and plasmacytoid subtype, or NE subtype	
Multifocal tumours	
Residual tumour or incomplete TURBT	
Aggressive	
Absence of CIS and LVI	High risk of progression
Solitary tumour	
Complete TURBT with no residual tumour	

CIS = carcinoma in situ; LVI = lymphovascular invasion; NE = neuroendocrine; TURBT = transurethral resection of the bladder tumour.

6.4 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 IPD analysis in primary patients that did not receive immediate BCG and the calculation of their progression scores (2021 EAU NMIBC scoring model, as presented in Sections 4.5 and 6.1.2) [257].

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

For factors for which IPD 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.

Table 6.2 provides the clinical compositions of the EAU NMIBC prognostic factor risk groups based on the 2004/2016 or 1973 WHO classification systems. A web-based (www.nmibc.net), iOS and Android App has been developed to facilitate determining a patient's risk group in daily clinical practice. Table 6.3 presents the individual probability of disease progression at one, five and ten years for the EAU NMIBC risk groups. Two studies have validated the 2021 EAU NMIBC scoring model in 529 and 1,268 patients who received BCG [271, 272], respectively. The authors found that the progression risk for the 2021 EAU NMIBC high- and very high-risk groups were substantially lower in BCG-treated patients than that in Table 6.3 [257]. A systematic review of the available risk stratification systems also observed an overestimation of progression rates for the 2021 EAU NMIBC model [273]. These lower risks may be attributed to the use of BCG.

A new risk model aimed to improve risk assessment using AI approaches has been developed that includes 14 clinico-pathological variables for the prediction of progression (PROGRxN-BCa) [274]. The model also accounted for variables such as re-TURBT and BCG therapy that were not included in the 2021 EAU NMIBC risk model. In comparison to the 2021 EAU NMIBC risk model, PROGRxN-BCa had significantly higher c-index and net benefit overall and across different subgroups. It also outperformed other guidelines-endorsed tools and a previously published AI model [274]. Pending further validation, PROGRxN-BCa may hold the potential to optimise risk-adapted management of NMIBC by incorporating additional clinical variables.

Table 6.2: Clinical composition of the 2021 EAU NMIBC prognostic factor risk groups based on the 2004/2016 or 1973 WHO grading classification systems [257]

- Only one of the two classification systems (1973 WHO or 2004/2016 WHO) is required to use this table.
- The category of LG tumours (2004/2016 WHO) 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 T1 G1, no CIS with all three risk factors • Ta HG/G3 or T1 LG, no CIS with at least two risk factors • T1 G2 no CIS with at least one risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all three risk factors • T1 G2 and CIS with at least two risk factors • T1 HG/G3 and CIS with at least one risk factor • T1 HG/G3 no CIS with all three risk factors

CIS = carcinoma in situ; EAU = European Association of Urology; G = grade; HG = high-grade; LG = low-grade; NMIBC = non-muscle-invasive bladder cancer; PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organization.

The scoring model is based on IPD, but does not consider patients with primary CIS, CIS of the prostatic urethra or with recurrent tumours, as well as some pathologic parameters such as subtypes of UC (see Section 4.8) and LVI. Nevertheless, based on data from the literature:

- All patients with CIS in the prostatic urethra, with certain subtypes of UC (see Section 4.8 and Table 6.1), or with LVI, should be included in the very high-risk group.
- Patients with primary (pure) CIS should be considered in the 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 6.3: Probabilities of disease progression at 1, 5 and 10 year(s) for the 2021 EAU NMIBC risk groups [257]*

Risk group	Probability of progression and 95% 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%)

** Table 6.3 does not include patients with subtypes of UC, 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 TURBT.*
BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; LVI = lymphovascular invasion; NMIBC = non-muscle-invasive bladder cancer; TURBT = transurethral resection of bladder tumour; UC = urothelial carcinoma; WHO = World Health Organization.

To sub-stratify the heterogeneous group of intermediate-risk NMIBC, a three-tier model initially proposed by the International Bladder Cancer Group (IBCG) was refined in 2022 [275]. This model is based on five clinical risk factors: tumour size and focality, timing and frequency of recurrence, and failure of previous intravesical treatment. A subsequent multi-centre clinical study validated this model in 677 primary and recurrent patients treated with adjuvant intravesical chemotherapy [276]. At one-year follow-up, the authors found that the progression risk of patients with no risk factors was similar to that of 2021 EAU NMIBC low-risk group while that of patients with ≥ 3 risk-factors aligned with that of 2021 EAU NMIBC high-risk group. The AI-based PROGRxN-BCa tool has been found to improve the categorisation of intermediate-risk patients proposed by IBCG. PROGRxN-BCa was able to sub-stratify 3,137 intermediate risk patients into three markedly distinct risk tertiles with estimated five-year progression risks of 2, 7, and 17% [274]. A further sub stratification was provided in 2,086 patients with primary intermediate-risk NMIBC according to 2021 EAU NMIBC risk group calculator. Tumour size (> 3 cm) and multi-focality were associated with a higher risk of first recurrence and were used to define intermediate-risk at "high" and intermediate-risk at "low" (unifocal, size < 3 cm) risk of recurrence [277].

6.5 Summary of evidence and recommendations for stratification of NMIBC

Summary of evidence	LE
The 2021 EAU NMIBC scoring model and risk tables predict the short- and long-term risks of disease progression in individual patients with primary NMIBC who did not receive BCG therapy, using the 2004/2022 or the 1973 WHO classification system (see Section 6.1.2.a).	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 1973 WHO classification system (see Section 6.1.1.a).	1b
In patients treated with five to six months of BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression using the 1973 WHO classification system (see Section 6.1.1.c).	1b
In patients receiving at least one 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 (1973 WHO) are the most important prognostic factors for OS (see Section 6.1.1.d).	1b

Recommendations	Strength rating
Stratify non-muscle-invasive bladder cancer (NMIBC) patients into four risk groups to predict **progression** without Bacillus Calmette-Guérin (BCG) therapy, according to Table 6.3. A patient's risk group can be determined using the 2021 European Association of Urology (EAU) risk group calculator available at www.nmibc.net.	Strong
Use the 2006 European Organisation for Research and Treatment of Cancer (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 Club Urologico Español de Tratamiento Oncologico (CUETO) risk scoring model to predict the risk of tumour recurrence and progression in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for one to three years of maintenance, the CUETO model for five to six 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 [278-280] as well as mortality in all BC patients [281]. 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 [280]. Patients should be counselled to stop smoking due to the general health risks associated with tobacco smoking [259, 282-284]. An RCT showed that a perioperative, intensive smoking-cessation program delivered around the time of TURBT significantly increased quit rates compared with standard care consisting of only brief advice on smoking cessation (36% vs. 6%). These findings support incorporating structured cessation interventions into routine perioperative management for smokers undergoing BC surgery [285].

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 [286, 287]. In a prospective RCT, laser photocoagulation with intravesical lidocaine in an outpatient setting proved non-inferior to standard TURBT under general anaesthesia for the four months recurrence rate in patients with recurrent Ta LG papillary lesions that are no more than 1.5 cm each. Notably, the laser fulguration procedure resulted in only a modest pain score (2.4) and was preferred by 98% of patients [288]. In a retrospective cohort of 270 patients with recurrent Ta LG, office fulguration showed favourable long-term outcomes, with ten years cancer-specific mortality and progression rates of 0% and 3.1% (95% CI: 0.8-5.4%), respectively [289]. In a prospective observational study, an outpatient modality of transurethral laser ablation (TULA) appeared to reduce the symptom burden compared with standard TURBT [290]. These findings are preliminary and require confirmation through additional studies.

7.3 Active surveillance

With recurrence in LG(G1) Ta tumours being more likely to be LG and non-invasive [291-293], the risk of progression to a higher grade or stage is infrequent to rare [294-296]. Therefore, expectant management or active surveillance (AS), offers an alternative to TURBT and office-based fulguration. Observing no progression to MIBC, Soloway *et al.*, first recommended this approach in 2003 [297], and Miyake *et al.*, subsequently proposed an algorithm for AS using changes in size and multifocality as triggers for intervention [298]. However, a subsequent review [299] reported that the level of evidence in favour of AS appears to be low, with observational studies having heterogenous selection criteria, triggers for intervention and surveillance tools. Conversely, the multicentre prospective Bladder Cancer Italian Active Surveillance (BIAS) project demonstrated that AS is feasible in selected patients [300, 301] and that its success is predicted by prognostic variables associated with Ta LG disease [302]. According to another study, IBCG stratification of intermediate-risk NMIBC correlated with duration on AS, with patients with three risk factors being three times more likely to undergo subsequent TURBT compared with patients with no risk factors [302]. Additional evidence from high-quality clinical trials is required to compare AS, office fulguration and TURBT in patients with recurrent LG Ta NMIBC.

7.4 Adjuvant intravesical treatment

Although TURBT by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the three-month recurrence rate indicates that the TURBT was incomplete or provokes recurrences in a high percentage of patients [164]. It is therefore necessary to consider adjuvant therapy in all patients.

7.4.1 Postoperative irrigation

Two systematic reviews [303, 304] and one meta-analysis [305] suggest efficacy of continuous saline bladder irrigation in the prevention of early recurrences. Therefore, if intravesical chemotherapy is not feasible, irrigation of the bladder might be considered as an alternative option. In an RCT, short-term postoperative irrigation with 2000 mL over three hours was shown to be non-inferior to overnight irrigation [306].

7.4.2 Intravesical chemotherapy

7.4.2.a A single, immediate, postoperative intravesical instillation of chemotherapy

Immediate SI has been shown to act by destroying circulating tumour cells after TURBT, and by an ablative effect on residual tumour cells at the resection site and on small, overlooked tumours [307-310]. Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURBT, SI significantly decreases the recurrence rate compared to TURBT alone [311-314]. In a systematic review and IPD meta-analysis of 2,278 eligible patients [311], SI reduced the five-year recurrence rate by 14%, from 59% to 45%. However, 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 [311-314].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin [311], as well as gemcitabine [314], have all been shown to lower the intravesical recurrence rate. Single instillation with gemcitabine was superior to saline in an RCT with approximately 200 patients per arm with remarkably low toxicity rates [315]. These findings are in contrast with a previous study that used a shorter instillation time [316]. In the 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 [316].

Prevention of tumour cell implantation should be initiated within the first few hours after TURBT. After that, tumour cells are firmly implanted and are covered by the extracellular matrix [307, 317-319]. 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 TURBT [320].

To maximise the efficacy of SI, flexible practices should be devised that enable the instillation to be given as soon as possible after TURBT, 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) [321, 322]. To allow for optimal compliance with this level 1 evidence, clinical teams are encouraged to explore barriers and facilitators within their practice [323].

7.4.2.b Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (see Tables 6.1 and 6.2), a SI reduces the risk of disease recurrence and is considered to be the standard of care treatment [311, 312]. For other patients, however, a SI remains an incomplete treatment due to the considerable likelihood of disease recurrence and/or progression (see Tables 6.1 and 6.2). Efficacy data for the following comparisons of application schemes were published.

Single installation only versus SI and further repeat instillations

In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [324].

Repeat chemotherapy instillations versus 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 TURBT alone [325]. 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 [326, 327]. Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy, independently of the type of intravesical chemotherapy [328-331]. However, BCG causes significantly more side effects than chemotherapy [330].

Single instillation plus further repeat instillations versus later repeat instillations only

Evidence from several studies in intermediate-risk patients is available showing that SI might have an impact on recurrence even when further adjuvant instillations are given [332-335]. An RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURBT (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at three years in favour of SI, from 36% to 27%. The effect was significant in the intermediate- and high-risk groups of patients receiving additional adjuvant MMC instillations [332]. 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 [336]. 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 high-risk BC patients [337].

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 [335]. 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 [338].

7.4.2.c Measures to improve the efficacy of intravesical chemotherapy

7.4.2.c.1 Adjustment of pH, duration of instillation, and drug concentration

Two prospective RCTs showed that optimised intravesical administration of MMC reduced recurrence rates, either by a combination of measures (higher MMC-dose, peroral sodium bicarbonate and refraining from drinking) [339] or by adding cytosine arabinoside [340], 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 [341]. Another trial reported that a one-hour instillation of MMC was more effective compared to a 30-minute instillation, but no efficacy comparisons are available for one- versus two-hour durations of instillation [342]. Another RCT using epirubicin has documented that concentration is more important than treatment duration [343]. In view of these data, instructions are provided in Section 7.7).

7.4.2.c.2 Device-assisted intravesical chemotherapy

Hyperthermic intravesical chemotherapy

Various technologies that increase the temperature of instilled MMC are available. A systematic review and meta-analysis including four RCTs suggests similar toxicity as for BCG with maintenance schedule [344].

Microwave-induced hyperthermia effect (RITE)

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia (RITE) in patients with high-risk tumours [345]. In one RCT comparing one year of BCG with one year of MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC-group was demonstrated [346].

Conductive chemohyperthermia

In an open-label phase II RCT including 259 patients, HIVEC chemohyperthermia failed to demonstrate an improvement in disease-free survival (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) [347]. These results are in line with the multicentre HIVEC 1 phase III 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 [348]. A small RCT including 135 patients with LG intermediate-risk NMIBC found that intravesical chemohyperthermia with MMC (HIVEC), conventional MMC or BCG were equally effective [349].

In a pilot phase II RCT on 50 high-risk NMIBC patients, HIVEC™ MMC showed early outcomes comparable to BCG (24 months RFS; 86.5% with HIVEC™ and 71.8% with BCG; p = 0.184) [350]. 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 [351]. The definitive conclusion, however, needs further confirmation. For application of device-assisted instillations in patients recurring after BCG treatment, see Section 7.8.3.

7.4.2.d 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 TURBT, a SI significantly reduces the recurrence rate compared to TURBT 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.	2a
Repeat chemotherapy instillations up to one year (with or without previous SI) improve RFS in intermediate-risk patients.	2a

7.4.3 Intravesical BCG immunotherapy

7.4.3.a Efficacy of BCG

7.4.3.a.1 Recurrence rate

Five meta-analyses have confirmed that BCG after TURBT is superior to TURBT alone or TURBT plus chemotherapy for preventing the recurrence of NMIBC [328, 352-355]. Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (IFN) [356], MMC [357], or epirubicin alone [329] and have confirmed the superiority of BCG for prevention of tumour recurrence. The effect is long lasting [329, 357] and was also observed in a separate analysis of patients with intermediate-risk tumours [329]. One meta-analysis [328] has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC versus 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 [358].

7.4.3.a.2 Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [326, 327, 355]. 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 two and a half years, tumours progressed in 9.8% of the patients treated with BCG compared to 13.8% in the control groups (TURBT alone, TURBT and intravesical chemotherapy, or TURBT with the addition of another 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 [327]. An RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [329]. In contrast, an IPD meta-analysis and Cochrane review were unable to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [328, 358].

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 [359].

7.4.3.a.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 [360]. However, in the IPD patient data meta-analysis, BCG maintenance was more effective than MMC in reduction of recurrence rate, both in patients previously treated and not previously treated with chemotherapy [328]. 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 [361]. 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 [362].

7.4.3.b BCG strain

Although smaller studies without maintenance demonstrated some differences between strains [362-364], 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 [365].

Similarly, a meta-analysis of prospective RCTs [327] published data from a prospective registry [366] as well as from a *post-hoc* analysis of a large phase II prospective trial assessing BCG and IFN-α in both BCG-naïve and BCG-failure patients that did not suggest any clear difference in efficacy between the different BCG strains [367]. The quality of data, however, does not allow definitive conclusions.

7.4.3.c BCG toxicity

Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [327, 358]. However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [368]. The incidence of systemic BCG infections after BCG instillations was 1 to 2% [359, 369]. These figures were recently confirmed in a Swedish nationwide database showing a cumulative incidence of reported diagnosis of tuberculosis (TB) of 1.1% at five years in 5,033 patients exposed to BCG. The highest incidence was reported in the first two years, while females had lower incidence than males [370].

Discontinuation of maintenance instillations due to adverse events (local and/or systemic) occur in similar proportions at 3, 6 and 12 months [368, 371, 372]. More than 50% of patients will fail to complete a one-year maintenance course [372]. In an RCT, comparing BCG alone with two years of maintenance versus BCG combined with systemic immunotherapy, 46% of patients in the BCG arm discontinued treatment within two years, nearly one in three due to adverse effects [373].

Side effects requiring treatment stoppage were seen more often in the first year of therapy [371], of which the most frequent were local side effects. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [374]. No significant difference in toxicity between different BCG strains was demonstrated [366]. Symptoms may be the result of side effects of the BCG treatment or may be 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 [375].

Major complications can appear after systemic absorption of the drug. Therefore, contraindications of BCG intravesical instillation should be respected (see Section 7.8). The presence of leukocyturia, non-visible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [142, 376]. Three RCTs and one meta-analysis showed reduced side effects by administering different quinolones in conjunction with the BCG-instillations [377-380]. The latter, using two doses of levofloxacin (at six and 12 hours after first voiding) in conjunction with each BCG-instillation, reduced the proportion of patients with HG side effects, both local (pollakiuria) and systemic (fever), without improving the completion rate of the maintenance regimen or the risk of severe BCG-related adverse events [379]. In addition, a systematic review and meta-analysis demonstrated improved completion rates for BCG induction with quinolones [380].

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients. Immunosuppression, for example human immunodeficiency virus (HIV) infection, or other agents causing immunosuppression - such as biologicals or anti-TNF - poses relative contraindications [381], although large registry data have shown similar efficacy and no increase in complications compared to non-immunocompromised patients [382]. The role of prophylactic anti-TB medication in these patients remains unclear [383-385]. Kidney transplant recipients can be safely treated with BCG [386]. A positive Mantoux tuberculin skin test or purified protein derivative (PPD) test should not preclude patients from receiving intravesical BCG. In a large cohort of 823 patients treated with BCG, no difference in treatment-related toxicity were observed between those who underwent baseline PPD testing and those who did not. Purified protein derivative test results were not associated with the occurrence or severity of BCG-related toxicity [387]. Therefore, routine skin testing prior to BCG initiation is not recommended in patients without risk factors for active TB [388].

Table 7.1: Management options for side effects associated with intravesical BCG [389-394]

Management options for local side effects (modified from IBCG)	
Symptoms of cystitis	Phenazopyridine, mirabegrone or 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 five days (repeat cycle if necessary).
	**If symptoms persist: anti-TB drugs + corticosteroids.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
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	Perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for three months.
	Cessation of intravesical therapy.
Epididymo-orchitis [391]	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 reactive 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 anti-TB drugs.
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 disease specialist.
BCG sepsis	Prevention: initiate BCG at least two weeks post-TURBT (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 six 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 in case of mild (local) reaction. Discontinue BCG in case of moderate- or severe systemic reaction.

** Persistent severe cystitis symptoms associated with BCG use have a high risk of a underlying complicated UTI (even in the absence of a positive culture) and therefore no restriction applies to the empirical use of quinolones by the Pharmacovigilance Risk Assessment Committee of the EMA (see also Section 3.7 of the EAU Guidelines on Urological Infections) [395, 396].*
*** The diagnostic performance of acid-fast bacilli staining, mycobacterial culture, and PCR-based analysis on urine during BCG treatment is uncertain [397] as are the dynamics during and after BCG intravesical instillations [398], and outcomes must be interpreted in relation to symptoms.*
BCG = bacillus Calmette-Guérin; EMA = European Medicines Agency; IBCG = International Bladder Cancer Group; NSAID = non-steroidal anti-inflammatory drugs; PCR = polymerase chain reaction; RC = radical cystectomy; TB = tuberculosis; TURBT = transurethral resection of the bladder tumour; UTI = urinary tract infection.

7.4.3.d Optimal BCG schedule

Induction BCG instillations are given according to the empirical six-weekly schedule [399]. For optimal efficacy, BCG must be given in a maintenance schedule [326-328, 355]. Many different maintenance schedules have been used, ranging from a total of ten instillations given in 18 to 27 weeks over three years [400]. The optimal three-year maintenance schedule is outlined in the recommendations provided in Section 7.10.

7.4.3.d.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 (three instillations in induction and two instillations at 3, 6 and 12 months) proved inferior to the standard schedule (six instillation in induction and three instillations at 3, 6 and 12 months) regarding the time to first recurrence [372]. In an RCT including 397 patients, CUETO showed that in high-risk tumours a maintenance schedule with only one instillation every three months for three years was not superior to induction therapy only, which suggested that one instillation may be suboptimal to three instillations in each maintenance cycle [401].

7.4.3.d.2 Optimal length of maintenance

A meta-analysis concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [326].

In an RCT of 1,355 patients, the EORTC demonstrated that full-dose BCG with three years of maintenance (three weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months) significantly reduces recurrence compared to one year in high-risk patients. In contrast, one year of maintenance appears to be sufficient in intermediate-risk patients, with no additional benefit from longer treatment maintenance. No differences were observed in progression or OS. However, in the three-year maintenance arm, only 34% of patients completed the full course: 10% discontinued due to toxicity; 20% due to recurrence; and 35.5% for unknown reasons. Overall, 36.1% of patients did not complete the three-year schedule [402].

7.4.3.e 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 [403, 404]. 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 [405]. 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 [371, 402]. In a meta-analysis of nine 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 recurrence [406].

7.4.3.f BGC 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.g Summary of evidence - BCG treatment

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical BCG after TURBT reduces the risk of tumour recurrence; it is more effective than TURBT alone or TURBT and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule. 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.	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.a 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 [407]. In an RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [351, 408]. Two meta-analyses demonstrated improved DFS, but no benefit in PFS in patients treated with combination treatment comparing to BCG monotherapy [408, 409].

7.4.4.b Combination treatment using interferon

In a Cochrane meta-analysis of four RCTs, a combination of BCG and IFN-2α did not show a clear difference in recurrence and progression over BCG alone [410]. 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 [411]. Additionally, an RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and IFN for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [412].

7.4.4.c Sequential chemotherapy instillations (gemcitabine plus docetaxel)

Preclinical data suggest that the efficacy of intravesical chemotherapy instillations can be improved by using combinations as opposed to the administration of only single agents [413]. Sequential (immediate) instillations of gemcitabine and docetaxel were initially reported in 2015 in the wake of BCG-shortage but also at times of limited access to MMC [414]. Subsequently other sequential chemotherapy combinations such as valrubicin and docetaxel have been suggested [415]. Over time, additional retrospective data have accumulated in which sequential gemcitabine and docetaxel instillations were used in patients recurring after induction BCG and BCG-unresponsive disease [416, 417]; in patients with recurrence after BCG-induction but not fulfilling the criteria for BCG-unresponsive disease [418]; as well as in BCG-naïve high-risk patients [419, 420]. Hence, in patients with BCG-unresponsive disease where the treatment standard (radical cystectomy [RC]) 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.

7.4.4.d Combination treatment with immune checkpoint inhibitors versus BCG alone

The non-negligible risk of recurrence in high-risk NMIBC following BCG, together with increased programmed death-ligand 1 (PD-L1) expression observed in preclinical models after BCG exposure [421], provides the rationale for evaluating treatment intensification through the combination of BCG and programmed death protein 1 (PD-1)/PD-L1 inhibitors in this disease setting.

The phase III CREST trial evaluated the addition of the systemic PD-1 inhibitor sasanlimab administered subcutaneously for two years to standard BCG induction and maintenance for up to two years versus BCG induction alone plus sasanlimab versus BCG induction and maintenance alone (as control arm) in patients with BCG-naïve high-risk NMIBC (HG Ta, T1 and/or CIS) [373]. At 36 months, event-free survival defined as HG recurrence, disease progression, persistence of CIS and any cause mortality was 82.1% in the sasanlimab plus BCG arm versus 74.8% with BCG alone (HR: 0.68; 95% CI: 0.49-0.94), meeting the prespecified threshold for statistical significance. The primary analysis was based on 150 of the 389 planned events, and longer follow-up is awaited. No benefit was observed for sasanlimab when given with BCG induction only (HR: 1.16; 95% CI: 0.87-1.55). Grade ≥ 3 treatment-related adverse events occurred in 29.8% of patients receiving sasanlimab plus BCG compared with 6.3% of those receiving BCG alone. Immune-related toxicities were reported in over 40% of

patients; these were grade ≥ 3 in 14% and required hospitalisation in 10%. Subgroup analyses suggested greater benefit among patients with CIS or T1 disease compared to Ta.

The phase III POTOMAC trial assessed whether adding one year of intravenous durvalumab to standard BCG induction plus up to two years of maintenance could improve outcomes in patients with high-risk NMIBC (HG Ta, T1, CIS, or multiple/recurrent large tumours) compared with BCG alone or BCG induction plus durvalumab. The trial met its primary endpoint, showing an early and sustained improvement in DFS - defined as absence of HG recurrence, progression, or death - with a significantly higher two-year DFS in the durvalumab plus full BCG regimen versus the control arm (86.5% vs. 81.6%; HR: 0.68; 95% CI: 0.50-0.93), while no significant benefit was seen when durvalumab was combined with BCG induction only. The greatest effect was observed in patients with higher-risk papillary disease (T1 HG/G3 or multiple large recurrent tumours). Grade 3-4 treatment-related adverse events, mostly immune-mediated, occurred in 21% of patients receiving durvalumab plus full BCG compared with 4% in the control group [422].

In contrast to the findings of CREST and POTOMAC, the phase III ALBAN trial found that adding one year of intravenous atezolizumab to one year of BCG maintenance did not improve event-free survival - defined as any HG or LG recurrence, persistent CIS, progression, development of UTUC, or death - compared with BCG maintenance alone in patients with high-risk NMIBC (HR: 0.98; 95% CI: 0.71-1.36; p = 0.9106) [423].

At present, sasanlimab and durvalumab may be considered potential add-on options to BCG in carefully selected, well-informed patients; however, these strategies should be approached cautiously, as more mature data are needed and any potential benefits must be weighed against toxicity within a shared decision-making framework.

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 TURBT or chemoresection of the tumour as a replacement of TURBT.

Neoadjuvant

Hypothesis-generating findings from an older RCT comparing immediate pre-operative device-assisted (EMDA) MMC with postoperative SI with MMC and TURBT only, showed improved long-term RFS among patients treated prior to TURBT [424], and thus even suggest a long-term effect after neoadjuvant instillations. While this has not been reproduced by other groups, two small neoadjuvant RCTs have reported conflicting results on the ability of neoadjuvant administration of MMC to improve outcomes over the standard approach [425, 426].

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 [427]; therefore making it possible to avoid TURBT. In recurrent LG [428] and recurrent Ta tumours [429], four and six 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 two weeks without preceding biopsy to standard TURBT, the 12-month RFS was 36% in the chemoablation group versus 43% in the TURBT group, with no statistically significant difference [429]. UGN-102, a mitomycin-containing reverse thermal gel, whether followed by TURBT or otherwise, was compared to TURBT alone in a randomised, phase III trial, including 282 patients with LG intermediate-risk NMIBC [430]. Notably, three-month complete response was similar between UGN-102 (once weekly for six weeks) and TURBT (65% vs. 64%). In an ongoing phase III single arm study, the same treatment schedule achieved a 79% complete response rate (CRR) at three months in 240 patients with recurrent LG intermediate-risk NMIBC, which was maintained in 82% at one year [431]. Despite the lack of long-term outcomes, chemoablation appears to be a promising treatment option for well-selected NMIBC patients and can potentially help to spare the toxicity associated with TURBT, specifically in patients with intermediate-risk NMIBC [432].

7.6 Radical cystectomy for NMIBC

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

- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
- Patients who experience disease progression to muscle-invasive stage might have a worse prognosis than those who present with ‘primary’ muscle-invasive disease [433, 434].

However, 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) [85, 203, 251, 253, 435-437].

Early RC is recommended in patients with BCG-unresponsive tumours and should be considered in BCG-relapsing HG tumours, as discussed in Section 7.8 and Table 7.5. A delay in RC may lead to decreased disease-specific survival [438]. In patients who refused RC or who are not eligible, new therapeutic options in the context of clinical trials should be preferred over BCG rechallenge.

In patients in whom RC is performed before progression to MIBC, the five-year DFS rate exceeds 80% [439-441].

7.7 Primary treatment by disease type

*7.7.1 **Primary treatment by risk category***

The type of further therapy after TURBT 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.a) to determine a patient's individual risk of disease recurrence as the basis to decide on further treatment.

- Treatment of low-risk disease
  Patients in the low-risk group have a negligible risk of disease progression; however, the risk of recurrence is between 10 and 35% at five years [442, 443]. The single postoperative instillation of chemotherapy reduces the risk of recurrence and is considered 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 ten years, according to the 2021 EAU NMIBC scoring model). The risk of recurrence is reported to be between 18 and 50% at five years [347, 431, 442, 443]. 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 [444]. One-year full-dose BCG treatment (induction plus three-weekly instillations at 3, 6 and 12 months), is an alternative option. In these patients, chemoablation, AS or office fulguration could also be considered. The final choice should reflect the individual patient's risk of recurrence and progression, as well as the efficacy and side effects of each treatment modality. A three-tier sub-stratification model based on the presence or absence of five key risk-factors has been proposed to guide treatment decision-making [275, 276].

- Treatment of high-risk disease
  Patients in the high-risk group have a high risk of disease progression (14% after ten years according to the 2021 EAU NMIBC scoring model). In these patients, full-dose intravesical BCG for one to three years (induction plus three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems associated with BCG shortage. Due to 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; however, it is 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 ten years, according to the 2021 EAU NMIBC scoring model). If adequate BCG therapy is administered, a more favourable prognosis than predicted by the EAU NMIBC risk stratification can be achieved, with progression rates between 14.9 and 22% after five years [271, 445]. Still, immediate RC should be discussed with these patients. If RC is not feasible or refused by the patient, full dose intravesical BCG for one to three years should be offered. Therefore, it is critical to tailor the therapeutic approach in every case.

7.7.2 *Treatment of carcinoma in situ*

Patients with CIS cannot be managed by an endoscopic procedure alone and should be offered either intravesical BCG instillations or RC. The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [251, 253]. In this case, further treatment according to the criteria summarised in Sections 7.4.2, 7.4.3 and 7.9 is mandatory. Bacillus Calmette-Guérin treatment of CIS increases the CRR, 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 [261].

7.7.2.a Cohort studies on intravesical BCG or chemotherapy

In retrospective evaluations of patients with CIS, a CRR 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 [264, 319, 400, 446].

7.7.2.b Prospective randomised trials on intravesical BCG or chemotherapy

Unfortunately, few RCTs have been carried out 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 [447].

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 [327]. The combination of BCG and MMC was not superior to BCG alone [448]. In summary, compared to chemotherapy, BCG treatment of CIS increases the CRR, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression.

7.7.2.c Treatment of carcinoma *in situ* in the prostatic urethra and upper urinary tract

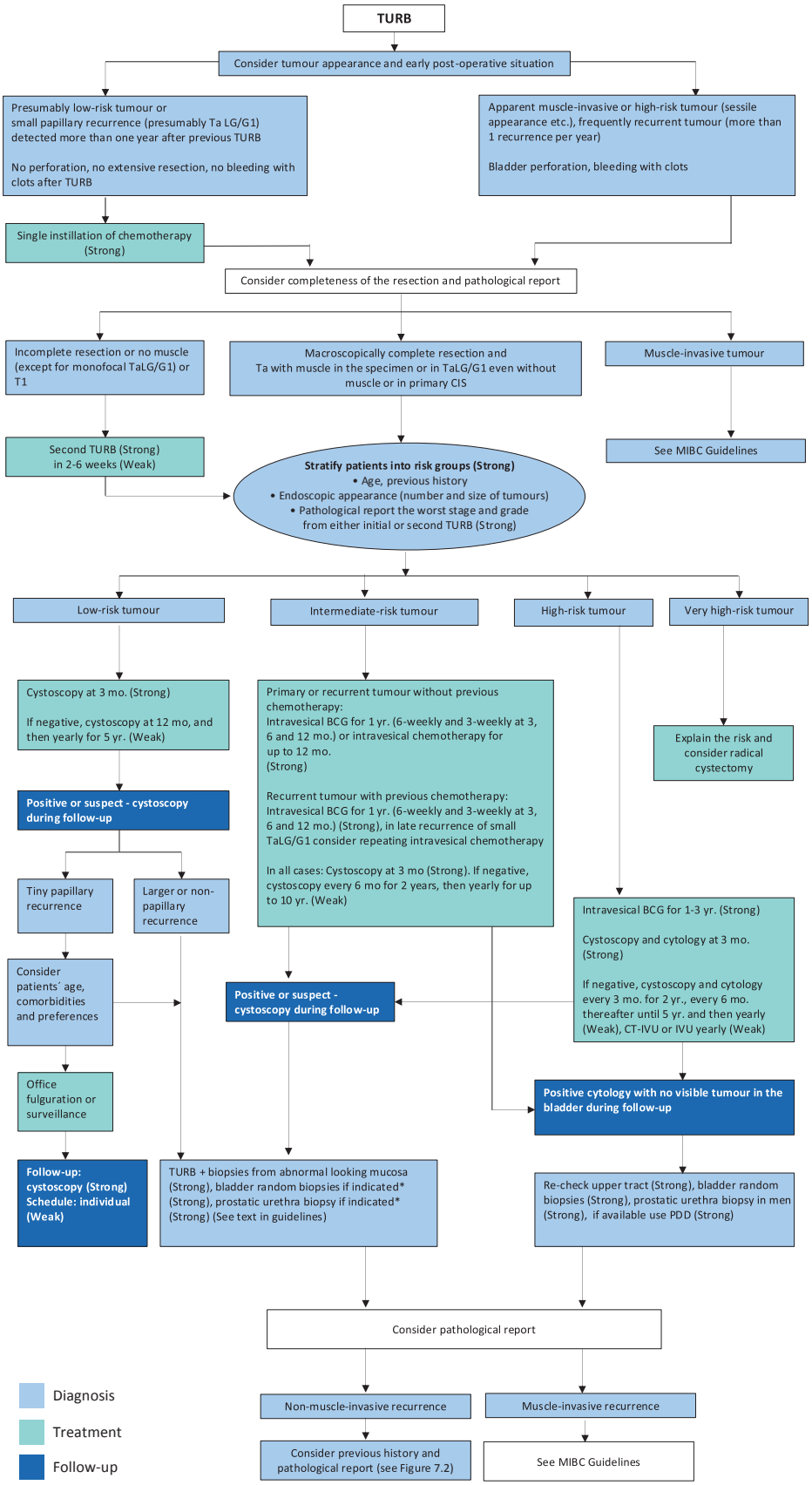
Patients with CIS are at high risk of extravesical involvement in the upper urinary tract and in the prostatic urethra. Solsona *et al.*, found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [449]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [449]. In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [450]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours) and for which radical cystoprostatectomy with neoadjuvant chemotherapy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection or laser enucleation of the prostate can improve contact of BCG with the prostatic urethra [151, 451]. However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

BCG has shown promising results in patients with prostatic duct involvement, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [451, 452].

7.7.2.d 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 CRR, the overall percentage of patients who remain disease free, and reduce the risk of tumour progression.	1b

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



** For details and explanations see the text of the Guidelines.*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURBT = transurethral resection of the bladder tumour.

7.8 Treatment of failure of intravesical therapy

*7.8.1 **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 [328].

*7.8.2 **Recurrence during or after intravesical BCG therapy***

7.8.2.a Definitions of BCG failure

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 [453].

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 [454, 455]. The category of BCG-unresponsive tumours comprises BCG-refractory and early BCG-relapsing tumours (see Table 7.2) [456]. The definition was developed in consultation with the United States Food and Drug Administration (FDA), in particular to promote single-arm trials to provide primary evidence of effectiveness in this setting [457]. Patients who experience recurrence with HG 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** [458, 459], 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 six 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 HG recurrence outside of the BCG-unresponsive window (> 6 months for Ta/T1 and > 12 months 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 three months [454, 455, 460]. 2. If Ta HG/G3 tumour is present after three months and/or at six months, after either re-induction or first course of maintenance [450]. 3. If CIS (without concomitant papillary tumour) is present at three months and persists at six months after either re-induction or first course of maintenance. If patients with CIS present at three months, an additional BCG course can achieve a complete response in > 50% of cases [76, 446, 450]. 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 [461].
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within six months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [456].
BCG-exposed tumour [458, 459]
1. BCG resistant 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 [389].

** 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 five of six doses of an initial induction course plus at least two out of six doses of a second induction course or two out of three doses of maintenance therapy.*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; G = grade; HG = high-grade; LG = low-grade; MIBC = muscle-invasive bladder cancer.

7.8.2.b Treatment of BCG unresponsive tumours

7.8.2.b.1 Introduction

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Several bladder preservation strategies are currently being investigated, such as cytotoxic intravesical therapies [417, 462-464], device-assisted instillations [465-467], intravesical immunotherapy [468, 469], systemic immunotherapy [470-472] and gene therapy [473-475], as well as various combinations of chemotherapies, intravesical or systemic immunotherapies [418, 419] and novel intravesical delivery systems of cytotoxic agents [471, 476] (Table 7.3 and 7.4).

A systematic review and meta-analysis including four RCTs and 24 single-arm studies (all currently available prospective studies) assessed bladder-sparing treatments following BCG failure [477]. 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.

A contemporary 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 one year, median progression-free rate of 89% at a median follow-up of 19 months) than CIS-containing tumours (median CRR of 17% at one 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 [478].

Another systematic review, including 57 studies, with 68 unique study arms totalling 2,589 patients, reported estimated three-month overall response rate (ORR) across all studies, CRR in concomitant CIS or CIS only disease, and recurrence-free rate in papillary disease of 52.4%, 52.8%, and 26.4%, respectively [479]. The 12-month ORR, CRR, and recurrence-free rate were estimated to be 78%, 27.8%, and 25.4%, respectively. The progression rate was estimated to be 13% and the mean proportion of patients treated with RC was estimated to be 24.7 (range 0-85.7).

7.8.2.b.2 Intravesical therapies

7.8.2.b.2.a Chemotherapy and chemotherapy combinations

Valrubicin, an anthracycline topoisomerase inhibitor that interferes with deoxyribonucleic acid (DNA) synthesis and metabolism by inhibiting the activity of DNA topoisomerase II, leading to cell cycle arrest in the G2 phase, was approved by the FDA in 1998, but its use has been limited due to the availability of more effective options [475, 476]. Other single-agent chemotherapies, including gemcitabine [480] and docetaxel [481], have been assessed in a small series of BCG-recurrent NMIBC patients usually not fulfilling the definition of BCG-unresponsive, with inconsistent results.

As outlined in Section 7.4.4.c, sequential intravesical administration of gemcitabine and docetaxel is an emerging treatment option in patients failing BCG. In a retrospective series of 102 patients with BCG-unresponsive NMIBC, with or without CIS, 6-, 12-, and 24-month HG RFS was 78%, 65% and 49%, respectively. Fifty-seven percent of patients experienced mild/moderate adverse effects, the most common being represented by urinary frequency/urgency (41%) and dysuria (21%) and leading to treatment delay in only 7% of cases [482]. Another retrospective series compared gemcitabine and docetaxel (n = 95) with further BCG (n = 204) at the time of BCG-unresponsive disease, favouring the combination in terms of PFS (HR: 2.6; 95% CI 1.1-5.0; p = 0.03) and CSS (HR: 3.7; 95% CI: 1.1-12.3; p = 0.03) [417]. Notably, published data on this combination are currently predominantly retrospective, with only one small prospective series reported in Table 7.4 [483].

7.8.2.b.2.b Device-assisted chemotherapy

In 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 (RITE) provided 35% overall DFS at two years as compared to 41% in the control arm (treated with either BCG, MMC or MMC and EDMA at the discretion of the investigator). In the pre-planned sub-analysis, MMC with microwave-induced thermotherapy showed lower response rates in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [467]. A prospective phase II single-arm study evaluating the efficacy and safety of the EMDA-MMC treatment in 26 consecutive patients with BCG-refractory HG NMIBC at three years follow-up, demonstrated DFSs of 75%, 71.4%, 50% and 25%, for Ta G3, T1 G3, CIS, Ta/T1 G3 + CIS, respectively [466].

7.8.2.b.2.c Gene therapy

Nadofaragene firadenovec (rAd-IFNα/Syn3) consists of rAd-IFNα, a non-replicating recombinant adenovirus vector-based gene therapy that delivers a copy of the human interferon alfa-2b gene to urothelial cells, and Syn3, a polyamide surfactant that enhances the viral transduction of the urothelium, leading to production of IFN-α2b protein. It is FDA approved for treating patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumours following a phase III multicentre RCT that showed a complete response in 53.4% of patients, which was maintained in 45% at one year in those who initially responded [484]. Five-year follow-up data from this trial found an estimated HG RFS at 57 months of 13% in the CIS cohort, and 33% in the Ta/T1 cohort. Of note, 25% of patients in the CIS cohort and 49% of patients in the Ta/T1 cohort had ongoing response at either end of follow-up or at last available follow-up. Cystectomy-free survival at month 60 was 49% (43% in the CIS cohort and 59% in the Ta/T1 cohort) [485]. Nadofaragene firadenovec was safe and well tolerated, with limited to transient bladder-related events, Grade 3 study drug-related adverse events not exceeding 4% and no Grade 4 or 5 toxicity [485].

Cretostimogene grenadenorepvec is an intravesically-administered, replication-competent oncolytic adenovirus (CG 0070) with a dual mechanism of action of direct tumour cell lysis and immune cell activation. In an interim analysis of 45 patients with Ta/T1, with or without CIS, the six-month CRR was 47% (32%-62%) with predominantly mild bladder toxicity [474].

7.8.2.b.2.d Immunotherapy

The QUILT 3.032 trial has evaluated the potential of the IL-15 superagonist nagopendekin alfa-inbakicept (NAI), administered intravesically in combination with BCG, in BCG-unresponsive HG NMIBC, demonstrating 3-, 6- and 12-month CRR of 55%, 56% and 45%, respectively, in patients with CIS (n = 82), with a median duration of 26.6 months. Among patients with Ta/T1 disease (n = 72), the 12-month estimated DFS rate was 55.4%, with median DFS of 19.3 months. Most treatment-emergent adverse events for patients receiving BCG plus NAI were Grade 1 to 2 (86%); three Grade 3 immune-related treatment-emergent adverse events occurred [486, 487].

7.8.2.b.2.e Novel intravesical delivery systems of cytotoxic agents

TAR-200 is an intravesical system for the continuous release of gemcitabine, providing a sustained dose to increase the therapeutic window of intravesical exposure and enhance targeted treatment within the bladder. Cohort 2 of the phase II SunRISe1 study evaluated the TAR-200 monotherapy in 85 patients with BCG-unresponsive CIS, with or without papillary NMIBC, demonstrating a CRR and median duration of response of 82.4% and 25.8 months, respectively. Rates of Grade ≥ 3 and of serious treatment-related adverse events were 12.9% and 5.9%, respectively [476].

7.8.2.b.3 ***Systemic therapies***

7.8.2.b.3.a New immunotherapies

Promising data on BCG-unresponsive cohorts of patients with CIS alone or concomitant to papillary tumours have been reported following checkpoint inhibitor immunotherapies. The efficacy and safety of systemic pembrolizumab monotherapy was assessed in the KEYNOTE-057 phase II prospective, multicentre trial. In cohort A (patients with CIS with or without Ta/T1 papillary disease), pembrolizumab monotherapy achieved a 41% CRR at three months, and 46% of responders maintained a response lasting at least 12 months, resulting in FDA approval of the study drug for this patient population [488]. In cohort B (patients with Ta/T1 papillary disease without CIS), the 12-month DFS was 43.5% [489]. In the SWOG S1605 phase II trial, atezolizumab only achieved a 27% CRR at six months in a cohort of 74 patients with CIS, with a median duration of response of 17 months not reaching the prespecified efficacy threshold. Among 55 patients with papillary disease only (Ta/T1), the 18-months actuarial event-free survival rate was 49% [471].

7.8.2.b.3.b Target therapies

The THOR2 trial compared oral erdafitinib, a selective pan-*FGFR* tyrosine kinase inhibitor, to investigator's choice of intravesical chemotherapy in patients with Ta/T1 HG recurrent, BCG-treated, and select FGFR alterations (found in 31% of this patient population) refusing or unfit for radical cystectomy. Median RFS was not reached for erdafitinib (95% CI: 16.9 months - not estimable) and was 11.6 months (95% CI: 6.4 - 20.1 months) for chemotherapy, with an estimated HR of 0.28. Oral erdafitinib exhibited 18% Grade 3 or more adverse events, the most common being stomatitis [490].

7.8.2.b.4 Combination intravesical and systemic therapies

The single-arm phase II study, CORE-001, assessed the combination of intravesical cretostimogene grenadenorepvec and intravenous pembrolizumab [491]. Of the participants, 83% with BCG unresponsive CIS containing NMIBC achieved a complete response at three months, and 57% achieved a complete response at 12 months post treatment. The safety profile was consistent with the known profile of each agent as monotherapy, and no toxic events were enhanced with combination treatment [491].

In cohort 1 of the open-label, phase II SunRISe1 study, 53 patients with CIS-containing BCG-unresponsive NMIBC received TAR-200 in combination with cetrelimab (a PD-1 monoclonal antibody) with no additional efficacy (67.9% CRR) compared to TAR-200 alone [476].

Table 7.3 reports the main bladder sparing treatment options for BCG-unresponsive disease, based on the currently available published data, separately for CIS-containing Ta/T1 disease and papillary-only NMIBC (Table 7.4).

7.8.2.b.5 Radical cystectomy

While an initial bladder sparing approach does not seem to compromise survival in selected BCG-unresponsive patients [492], treatments other than RC are currently considered oncologically inferior in patients with BCG-unresponsive disease [454, 455, 460].

7.8.2.c Treatment of BCG-exposed tumours and BCG relapses

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 that do not meet the criteria of BCG-unresponsive disease) [459, 493]. BCG-exposed patients and late BCG relapses (beyond 24 months) are likely to benefit from further BCG [458, 459].

7.8.2.d Low-grade recurrences after BCG

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. Importantly, LG recurrence after BCG in an intermediate-risk NMIBC setting should be distinguished from LG events occurring in patients originally classified as high-risk or very high-risk, as the latter generally warrant a more intensive therapeutic and follow-up approach. Several tumour-related factors have been identified that may guide treatment selection for LG recurrence after BCG, including multiple tumours, early recurrence (< 1 year), frequent recurrence (> 1/year), and tumour size ≥ 3 cm.

Table 7.3: Treatment options for BCG-unresponsive tumours - Papillary Ta/T1

Papillary Ta/T1								
Compound	**Study design**	**n**	**FU (mo.)**	**DFS (%)**			**PFS**	**≥ Grade 3 adverse events**
				3 mo.	**6 mo.**	**12 mo.**		
Intravesical								
NADOFARAGENE FIRADENOVEC* [484]	Phase III Ta/T1 Cohort NCT02773849	48	20.2	72.9		42.8		G1-2 66.0% G ≥ 3 4%
CREMOSTIMOGENE GRENADENOREPVEC [474]	Phase II BOND II NCT02365818	9		33 Ta 50, T1 0				G1-2 82.5% G ≥ 3 4.5%
N-803 Nogapendekin Alfa Inbakicept + BCG* [486]	Phase II/III QUILT 3032 CB	82	20.7			55.4		G1-2 86% G ≥ 3 23%

TAR 200* [476]	Phase II b SunRISe-1 C4 NCT04640623	52	12.8		85.3	70.2	78.8	Any G 80.8% G ≥ 3 13.5%
RITE [467]	Phase III HYMN NCT01094964	33	36			53 vs. 24 c at 18 mo n/s		G1-2 81%
EMDA-MMC [466]	Phase II	18	35	77.7		72.2		23.1 % local / 11.5 Allergic
Systemic								
PEMBROLIZUMAB* [489]	Phase II Cohort B KEYNOTE-057 NCT02625961	132	45.4	85		43.5% (HR) 41.7%		G1-2 59% G ≥ 3 15%
ATEZOLIZUMAB [471]	Phase II Cohort B SWOG 1605 NCT02844816	55	41	67	53	49	90.9	G1-2 70% G ≥ 3 14%
ERDAFITINIB [490]	Phase II THOR-2 Cohort 1 NCT04172675	73	13.4		96% vs. 73%	77 % vs. 41%		G1-2 100% vs. 83% G ≥ 3 36.7% vs. 0%

**FDA-approved drug*
BCG = bacillus Calmette-Guérin; DFS = disease-free survival; FDA = United States Food and Drug Administration; FU = follow-up; G = grade; HR = high-risk; n = number; PFS = progression-free survival.

Table 7.4: Treatment options for BCG-unresponsive tumours - Carcinoma *in situ* ± papillary

Carcinoma *in situ* ± papillary								
Compound	**Study design**	**n**	**FU (mo.)**	**Complete response (%)**			**PFS**	**Adverse events**
				3 mo.	**6 mo.**	**12 mo.**		
Intravesical								
NADOFARAGENE FIRADENOVEC* [484]	Phase III Cis Cohort NCT02773849	103	19.7	53.4	40.8	24.3		G3 4%
CREMOSTIMOGENE GRENADENOREPVEC (CG0070) [474]	Phase II	45			58 CIS 50 CIS+P			G1-2 82.5% G ≥ 3 4.5%
N-803 Nogapendekin Alfa Inbakicept + BCG* [486]	Phase II/III QUILT 3032 CA	82	23.9	55.0	56.0	45.0		G1-2 86% G ≥ 3 23%
TAR 200* [476]	Phase II b SunRISe-1 C2 NCT04640623	81	20.2	78.8	58.8	45.9	94.3	Any G 83.5% G ≥ 3 12.9%
RITE [467]	Phase III HYMN NCT01094964	61	36	30 vs. 47				G1-2 81%
EMDA-MMC [466]	Phase II	8	36	62.5		35.5		23.1 % local / 11.5 Allergic
VALRUBICIN* [494, 495]	Phase III	87	30		21			86% Bladder 50% other 20 SAEs 2 TRSAEs
GEMCITABINE DOCETAXEL [483]	Phase II	19	14		75 HR RFS	69 HR RFS	91.4	G1-2 75% G ≥ 3 2.5%
Systemic								
PEMBROLIZUMAB* [488]	Phase II Cohort A KEYNOTE-057 NCT02625961	96	36.4	41.0		18.7		G1-2 53.0% G ≥ 3 13%

ATEZOLIZUMAB [471]	Phase II Cohort A SWOG 1605 NCT02844816	74	41	43	27.0		90.5	G1-2 70.0% G ≥ 3 14%
CETRELIMAB [476]	Phase II b SunRISe-1 C3 NCT04640623	28	29.2			38.5		Any G 53.6% G ≥ 3 7.1%
Combination intravesical and systemic								
CREMOSTIMOGENE GRENADENOREPVEC + PEMBROLIZUMAB [491]	Phase II CORE-001 Trial NCT04387461	35	26.5	82.9%	57.1%	51.4 %		G3 14.3%
TAR 200 + CETRELIMAB [476]	Phase II b SunRISe-1 C1 NCT04640623	53	33.4			55.6		Any G 92.5% G ≥ 3 37.7%

**FDA-approved drug*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; DFS = disease-free survival; FDA = United States Food and Drug Administration; FU = follow-up; G = grade; HR = high-risk; n = number; PFS = progression-free survival; RFS = recurrence-free survival.

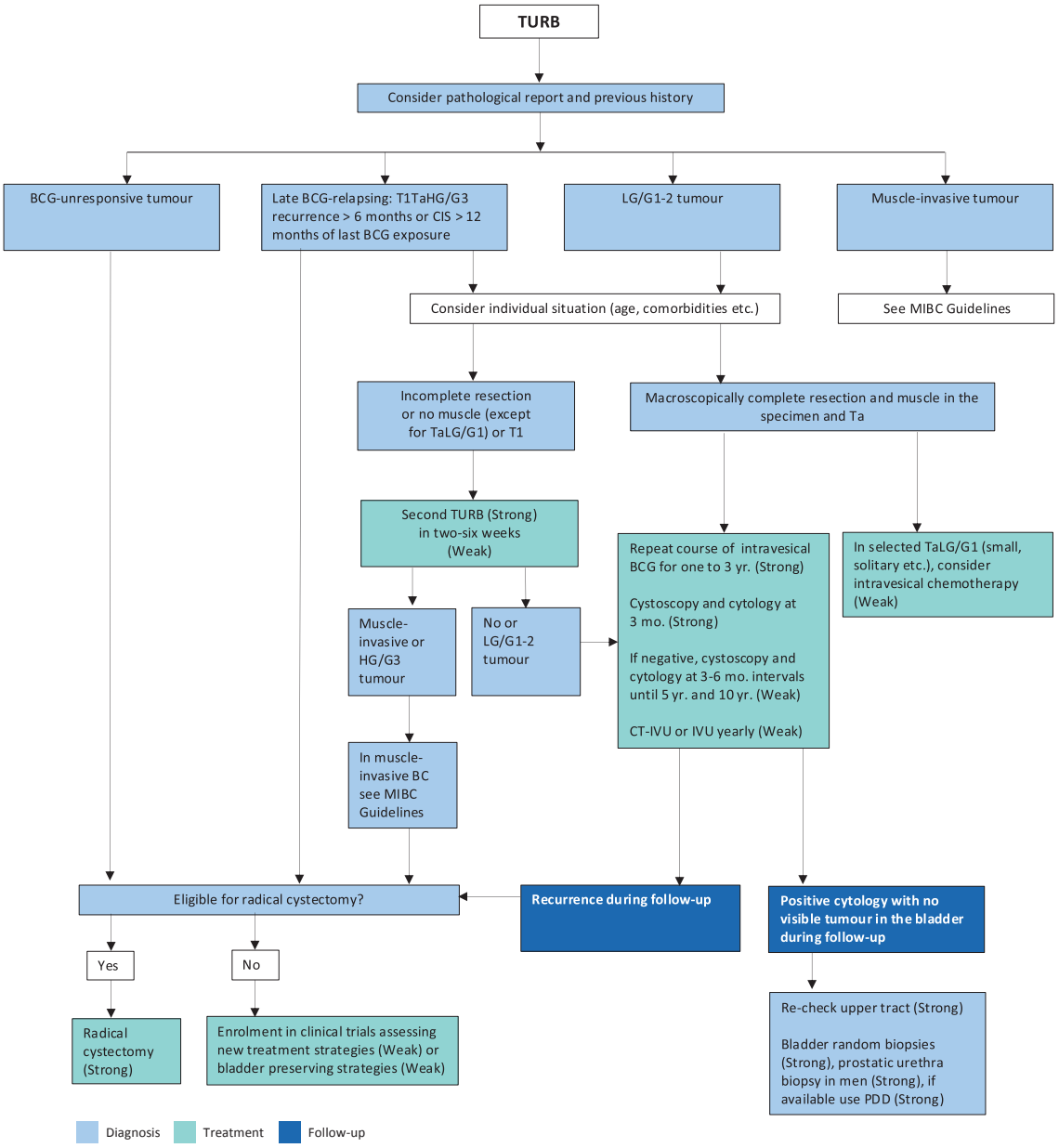
*7.8.3 **Summary of evidence - treatment failure of intravesical therapy***

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

7.9 Multidisciplinary tumour board

A multidisciplinary tumour board (MTB) approach, including reassessment of radiology and pathology, is associated with a changed treatment plan in up to 44% of BC patients [248, 249, 496, 497], such as refraining from or recommending cystectomy in 7% of stage T1 patients [249, 496, 497], often as a result of the pathologic review [79, 249]. Thus, patients with high-risk and very high-risk NMIBC will especially benefit from MTB discussion and such an approach is recommended for these patients. Figure 7.1 presents a treatment flowchart based on risk category, which may guide management of an individual patient.

Figure 7.2: Treatment strategy in recurrence during or after intravesical BCG



BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CT = computed tomography; HG = high-grade; IVU = intravenous urography; LG = low-grade; PDD = photodynamic diagnosis; TURBT = transurethral resection of the bladder tumour.

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

Recommendations - general	**Strength rating**
Counsel smokers to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder tumour (TURBT) 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 European Association of Urology (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 TURBT, 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 (LG) Ta tumours can be effectively and safely offered office fulguration.	Strong
Offer active surveillance (AS) and/or chemoablation to selected patients with presumed LG tumours as an alternative to endoscopic ablation.	Weak
In patients with high-risk tumours, full-dose intravesical bacillus Calmette-Guérin (BCG) for one to three years (induction plus three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and access to BCG. Immediate radical cystectomy (RC) should also be discussed with the patient.	Strong
In patients with very high-risk tumours, discuss immediate RC. Intravesical full-dose BCG instillations for one to three years remain an option for selected patients, particularly those who decline or are unfit for RC.	Strong
Discuss the benefits and harms of adding sasanlimab and durvalumab to BCG with maintenance in selected BCG-naïve patients with high- and very high-risk NMIBC.	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 because it most precisely defines the patients who are unlikely to respond to further BCG instillations.	Strong
Offer an RC to patients with BCG-unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, or who decline RC, 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.	Strong
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURBT.	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 TURBT; • in patients with visible haematuria; • after traumatic catheterisation; and • 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 [395].*

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

Recommendations	Strength rating
European Association of Urology (EAU) risk group: Low	
Offer one immediate instillation of intravesical chemotherapy after transurethral resection of the bladder tumour (TURBT).	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 Bacillus Calmette-Guérin (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 TURBT.	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 7.5: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy. 2. Enrolment in clinical trials assessing new treatment strategies. 3. Other bladder-preserving strategies in patients ineligible for or refusing RC, including approved new treatment strategies when available.
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. Enrolment in clinical trials assessing new treatment strategies. 3. Other bladder-preserving strategies.
BCG exposed	1. Repeat BCG course or RC according to a patient's individual situation. 2. 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.

BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; LG = low-grade; RC = radical cystectomy.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

Due to the risk of recurrence and progression, patients with NMIBC require follow-up after treatment. The first cystoscopy after TURBT at three months is an important prognostic indicator for recurrence and progression [264, 265, 292, 295, 498]. Therefore, the first cystoscopy should always be performed three months after TURBT 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 (Chapter 6) which predict the short- and long-term risks of recurrence and progression in individual patients (Section 8.1) [251, 253]. 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

The 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 [294, 499]. In addition, recurrence after five recurrence-free years is low [295]. Therefore, in low-risk tumours, after five years of follow-up, discontinuation of cystoscopy or its replacement with less invasive methods should be considered [498, 500, 501]. For example, one study found that a negative dipstick test for haematuria has a high negative predictive value in two cohorts with low-risk tumours at follow-up (0.89 and 0.94, respectively), suggesting its possible use as a surveillance strategy with limited costs [502].

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 [257]; 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 of multiple and/or recurrent grade 1 and 2 tumours [503], these patients can be safely followed-up with a cystoscopy at three months and, if negative, with six monthly cystoscopies for two years followed by yearly cystoscopies up to ten years. This surveillance scheme for this disease category has already been adopted by the Scottish Access Collaborative Workstream [504]. Due to lack of data supporting the safety of a reduced scheme in the subgroup of HG intermediate-risk NMIBC, the Panel recommend this group be followed-up in the same way as high-risk NMIBC.

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

In originally high-risk or very high-risk tumours that were 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 voided urine cytology. Recurrences after ten years tumour-free are not unusual [505]. Therefore, the optimal surveillance strategy for these patients includes initial frequent cystoscopy and voided urine cytology and life-long follow-up [498].

8.1.4 Follow-up of extravesical sites urothelium

The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in males and upper urinary tract in both genders, particularly after double-J stenting during TURBT) [506]. This risk becomes significant for both sites in high-risk tumours [107], with ten-year tumour rates in the upper urinary tract varying between 1.9% in T1 tumours [507] and 25% in patients with multiple and recurrent high-risk NMIBC [508]. In a population-based study, 3.6% of patients with high-risk tumours (Ta G3 and CIS) developed upper urinary tract disease within ten years of diagnosis [509]. Voided 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.a Enhanced visualisation

There may be a role for newer methods of tumour visualisation in follow-up cystoscopy. However, a systematic review and meta-analysis including two randomised trials showed that 100 blue light flexible cystoscopies (BLFC) are needed to detect any additional tumour and 50 to detect one CIS when consecutively applying BLFC during follow-up, suggesting a risk stratified strategy when considering BLFC during follow-up [510].

8.1.5.b 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 if cystoscopy is not possible or refused by the patient [144, 511, 512].

8.1.5.c Urine cytology

Non-invasive follow-up strategies include urine cytology as an adjunct (or companion) test to improve detection of HG disease at the time of flexible cystoscopy. With the implementation of the Paris system when reporting urinary tract cytology with the emphasis on improving the detection of HG tumours and recognising the limitation of cytology in diagnosing LG disease, urine cytology is not recommended for follow-up in the low-risk group and intermediate-risk group (with the exception of HG/G3 tumours). However, the Paris system has improved the clinical utility in HG disease as demonstrated in a systematic review where the average proportion HG malignancy for the three categories atypical urothelial cells (atypia), suspicious for HG UC (suspicious), and HG/G3 UC (malignant) were 40%, 81%, and 91%, respectively [513].

8.1.5.d Urinary molecular markers

Non-invasive follow-up strategies include urinary cytology and urinary molecular marker tests as an adjunct test to improve detection of HG disease at the time of flexible cystoscopy or as replacement tests to reduce the number of flexible cystoscopies (marker guided use). In order to reduce or replace cystoscopy altogether, urinary markers should be able to detect recurrence in all or specific risk groups. However, the reported low sensitivity for LG recurrences limits their utility in this group [141, 514] although more recent studies have shown reasonable sensitivity of 40-65% in detecting LG recurrences [515, 516].

For clinical implementation of urinary molecular markers for NMIBC surveillance, some key issues are relevant [143]:

- Inflated negative predictive value (NPVs): Prevalence of recurrence influences both NPV and PPV at a given sensitivity and specificity, i.e. a low proportion of recurring patients in a cohort automatically renders a higher NPV. For example, a urinary marker missing all recurrences in a cohort in which 15% recur will display an NPV of 0.85 despite not being clinically useful.
- Clinical context: In a patient with high- or very high-risk NMIBC, the consequence if a urinary marker test misses recurrent disease is more severe than in a patient with either low- or intermediate-risk NMIBC. In these lower risk categories, the clinical utility of a urinary marker would be to postpone or even replace a cystoscopy (marker guided use). Moreover, in a high-risk NMIBC scenario, a marker-enforced application would be simultaneously relevant to improve detection of a HG recurrence.
- Patient preferences: Patients prefer certainty over the burden of cystoscopic surveillance [517].
- Cost-effectiveness: Must be shown prior to implementation, i.e. to calculate quality-adjusted life-years (QALY), total costs, and incremental cost effectiveness ratios (ICERs) for different follow-up scenarios.

Some urinary markers, chiefly those detecting multiple genetic alterations in the urine (so-called “multiplex” urine 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 [516, 518-520] (Table 8.1). Additionally, two randomised trials explored the use of marker-guided surveillance in low- and intermediate-risk patients [127] and the role of alternating a specific urinary marker (the Xpert BC Monitor) with cystoscopies in HG tumours [128], respectively, with both studies showing non-inferiority compared to standard surveillance. In the low- and intermediate-risk setting, a panel of urinary molecular markers were applied every six months after a negative three-month cystoscopy, which altogether detected > 80% of recurrences according to the study hypothesis. However, the marker or combination of markers to be adopted remains unclear [127]. In patients with HG tumours and a negative follow-up cystoscopy, alternating the urine marker with current standard surveillance (a cystoscopy at follow-up year one and two) significantly reduced the number of follow-up cystoscopies without affecting detection of any recurrence at a median of two years follow-up [127]. XPERT BC® MONITOR showed high sensitivity (91%) for the detection of HG disease at the price of 16% PPV (false positive result in nearly one out of three patients). Table 8.2 summarises the current recommended follow-up scheme for NMIBC according to the disease risk category.

Table 8.1: Performance of multiplex urine markers in the surveillance setting

Multiplex urinary marker	Target	Sensitivity Overall*	HG*	Specificity Overall*	HG*	N studies/patients
XPERT BC® MONITOR [134]	5 mRNAs *(ABL1, CRH, IGF2, ANXA10, UPK1B)*	52-91	79-100	41-91	76-91	11 studies 2,800 pts
EpiCheckTM [133]	15 DNA methylations	62-90	78-95	82-88		6 studies 2,236 pts
CX BLADDER [521]	5 mRNAs *(IGF, HOXA, MDK, CDC, IL8R)*	93	95	61	-	1 study 763 pts
UROMONITOR [522, 523]	DNA mutations *FDFR 3 + TERT + KRAS*	49-93	-	86-99	-	5 studies 1,190 pts
Galeas Bladder [524]	Multiple DNA mutations (n = 443 in 23 genes)	86	100	63	-	1 study 293 pts

DNA = deoxyribonucleic acid; FDFR = fibroblast growth factor receptor; HG = high-grade; KRAS = Kirsten rat sarcoma viral oncogene homolog; mRNA = messenger ribonucleic acid; n = number; TERT = telomerase reverse transcriptase.
** Ranges refer to the lowest and the highest value respectively reported from available individual studies or systematic reviews.*

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	Computed tomography (CT) annually up to 5 years, then CT every 2 years up to 10 years Life long	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 TURBT for NMIBC

Summary of evidence	LE
The first cystoscopy after TURBT at three 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 intermediate-risk Ta low-grade tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy can be repeated every six months for two years, and then annually for ten years. The subgroup of patients with intermediate-risk Ta that are high-grade should be followed up as high-risk (see below).	Weak

Patients with high-risk and those with very high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then annually lifelong.	Weak
Take yearly and long-term upper tract imaging (computed tomography [CT] urography) for high-risk and very high-risk tumours.	Weak
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping biopsies or photodynamic diagnosis-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 Patient Reported Outcome Measures and Patient Reported Experience Measures 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 [525, 526]. 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 [527]. In an effort to add further outcome measures of importance to patients with NMIBC, a NMIBC Symptom Index (NMIBC-SI) has been developed [528].

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 PROMs for patient-centred research design. A prospective evaluation, where 108 patients filled out the ICIQ-LUTS questionnaire regarding urinary symptoms, postoperative side effects, and QoL (EQ-5D-3L) at days one and 14 postoperatively, found that the most frequently reported outcomes were postoperative haematuria and pain. Patients undergoing TURBT reported longer lasting haematuria, a higher perception of pain, and a more negative impact on QoL, compared to patients undergoing TULA [290]. From the ENVISION single arm trial, where patients received chemo-ablation with Mitomycin (UGN-102) instead of TURBT, patients perceived that TURBT interfered more with their routine/responsibilities; urinary symptoms were perceived to be similar, but bleeding, catheter issues, and time to resuming sexual activity lasted longer with TURBT, and patients would recommend UGN-102 to other patients as it was perceived to be less invasive, less painful, and less time-consuming than TURBT [529].

9.2 Quality Indicators in bladder cancer

Evidence based QIs and 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 [530]. 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 BC have been suggested [531-534]. The table below represents the general and NMIBC-related QIs adapted from Leow *et al.*, [533] and the Scottish QPI programme [534]. Quality indicators and QPIs should be SMART (Specific, Measurable, Achievable, Relevant, Trainable) [530]. In 2014, Scotland introduced such a programme for BC [534] and have been an exemplar by demonstrating high levels of compliance to QPIs while reducing practice variation across the country, and also demonstrating the clinical value of such a programme [184], including development of prognostic models [504].

Successful implementation of a QI programme has the potential to inspire and catalyse clinical excellence in contemporary BC practice [530]. It is equally important that prospective audit-feedback mechanisms are utilised to improve outcomes and modify QIs using emerging evidence, to ensure they are fit for purpose [535].

Table 9.1: Quality indicators for general aspects of BC and NMIBC care, adapted from [533, 534]

General aspects of BC care	Recommended Quality Indicators
Appropriate imaging for patients newly diagnosed with BC.	Newly diagnosed BC patients who have cross-sectional imaging of upper urinary tract (e.g. CT, MRI or US), as recommended in Section 5.4.
Participation in clinical trials	Availability of clinical trials to BC 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 Ta LG disease).
	Use of a Bladder Diagram, as per Figure 5.1.
Re-staging TURBT	Restaging TURBT should be performed within two to six weeks of the initial TURBT and include resection of the primary tumour site, as recommended 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 (e.g. 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 BC	Appropriate intervals between cystoscopic surveillance, as per Table 8.2.
	Appropriate assessment of the upper urinary tract in high-risk patients.

BC = bladder cancer; BCG = bacillus Calmette-Guérin; CT = computed tomography; EAU = European Association of Urology; EORTC = European Organisation for Research and Treatment of Cancer; MRI = magnetic resonance imaging; NMIBC = non-muscle-invasive bladder cancer; TURBT = transurethral resection of the bladder tumour; US = ultrasound.

10. PRAGMATIC DE-INTENSIFICATION STRATEGY IN NMIBC

The challenges that face contemporary management of patients with NMIBC are a direct corollary to the global burden of an aging population and the rising cost of healthcare provision. It is therefore vital that healthcare systems and clinical processes are both effective and efficient, while being cognisant and respectful of impacts on patient QoL, as well as family or other informal caregivers [536].

With improvements and the wider conscious efforts to improve the quality of NMIBC care, recurrence and progression rates have fallen in the recent past. However, as these improvements come with added complexity and cost to healthcare, clinicians must consider commensurate de-intensification of interventions along the pathway of selected patients. Utilisation of contemporary definitions of progression, for instance, will also ensure interventions are targeted towards appropriate and pragmatic outcomes [456]. A review exploring the efficacy and safety of de-intensified treatment strategies for recurrent Ta LG NMIBC revealed that AS, chemoablation and office fulguration are valid treatment options for recurrent Ta LG NMIBC without compromising oncological safety [537].

Approaches to healthcare, particularly in the elderly and frail, must be realistic. Scotland, for example, introduced a national “Realistic Medicine” programme with several pragmatic principles in this regard, creating an environment emphasising shared decision-making [538]. A multidisciplinary oversight with expert clinician involvement is essential to making this work and is expected to facilitate effective diagnostic and therapeutic interventions, safeguarding patients from healthcare-related harm. Additionally, processes of audit-feedback and achieving benchmarks must be central to ensuring real-world translation of effective interventions.
The Guidelines Panel have therefore considered several of these aspects within some of the Sections, where interventions could be de-intensified based on a shared decision-making process in fully informed and consenting patients:

1. Resection of detrusor muscle can be avoided in patients with LG Ta NMIBC - Section 5.10
2. The single post-TURBT chemotherapy instillation (SI-IVC) is very effective in reducing recurrence in patients with LG Ta NMIBC. Cystoscopic prediction of this group of patients will allow for selective utilisation of SI-IVC - Section 7.4.2.a
3. Selective Re-TURBT in high-risk NMIBC - Section 5.13
4. Active Surveillance in recurrent LG Ta - Section 7.3 - and/or office fulguration for recurrent LG Ta - Section 7.2 - and/or chemo-ablation in recurrence LG Ta - Section 7.5
5. Bacillus Calmette-Guérin instead of cystectomy as an option for very high-risk NMIBC - Section 7.6 - and new evidence in favour of BCG in this group of patients [539]
6. Bladder preservation options for BCG-unresponsive disease - Section 7.8.2
7. Reduced frequency/intensity of surveillance (cystoscopy and CT urography) in NMIBC or cystoscopy in case of haematuria only - Section 8.1.2
8. Consideration of “doing nothing” and taking a supportive approach in selected frail patients. Perhaps using PROMS/PREMS for monitoring remotely instead - Section 9.1.

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12. CONFLICT OF INTEREST

All members of the NMIBC 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 provided below and is also publicly available on the EAU website: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/panel.

This Guidelines document was developed with the financial support of the EAU. 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.

Disclosures: The EAU Guidelines Office certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g. employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following:

P. Gontero (Chair) reported receiving company speaker honoraria fees from Merck, Janssen and Medac; serving as a company consultant to Ferring, Medac, Pfizer, Photocure, MSD and AstraZeneca; receiving grants or research support from Intuitive Surgical, Astellas and Ferring; acting as chair of the institution for clinical trials by Johnson & Johnson; and participation in clinical trials by Ferring and Catalym. J. Baard reported receiving company honoraria or consultation fees from Astellas, Boston Scientific, Coloplast, Cook, GSK, Olympus, Storz, TSC life and UroGen Pharma; and receiving fellowship or travel grant support from Astellas. A. Birtle reported receiving company speaker honoraria fees from Johnson & Johnson, Astellas, MSD, Merck, Accord and Bayer;

serving as a company consultant to MSD, Bayer, Macrogenics and Ipsen; serving on the advisory board of Macrogenics, Johnson & Johnson, Astellas, Merck and AstraZeneca; being a trustee/medical advisor to Fight Bladder Cancer; and being a member of the ESMO Educational Committee. E.M. Compérat reported serving as a company consultant to Daiitchi, Johnson & Johnson and Astra. J.L. Dominguez-Escrig reported receiving company speaker honoraria fees from Presurgy, BMS and Angiodynamics; attending advisory board meetings as a company consultant to Astellas; and participation in clinical trials by Janssen, Arquer, Physion, Combat BRS, Ipsen, Storz, Uromonitor, Fidia Farmaceutici and Angiodynamics. P. Mariappan reported receiving company speaker honoraria fees from BMS, Janssen Cilag, Medac Pharma and Photocure; serving on the core committee of the International Bladder Cancer Group; receiving grants or research support from Nucleix; and participation in clinical trials by Nucleix. A. Masson-Lecomte reported receiving company speaker honoraria fees from Astellas Pharma, BMS, Ferring, Medac and MSD; attending advisory board meetings as a company consultant to Janssen Global Bladder Cancer and Pfizer; being an academy faculty advisor to Photocure; receiving grants or research support from Ferring and Ipsen Pharma; and participation in clinical trials by Janssen Cilag and MSD. B. Pradere reported receiving company honoraria or consultation fees from Astellas Pharma, Ferring, Johnson & Johnson, Laboratoires MSD, Ipsen Pharma and Photocure; serving as a company consultant to Johnson & Johnson; and participation in clinical trials by AstraZeneca and Johnson & Johnson. B.P. Rai reported receiving company speaker honoraria fees from Ipsen, Janssen-Cilag and Bayer. B.W.G. van Rhijn reported receiving advisory board meeting company consultation fees from Cepheid. T. Seisen reported receiving company honoraria or consultation fees from ADACAP, Astellas, Bayer, BMS, Ipsen, Janssen, MSD, Pfizer and VitaDX; receiving grants or research support from Institut de Recherche Servier and Ipsen; receiving fellowship or travel grant support from Institut de Recherche Servier; and participation in clinical trials by AstraZeneca, Ferring, Janssen and Roche. S.F. Shariat reported receiving company honoraria or consultation fees from Astellas Pharma, AstraZeneca, Bayer Austria, BMS, Ferring, Johnson & Johnson, MSD and Pfizer; and is the owner of four patents. J. Teoh reported receiving company speaker honoraria fees from Ferring Pharmaceuticals, Olympus Corporation and Astellas; serving as a company consultant to Johnson & Johnson, Ferring and MSD; receiving grants or research support from Olympus Corporation; and participation in clinical trials by AstraZeneca, BMS and Johnson & Johnson. E.N. Xylinas reported receiving company honoraria or consultation fees from Pfizer, Astellas, AstraZeneca, Boston Scientific, BMS, Ferring, Johnson & Johnson, Merck, MSD and Pfizer; receiving grants or research support from AstraZeneca, Boston Scientific and Ferring; participation in clinical trials by AstraZeneca, Janssen Cilag, MSD and Pfizer; and serving in a leadership role for the Association Française d'Urologie. D. D'Andrea reported receiving company speaker honoraria fees from Merck, Photocure, Olympus and Pfizer; and serving as a company consultant to Cepheid. O. Capoun reported receiving company honoraria or consultation fees from Accord Healthcare, Astellas Pharma, AstraZeneca, Bayer, Janssen and Novartis; and participation in clinical trials by Bayer and Janssen. M. Moschini reported receiving company honoraria or consultation fees from Janssen Cilag, Medac Pharma, Photocure and Johnson & Johnson; and serving as a company consultant to Pfizer Italiana. F. Soria reported receiving company honoraria or consultation fees from Medac Pharma, Johnson & Johnson, Photocure, Pfizer, AstraZeneca and Cepheid; and participation in clinical trials by Fidia Farmaceutici, Janssen, Steba biotech and Catalym. F. Liedberg, V. Soukup, E. Fiorini and R. Wood have nothing to declare.

13. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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