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

P. Gontero (Chair), A. Birtle, E. Compérat,
J.L. Dominguez Escrig, F. Liedberg, P. Mariappan,
A. Masson-Lecomte, B.W.G. van Rhijn, T. Seisen,
S.F. Shariat, J. Teoh, E.N. Xylinas
Patient Advocates: L. Makaroff, R. Wood
Guidelines Associates: O. Capoun, M. Moschini,
B. Pradere, B.P. Rai, F. Soria, V. Soukup
Guidelines Office: E.J. Smith

European Association of Urology

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). The information presented is limited to urothelial carcinoma (UC), unless specified otherwise. The aim is to provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation. Separate EAU Guidelines are available addressing upper tract urothelial carcinoma (UTUC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2] and primary urethral carcinoma [3].

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

1.2 Panel composition

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

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2024 [4]. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer. A EAU Guidelines App for iOS and Android devices is also available 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 Bladder Cancer were first published in 2000. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates This 2025 NMIBC Guidelines present a limited update of the 2024 publication.

*1.4.2 **Summary of changes***

For the 2025 NMIBC Guidelines new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. This resulted in the inclusion of 36 updated studies across the Guidelines. Key changes include:

- The addition of a new recommendations to Section 5.9 related to the timing of MRI for local staging of bladder cancer. In addition, in Section 5.9 the recommendation on the use of flexible cystoscope in men and women has also been updated.
- A new section, Section 6.3, on histological subtypes has been added to the guideline including Table 6.1 which outlines subtype prognostic factors and risk of progression.
- Section 7.9.2 “Recurrence during or after intravesical BCG therapy” has been restructured to more clearly present the definitions of BCG failure and the treatment options for BCG-unresponsive tumours.
- Adaption of the recommendation on active surveillance in Section 7.10.
- Significant adaption and expansion of Section 8.1.5.4 “Urinary molecular markers” including the inclusion of a new table on the performance of multiplex urine markers in the surveillance setting.
- Addition of a new section, Section 10, on pragmatic de-intensification strategy for NMIBC.

2. METHODS

2.1 Data Identification

For the 2025 NMIBC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive scoping exercise covering all areas of the NMIBC Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between the 1st May 2023 and 1st May 2024. A total of 743 unique records were identified, retrieved, and screened for relevance. A total of 36 new references were added to the 2025 NMIBC Guidelines. A detailed search strategy is available online: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/publications-appendices.

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

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

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

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

2.2 Review

The 2024 publication was peer reviewed prior to publication.

2.3 Future goals

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

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

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

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

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

3.2 Aetiology

*3.2.1 **Main risk factors***

3.2.1.1 Tobacco

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

3.2.1.2 Occupational exposure

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

*3.2.2 **Genetic***

Family history seems to have little impact [19]; 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 [20]. To date, no clinically relevant genetic alteration has been linked to BC. Genetic predisposition may lead to a higher susceptibility to other risk factors, and thereby explain the familiar clustering of BC in first- and second-degree relatives (HR: 1.69; 95% CI: 1.47–1.95) [8, 21-26] that has been confirmed more recently [27]. A recent study identified three single nucleotide polymorphisms related to the development of aggressive NMIBC [28]. Currently, there is insufficient evidence to support genetic screening for BC.

*3.2.3 **Dietary habits***

Dietary habits seem to have limited impact on the risk of developing BC. A protective impact of flavonoids has been suggested [29]. 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) [30-34]. Western diet (high in saturated fats) and organ meat has been shown to increase the risk of BC in a recent meta-analysis [35, 36]. The impact of an increased consumption of fruits has been suggested to reduce the risk of BC. This effect has been demonstrated to be significant in women only (HR: 0.92; 95% CI: 0.85–0.99) [37]. This gender discrepancy was also evident in the BLEND study which

showed that in men moderate or high intake of vitamins B1, B2 and vitamins related to energy metabolism were found to be associated with an increased BC risk, whereas in women high intake of the same vitamins and vitamin combinations was shown to have a protective effect with the exception of the entire B group vitamin complex [38]. One possible explanation for this gender discrepancies is the difference in the main source of vitamin intake among study participants, being meat in men and fruits/vegetables in women. In addition, higher consumption of tea has also been associated with a reduction in risk of BC in men but through an interaction with tobacco smoking; therefore, making the protective effect of this compound questionable [39]. 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 [40]. 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 risk of recurrence and progression [41]. 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. Additionally, exposure to arsenic in drinking water has been suggested to increase the risk of BC [8, 42]. Arsenic intake and smoking have a combined effect [43]. Conversely, chronic exposure to nitrate in drinking water does not seem to be associated with increased risk of BC [44].

The association between personal hair dye use and risk of BC remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow NAT2 acetylation phenotype [8] but a large prospective cohort study could not identify an association between hair dye and risk of cancer and cancer-related mortality [45].

*3.2.5 **Pelvic radiation***

Exposure to pelvic ionising radiation is associated with an increased risk of BC [46, 47]. 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 [46]. 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 [47].

*3.2.6 **Other***

The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol, and triglycerides) remains uncertain [48]. However, data suggest that high circulating levels of vitamin D and physical exercise are associated with a reduction in the risk of BC [49, 50]. Schistosomiasis, which is an infection caused by a parasitic trematode, can lead to BC [8]. A weak association was also suggested for cyclophosphamide and pioglitazone [8, 42, 51].

3.3 Summary of evidence for epidemiology and aetiology

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

4. PATHOLOGICAL STAGING, GRADING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Urothelial tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system [52]. Intra-epithelial, high-grade (HG) tumours confined to the mucosa are classified as CIS (Tis). All of these tumours can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. The term 'Non-muscle-invasive BC' represents a group definition and all tumours should be characterised according to their stage, grade, and further pathological characteristics (see Sections 4.5 and 4.7 and the International Collaboration on Cancer Reporting website: http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/bladder. The term 'superficial BC' should no longer be used as it is incorrect.

4.2 Tumour, Node, Metastasis Classification (TNM)

The latest TNM classification approved by the Union International Contre le Cancer (UICC) (8th Edn.) is referred to (Table 4.1) [52].

Table 4.1: 2017 TNM classification of urinary bladder cancer

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

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 sub-staging) has been demonstrated to be of prognostic value in retrospective cohort studies [52, 53]. Its use is recommended by the most recent 2022 World Health Organization (WHO) classification [54, 55]. T1 sub-staging methods are based either on micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles; however, the optimal classification system remains to be defined [56, 57].

4.4 Lymphovascular invasion

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with an increased risk of pathological upstaging and worse prognosis [58-62]. Immunohistochemistry for confirmation is not mandatory [54] .

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

4.5.1 Types of histological grading systems

In 2004 the WHO published a histological classification system for UCs including papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive papillary carcinoma low grade (LG) and HG. This system was also taken into the updated 2016/2022 WHO classifications [54, 55]. It provides a different patient stratification between individual categories compared to the older 1973 WHO classification, which distinguished between grade 1 (G1), grade 2 (G2) and grade 3 (G3) categories [56, 63].

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) [64, 65]. According to a multi-institutional individual patient data analysis, the proportion of tumours classified as PUNLMP (WHO 2004/2016) has decreased to very low levels in the last decade [66].

4.5.2 Prognostic value of histological grading

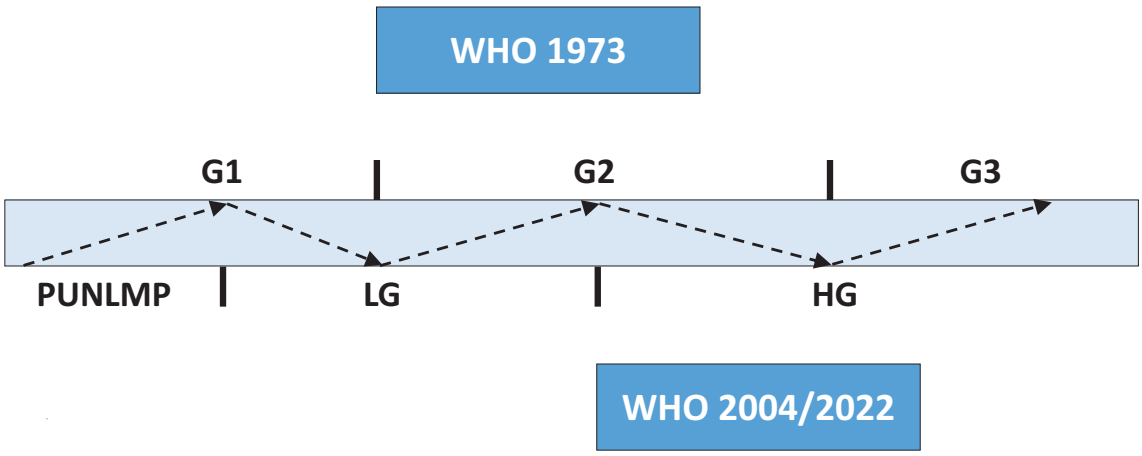
A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression [64].

To compare the prognostic value of both WHO classifications, an individual patient data analysis of 5,145 primary TaT1 NMIBC patients from 16 centres throughout Europe and one in Canada was conducted. Patients had a transurethral resection of bladder tumour (TURBT) followed by intravesical instillations at the physician's discretion. In this large study, the WHO 1973 and the WHO 2004/2016 were both prognostic for progression but not for recurrence. When compared, the WHO 1973 was a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 3-tier (LG/G1-G2, HG/G2 & HG/G3) or a 4-tier hybrid combination LG/G1, LG/G2, HG/G2 and HG/G3) of both classification systems proved to be superior to either classification system alone, as it divides the large group of G2 patients into two subgroups (LG/HG) with different prognoses [67]. In a subgroup of 3,311 patients with primary Ta bladder tumours, a similar prognosis was found for PUNLMP and Ta LG carcinomas [66].

4.5.3 Clinical application of histological grading systems

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

Figure 4.1: Schematic representation of tumours according to grade in the WHO 1973 and 2004/2022 classifications [67]*



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

Note: the 2004/2022 WHO classification is the updated version of 2004/2016 WHO classification. According to a series of 5,145 primary Ta-T1 patients, the distribution of G1, G2 and G3 in the WHO 1973 classification is 23.5, 49.3 and 27.2%, respectively while the corresponding PUNLMP, LG and HG rates for the WHO 2004/2022 system are 1.5, 49.8 and 48.7%, respectively [67]. Figure reproduced with permission from Elsevier from [67].

4.6 Carcinoma *in situ*

Carcinoma *in situ* is an intra-epithelial, HG, non-invasive UC. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract (UUT), prostatic ducts and urethra [68].

From a clinical point of view, CIS may be classified as [69]:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

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

There is significant variability among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70–78% of cases [70]. There is also inter-observer variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2022 classifications. The general conformity between pathologists in staging and grading is 50–60% [71-74]. The WHO 2004/2022 classification provides slightly better reproducibility than the 1973 classification [64].

4.8 Subtypes of urothelial carcinoma

Currently the following differentiations of UC are used [75, 76]:

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

In the new WHO 2022 all subtypes are considered HG [55]. Up to 14.6% of NMIBC may harbour a urothelial subtype [77]. The percentage of subtype in the specimen should be reported since it has been shown to be of prognostic value [78]. The WHO 2022 classification considers all subtypes UC (LG and HG) with more than 5% of HG as a HG tumour [2, 78-85]. 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 [86-90]. 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 [57, 91, 92].

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.	2a
Tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis).	2a
Histological grading of urothelial NMIBC is classified according to the WHO 2004/2016/2022 (PUNLMP, LG/HG) systems and/or WHO 1973 (G1–G3).	2a

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

Recommendations	Strength rating
Use the 2017 Tumour, Node, Metastasis Classification (TNM) system for classification of the depth of tumour invasion (staging).	Strong
Provide T1 sub-stage if the lamina propria is adequately sampled using either micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles.	Weak
Use both the 1973 and 2004/2022 WHO grading classification systems, or a hybrid system.	Weak
Do not use the term 'superficial' bladder cancer.	Strong

5. DIAGNOSIS

5.1 Patient history

A focused patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher stage at diagnosis disease compared to nonvisible haematuria [93]. 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 [94, 95].

Intravenous urography (IVU) is an alternative if CT is not available [96], but CT urography provides more information particularly in muscle-invasive tumours of the bladder and in UTUCs (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography once a bladder tumour has been detected is questionable due to the low incidence of significant findings which can be obtained [97-99]. The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [98]. The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [100].

*5.4.2 **Ultrasound***

Ultrasound (US) may be performed as an adjunct to physical examination as it has moderate sensitivity to a wide range of abnormalities in the upper- and lower urinary tract. It permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder, but cannot rule out all potential causes of haematuria [101, 102]. 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) may provide additional information regarding the local staging of BC. A standardised methodology of MRI reporting (Vesical Imaging-Reporting and Data System [VI-RADS]) in patients with BC has been developed [103]. 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 [104]. A diagnosis of CIS cannot be made with imaging methods alone (CT urography, IVU, US or MRI).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG and G3 tumours (84%), but low sensitivity in LG/G1 tumours (16%) [105]. The sensitivity in CIS detection is 28–100% [106]. A recent report applying the Paris system found a sensitivity of 46% for HG disease [107]. Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours; it is not designed to detect LG tumours. Positive voided urinary cytology can indicate an UC anywhere in the urinary tract; negative cytology, however, does not exclude its presence.

Cytological interpretation is user-dependent [108, 109] and evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations: although in experienced hands specificity exceeds 90% [110]. Artificial intelligence algorithms combined with digital image processing (VisioCyt test) improved the sensitivity of cytology for HG tumours up to 92% [111].

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 [112]:

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

The principle of the system and its terminology underlines the role of urinary cytology in detection of G3 and HG tumours. The Paris system for reporting urinary cytology has been validated in several retrospective studies [113, 114]. A prospective study suggests that voided urine cytology can be used to risk-stratify patients with NMIBC prior to TURB, 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% PPV [115].

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [112]. In patients with suspicious cytology repeat investigation is advised as the underlying risk of a high grade lesion is between 24-53% [116].

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 [117, 118]; however, none of these markers have been accepted as routine practice by any clinical guidelines for diagnosis or follow-up.

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

- Sensitivity is usually higher at the cost of lower specificity compared to urine cytology [112].
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests [119].
- Requirements for sensitivity and specificity of a urinary marker test largely depend on the clinical context of the patient (screening, primary detection, follow-up [high-risk, low/intermediate-risk]) [112].
- Several commercially available urinary biomarkers, assessing multiple targets to increase sensitivity, have been tested in prospective multicentre studies [120-124].
- 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 (FGFR3) or Telomerase Reverse Transcriptase promotor (TERT) gene and microsatellite analysis may identify patients more likely to experience disease recurrence and possibly progression [125-132].
- Practical and cost-effectiveness dimensions and certification of *in vitro* diagnostics (CE-IVD) should be considered before clinical implementation of urinary molecular marker tests [133].

5.7 Potential application of urinary cytology and markers

Urine cytology and/or other urinary markers have been assessed in the following clinical contexts.

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 (MLPA) methylation detection in urine) in case of positive dipstick has been reported in BC screening in high-risk populations [134]. However, the low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness of BC screening [128, 134]. Thus, routine screening for BC is not recommended [128, 134, 135].

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 [136]. In addition, Xpert Bladder® had higher sensitivity and negative-predictive value than both cytology or UroVysion™ for the detection of BC in patients with haematuria [137].

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

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

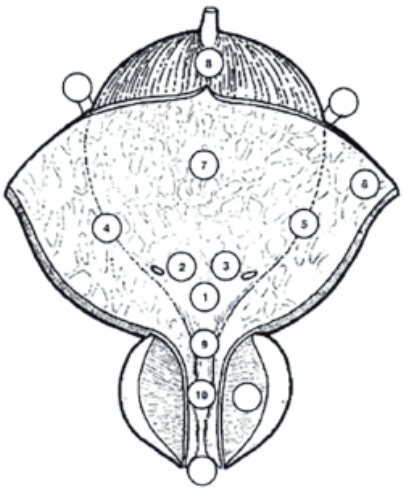
5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection. Carcinoma *in situ* can be suspected through cystoscopy and urine cytology and confirmed by histological evaluation of multiple bladder biopsies [138].

Cystoscopy can be performed as an outpatient procedure. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [139, 140].

Two randomised trials, both including male patients only, showed that the irrigation 'bag squeeze' technique could significantly reduce pain during the flexible cystoscopy procedure [141, 142].

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 is necessary for the diagnosis of BC.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
If an MRI is performed for local staging of bladder cancer it should be done before TURB.	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
Use a flexible cystoscope, if available, in both men and women. In men apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	Strong
Describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. First morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris System 2nd Edn., for cytology reporting.	Strong

5.10 Transurethral resection of TaT1 bladder tumours

*5.10.1 **Strategy of the procedure***

The goals of TURB in TaT1 BC is to establish accurate pathological diagnosis/staging and completely remove all visible lesions. It is a crucial procedure in the management of BC. Transurethral resection of the bladder tumours should be performed systematically in individual steps [143, 144] (see Section 5.14).

The operative steps necessary to achieve a successful TURB include identifying the factors required to assign disease risk (number of tumours, size, architecture, location, concern for the presence of CIS, recurrent vs. primary tumour), clinical stage (bimanual examination under anaesthesia, assignment of clinical tumour stage), adequacy of the resection (visually complete resection, visualisation of muscle at the resection base), visualisation of tumour in the distal ureter and presence of complications (assessment for perforation) [143, 145].

Documentation of cystoscopic tumour characteristics and consequent clinically predicted tumour grade and stage can help assign patients to post-TURB single instillation of chemotherapy (low grade non-invasive) and muscle invasive cancers to be fast tracked to definitive treatment [146]. To measure the size of the largest tumour, one can use the end of the cutting loop, which is approximately one cm wide, 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 [147].

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

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

A complete resection, performed by either fractioned or en-bloc technique, is essential to achieve a good prognosis [144, 148].

- 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 [149]. Whilst this technique is carried out using a loop with diathermy (monopolar or bipolar), the Thulium-YAG laser is potentially a feasible alternative [150].

- En-bloc resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG or KTP-Green Light lasers is feasible in selected exophytic tumours. It provides high-quality resected specimens with the presence of detrusor muscle in 96–100% of cases [144, 151-158]; however, its superiority over conventional TURB remains debatable [159, 160]. Detrusor muscle sampling rates were no different between these techniques in a systematic review of 1,142 patients [161], and in a single centre RCT showing similar detrusor muscle sampling rates of 95% between conventional TURB and en-bloc resection [159]. Conversely, another systematic review of 4,484 patients revealed higher detrusor muscle sampling rates in favour of en-bloc resection [151], and a multicentre RCT found significantly higher detrusor muscle rates with en-bloc compared to conventional TURB (80.7 vs 71.1) [160]. Respect for tumour architecture increases the accuracy of T1 staging and the possibility of sub-staging while potentially reducing the risk of bladder perforation [151, 156-159]. With regards oncological outcomes, two RCTs did not reveal a difference in time to recurrence between en-bloc resection and conventional TURB [159, 160]. This has also been shown in two systematic reviews [151, 161]. However, a RCT comparing en-bloc resection and conventional TURB in patients with tumours < 3 cm, en-bloc resection resulted in a significant reduction in one-year recurrence rate from 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 [162].

The technique selected is dependent on the size and location of the tumour and experience of the surgeon. The tumour size feasible for retrieval en-bloc is limited by the currently available endoscopic equipment and it has been shown that technical success declines with tumours larger than three cm [163]. With better detection of tumours and abnormal margins, methods of optical enhancement are expected to improve complete resection rates (see Section 5.11).

5.10.2.2 Evaluation of resection quality

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence, and tumour under-staging [164]. The presence of detrusor muscle in the specimen is considered as a surrogate criterion of the resection quality [164] and is required (except in Ta LG/ G1 tumours). Surgical checklists and quality performance indicator programmes have been shown to increase surgical quality (accurate documentation of factors required to assign risk and sample detrusor muscle) and decrease recurrence rates [143, 145, 165-167]. More recently, it has been shown that achieving quality benchmarks for sampling detrusor muscle and single post-TURB instillation of Mitomycin-C in 2,688 patients were associated with lower recurrence and progression rates when compared to not achieving these benchmarks [168]. The Panel have included a sample TURB checklist in Table 5.1 and reported quality indicators for the procedure in Table 9.1.

It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [164, 169]. Virtual training on simulators is an emerging approach [170]. Its role in the teaching process still needs to be established [143]. Surgical experience and/or volume has been associated with risk of complications [171], recurrence [172] and survival [173] in retrospective studies. Despite a relatively low overall rate of detrusor muscle (DM) sampling, a collaborative study of 503 patients demonstrated that higher utilisation of surgical checklists by residents was associated with a higher rate of detrusor muscle sampling (62.9%) vs. 'experts' (50.6%) whose utilisation of checklists was lower [143, 167].

5.10.2.3 Monopolar and bipolar resection

Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and to produce better specimens. Currently, the results remain controversial [174-176], with significant inherent limitations due to selection bias, heterogeneity of surgical approach or inability to qualify surgeon experience. A systematic review of 13 RCTs (2,379 patients) showed no benefit of bipolar vs. monopolar TURB for efficacy and safety [176] while one meta-analysis of RCTs (n=2,099) suggests a lower fall in haemoglobin and shorter hospital stay with bipolar resections [174] and another systematic review of RCTs and observational studies (n=19,927) suggests lesser thermal artifacts in the specimen [175].

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

It is not uncommon to incidentally detect bladder tumours during TURP in men with benign prostatic hyperplasia. Provided these tumours are papillary, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate [177, 178]. Simultaneous TURB and TURP does not appear to lead to any increased risk of tumour recurrence or progression [179]. Whilst most reports have suggested surgeons prefer to undertake saline irrigation following the combined TURB and TURP, post operative single instillation of chemotherapy also appears to be feasible and safe provided there is no capsular or bladder perforation [180].

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 [181, 182]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [181, 182]. If the equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy (see Section 5.12.1).

*5.11.2 **Prostatic urethral biopsies***

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.*, showed that in 128 men with T1G3 UC, the incidence of CIS in the prostatic urethra was 11.7% [183]. The risk of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [184]. Based on this observation, a biopsy from the prostatic urethra is necessary in some cases [183, 185, 186]. Biopsies should preferably be from the pre-collicular area (between 5 and 7 o'clock position next to the veru montanum) using a resection loop.

5.12 New methods of tumour visualisation

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

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

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

5.12.1.1 Impact on bladder cancer detection

It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly CIS [187, 188]. In a systematic review and meta-analysis, PDD had higher sensitivity than WL endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [188]. A prospective RCT did not confirm a higher detection rate in patients with known positive cytology before TURB [189].

Photodynamic diagnosis had lower specificity than WL endoscopy (63% vs. 81%) and it does not help to rule out prostatic involvement [188]. False- positivity can be induced by inflammation or recent TURB and during the first three months after BCG instillation [190, 191].

5.12.1.2 Impact on bladder cancer recurrence

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURB was evaluated. A systematic review and analysis of 14 RCTs including 2,906 patients, 6 using 5-ALA and 9 HAL, demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates. The analysis demonstrated inconsistency between trials and potential susceptibility to performance and publication bias [192]. While a recent systematic review and meta-analysis of 12 RCTs (n=2,288) revealed lower risk of recurrence and improved time to recurrence (at least in the first 2 years and possibly up to 5 years) with PDD [193], the most recent Cochrane systematic review and meta-analysis of 16 RCTs (n=4,325) demonstrated that PDD-assisted TURB may prolong not only recurrence over time but also risk of progression, albeit supported only by low certainty evidence [194]. This finding has been corroborated in a systematic review and meta-analysis of 12 RCTs involving 2,775 patients [195].

Contrary to previous evidence, a multicenter RCT from UK showed that PDD-guided TURB did not reduce recurrence rates, nor was it cost-effective compared with WL cystoscopy at three years [196].

*5.12.2 **Narrow-band imaging***

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection [197-200] (LE: 3b). Two RCTs assessed the reduction of recurrence rates if NBI is used during TURB [200, 201]. Although the overall results were negative, a benefit after three and twelve months was observed for low-risk tumours (pTa LG, < 30 mm, no CIS) [201].

A systematic review and meta-analysis (17 RCTs and non-RCTs) demonstrated improved detection (diagnostic accuracy) of bladder tumours with either PDD or NBI over WL cystoscopy [202], while another one (including 5,217 patients) showed improved RFS with either enhancement technique [203]. Conversely, a systematic review and network meta-analysis that took into account the use of single post- operative instillation of chemotherapy, concluded that there was a lower likelihood of recurrence at one year only following PDD-guided TURB (with or without single instillation) but not with NBI-guided surgery [204].

5.12.3 IMAGE1 S™, and other technologies

IMAGE1 S™ (formerly named SPIES) is an image enhancement system based on a computerised processing of different colour components that uses specific light filters. Limited evidence has been produced so far in an attempt to validate the four different light spectra modalities, suggesting an improvement in the diagnostic accuracy of WL [205, 206]. 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 [207, 208].

Confocal laser micro-endoscopy is a high-resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [209].

5.13 Second resection (second TURB)

5.13.1 Detection of residual disease and tumour upstaging

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [148]. This residual cancer has the potential to worsen oncological outcomes and therefore further emphasises the importance of an effective initial TURB. As patients with an initial incomplete TURB (either from extensive tumour or intra-operative complications) will require a second completion resection, documentation of resection completeness at the time of the initial TURB is essential.

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

A systematic review analysing data of 8,409 patients with Ta or T1 HG UC demonstrated a 51% risk of persistence and an 8% risk of under-staging in T1 tumours. The analysis also showed a high risk of residual disease in Ta tumours, but this observation was based only on a limited number of cases. Most of the residual lesions were detected at the original tumour location [210]. 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 visual enhanced TURB significantly improved residual tumour rates at repeat TURB [211].

Another systematic review and meta-analysis of 3,556 patients with T1 tumours showed that the prevalence rate of residual tumours and upstaging to invasive disease after TURB remained high even in a subgroup with detrusor muscle sampled at the initial TURB. In the subgroup of 1,565 T1 tumours with detrusor muscle present, persistent tumour was found in 58% and under-staging occurred in 11% of cases [212].

Prospective trials suggest that post-operative positive urine cytology [213] and Xpert Bladder® (urine mRNA test) [214] are independently associated with residual disease at second resection and risk of future recurrences, respectively. These data, however, need to be confirmed in further studies.

5.13.2 The impact of second resection on treatment outcomes

A second TURB can increase recurrence-free survival (RFS) [215-217], improve outcomes after BCG treatment [218] and provide prognostic information [219-222].

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 [223]. In a retrospective analysis of 7,666 patients diagnosed with T1 cancer in Ontario, 2,162 underwent a second resection; after adjusting for the effects of confounding variables, only OS (and not CSS) was better in patients who underwent second resection [173]. This apparent improved survival could also be the result of selection bias with fitter patients undergoing second resections. Whilst a single centre retrospective review revealed survival benefit in 209 HGTa patients who underwent a second TURB [224], further evidence is required to identify specific sub-groups of patients with high-grade cancer who are most likely to benefit from a second resection. From a contemporary systematic review and meta-analysis of 81 studies, patients undergoing repeat TURB 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 [211].

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 [225]. Based on this currently available evidence, a second TURB is recommended in selected cases two to six weeks after initial resection [225] (for recommendations on patient selection, see Section 5.14).

5.13.4 Recording of results

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

5.14 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the decision-making process for BC [226]. Close co-operation between urologists and pathologists is required. Clinical information and high quality of resected and submitted tissue is essential for correct pathological assessment. To obtain all relevant information, the specimen collection, handling and evaluation, should respect the recommendations provided below (see Section 5.14) [227]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered.

Table 5.1 TURB checklist*

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

**Adapted from Mostafid et al., and Suarez-Ibarrola et al., [143, 228].*
NBI = narrow-band imaging; PDD = photodynamic diagnosis; TURB = transurethral resection of bladder.

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

Summary of evidence	**LE**
Transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the management of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour under-staging (with the exception of Ta LG/G1 tumours).	2b

A second TURB can detect residual tumours and tumour under-staging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2
Photodynamic diagnosis has been shown to improve the detection of bladder cancer, especially CIS.	1a

Recommendations	**Strength rating**
Perform a transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step in patients suspected of having bladder cancer.	Strong
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia before starting the procedure and at the end; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record including visual impression of grade/stage; • precise description of the specimen(s) for pathology evaluation.	Strong
Performance of individual steps	
Perform en-bloc resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium.	Strong
Take multiple biopsies (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) or perform fluorescence-guided (PDD) biopsies, in case of normal looking urothelium and positive urine cytology.	Strong
Take a sample of the prostatic urethra if there is positive urine cytology without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible (see Section 5.11.2).	Strong
Take a sample biopsy of the prostatic urethra in cases of bladder neck tumour, suspicion of bladder 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 (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers. Submit the tumour base separately especially in large and multifocal tumours or when en-bloc resection is not feasible.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, extent, macroscopic completeness of resection as well as any complications.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB; • if there is no detrusor muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within two to six weeks after the initial resection. This second TURB should include resection of the primary tumour site.	Weak
Record the pathology results of the second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, subtypes of urothelial carcinoma, presence of CIS and detrusor muscle.	Strong

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

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

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

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

To be able to predict both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group (GUCG) published a scoring system and risk tables based on the WHO 1973 classification in 2006 [229]. The scoring system is based on the six most significant clinical and pathological factors in patients mainly treated by intravesical chemotherapy:

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

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

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

Patients with Ta G1/G2 tumours receiving chemotherapy were stratified into three risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy [230].

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

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

- gender;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- WHO 1973 tumour grade.

Using this model, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [231]. 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 [232] and by long-term follow-up in another patient population [233].

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

In 1,812 intermediate- and high-risk patients without CIS treated with 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 WHO 1973 grade for disease progression and disease- specific survival, while age and WHO 1973 grade were the most important prognostic factors for OS. T1 G3 patients did poorly, with 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 [234].

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

6.1.2.1 EAU NMIBC 2021 scoring model

To update the risk of disease progression and create new prognostic factor risk groups using both the WHO 1973 and WHO 2004/2016 classification systems, individual patient data from 3,401 primary patients treated from 1990 to 2018 were used [235] (see Section 4.5). Only patients treated with TURB ± intravesical chemotherapy were included, those treated with adjuvant intravesical BCG were excluded because BCG may reduce the risk of disease progression. From the multivariate analyses, tumour stage, WHO 1973 grade, WHO 2004/2022 grade, concomitant CIS, number of tumours, tumour size and age were independent predictors of disease progression [235].

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

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

*6.1.3 **Further prognostic factors***

Further prognostic factors have been described in selected patient populations:

- In T1 HG/G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with an induction course only) [183, 236].
- 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 [237].
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [220-222].
- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [238].
- 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 [233, 239].

6.2 Primary carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [240]. There are no reliable prognostic factors, but some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [241, 242], in extended CIS [243] and in CIS in the prostatic urethra [183]. The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [231, 232, 238]. Approximately 10 to 20% of complete responders eventually experience disease progression to muscle-invasive disease, compared with 66% of non-responders [244, 245].

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) [246]. 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 neuroendocrine subtypes, are associated with a higher risk of progression and recurrence [247, 248]. Literature on these subtypes remains limited, but 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 [249, 250]. Identifying unfavourable and favourable prognostic factors can assist in tailoring patient management. The following table highlights key factors influencing prognosis based on subtype.

Table 6.1: Histological subtypes [55]

Prognostic factors in subtypes	Risk of progression
Unfavourable	
High percentage of subtype(s)	Very high risk of progression
Presence of carcinoma *in situ* (CIS)	
Lymphovascular invasion (LVI)	
Pure Micropapillary, Sarcomatoid, nested and plasmacytoid subtype, or neuroendocrine subtype	
Multifocal tumours	
Residual tumour or incomplete TURB	
Favourable	
Absence of CIS and LVI	High risk of progression
Focal* involvement	
Solitary tumour	
Complete TURB with no residual tumour	

** "Focal" involvement with a 25% cutoff has been associated to a less aggressive behaviour in micropapillary subtype [78].*

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 guidelines are based on an individual patient data analysis in primary patients and the calculation of their progression scores (2021 EAU NMIBC scoring model) as presented in Sections 4.5 and 6.1.2) [235].

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

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

The clinical compositions of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or WHO 1973 classification systems are provided in Table 6.2. Applications for the web (www.nmibc.net), iOS and Android have been developed to facilitate determining a patient's risk group in daily clinical practice. The individual probability of disease progression at one, five and ten years for the new EAU NMIBC risk groups is presented in Table 6.3. A single-centre study validated the EAU NMIBC 2021 scoring model in 529 patients who received BCG [251]. The authors found that the progression risk for the EAU 2021 high- and very high-risk groups were significantly lower in BCG-treated patients than that in Table 6.2 [235]. These lower risks may be attributed to the use of BCG.

Table 6.2: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems [235]

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

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

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

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

Table 6.3: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [235]*

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

WHO = World Health Organization.

**Table 6.3 does not include patients with subtypes of urothelial carcinoma (variant histologies), LVI, CIS in the prostatic urethra, primary CIS or recurrent patients.*

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

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 [252]. This model is based on five clinical risk factors: tumour size and focality, timing and frequency of recurrence and failure of previous intravesical treatment. Recently, a multi-center clinical study validated this model in 677 primary and recurrent patients with intermediate-risk disease treated with adjuvant intravesical chemotherapy [253]. At one-year follow-up, the authors found that the progression risk of patients with no risk-factors was similar to that of EAU2021 low-risk group while that of patients with ≥ 3 risk-factors aligned with that of EAU2021 high-risk group. Longer follow-up and external validation are warranted to confirm this model.

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

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

Recommendations	Strength rating
Stratify patients into 4 risk groups to predict progression, according to Table 6.2. A patient's risk group can be determined using the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours, not treated with bacillus Calmette-Guérin (BCG), use the data from Table 6.3.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with BCG.	Strong
Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 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 [254-256] as well as mortality in all BC patients [257]. 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 [256]. Patients should be counselled to stop smoking due to the general health risks associated with tobacco smoking [237, 258-260].

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 [261, 262]. In a prospective RCT, laser photocoagulation with intravesical lidocaine in an outpatient setting proved non inferior to standard TURB under general anaesthesia for the four months recurrence rate. Notably, the laser fulguration procedure resulted in only a modest pain score (2.4) and was preferred by 98% of patients [263].

7.3 Active Surveillance

With recurrence in LG(G1) Ta tumours being more likely low grade and non-invasive [264-266] the risk of progression to a higher grade or stage is infrequent to rare [267-269]. Expectant management or active surveillance (AS), offer an alternative to TURB and office-based fulguration. Observing no progression to MIBC, Soloway *et al.*, first recommended this approach in 2003 [270] and Miyake *et al.*, subsequently proposed an algorithm for AS using changes in size and multifocality as triggers for intervention [271]. However, from a review undertaken by the EAU Young Academic Urology group [272], it appears that the level of evidence in favour of AS is low, with observational studies having heterogenous selection criteria, triggers for intervention and surveillance tools. The multicentre prospective Bladder Cancer Italian Active Surveillance (BIAS) project, conversely, demonstrated that AS is feasible in selected patients [273, 274] and its success be predicted by prognostic variables associated to TaLG disease [275]. According to a recent 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 TURB compared with patients with no risk factors [275]. Additional evidence from high quality clinical trials is required to compare AS, office fulguration and TURB in patients with recurrent LGTa NMIBC.

7.4 Adjuvant intravesical treatment

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the three-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [148]. It is therefore necessary to consider adjuvant therapy in all patients.

*7.4.1 **Post-operative irrigation***

Two systematic reviews [276, 277] and one meta-analysis [278] suggest efficacy of continuous saline bladder irrigation in the prevention of early recurrences. Therefore, in case intravesical chemotherapy is not feasible, irrigation of the bladder might be considered as an alternative option. Optimal volume infused and optimal duration of irrigation remain to be evaluated.

*7.4.2 **Intravesical chemotherapy***

7.4.2.1 A single, immediate, post-operative intravesical instillation of chemotherapy

Immediate single instillation (SI) has been shown to act by destroying circulating tumour cells after TURB, and by an ablative effect on residual tumour cells at the resection site and on small overlooked tumours [279-282]. Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURB, SI decreases significantly the recurrence rate compared to TURB alone [283-286]. In a systematic review and individual patient data meta-analysis of 2,278 eligible patients [283], 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 [283-286].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin [283], as well as gemcitabine [286], have all shown to lower the intravesical recurrence rate. Single instillation with gemcitabine was superior to saline in a RCT with approximately 200 patients per arm with remarkably low toxicity rates [287]. These findings are in contrast with a previous study which used a shorter instillation time [288]. In the Böhle *et al.*, study, continuous

saline irrigation was used for 24 hours post-operatively in both arms, which could explain the low recurrence rate in the control arm [288].

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by the extracellular matrix [279, 289-291]. In all SI studies, the instillation was administered within 24 hours. Two RCTs found no overall impact of SI with apaziquone, a bio reductive prodrug similar to MMC; in contrast, a *post-hoc* analysis did find a reduction of recurrence risk in patients receiving apaziquone within 90 minutes following TURB [292].

To maximise the efficacy of SI, flexible practices should be devised that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre. As severe complications have been reported in patients with drug extravasation, safety measures should be maintained (see Section 7.7) [293, 294]. To allow for optimal compliance with this Level 1 evidence, clinical teams are encouraged to explore barriers and facilitators within their practice [295].

7.4.2.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1 and 6.2), a SI reduces the risk of disease recurrence and is considered to be the standard of care treatment [283, 284]. For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of disease recurrence and/or progression (Tables 6.1 and 6.2). Efficacy data for the following comparisons of application schemes were published.

Single installation only vs. SI and further repeat instillations

In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [296].

Repeat chemotherapy instillations vs. no adjuvant treatment

A large meta-analysis of 3,703 patients from 11 RCTs showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [297]. 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 [298, 299] (see Section 7.2.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [300-302] (see Section 7.2.2.1). However, BCG causes significantly more side effects than chemotherapy [302].

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

There is evidence from several studies in intermediate-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given [303-306]. A RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURB (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at 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 [303]. Since the authors' definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [307]. The results of this study should be considered with caution since some patients did not receive adequate therapy. Another RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC patients [308].

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 [306]. 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 [309].

7.4.2.3 Measures to improve the efficacy of intravesical chemotherapy

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

Two prospective RCTs showed that optimised intravesical administration of MMC reduced recurrence rates, either by a combination of measures (higher MMC-dose, peroral sodium bicarbonate, and refraining from drinking) [310] and by adding cytosine arabinoside [311], 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 [312]. Another trial reported that duration of a one-hour instillation of MMC was more effective compared to a 30-minute instillation, but no

efficacy comparisons are available for one- vs. two-hour durations of instillation [313]. Another RCT using epirubicin has documented that concentration is more important than treatment duration [314]. In view of these data, instructions are provided (see Section 7.7).

7.4.2.3.2 Device-assisted intravesical chemotherapy

Hyperthermic intravesical chemotherapy

Different technologies which increase the temperature of instilled MMC are available. A recent systematic review and meta-analysis including four RCTs suggests similar toxicity as for BCG with maintenance schedule [315].

Microwave-induced hyperthermia effect (RITE)

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [316]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [317].

Conductive chemohyperthermia

In an open-label phase II RCT including 259 patients, HIVEC chemo-hyperthermia failed to demonstrate an improvement in DFS at 24 months over standard adjuvant intravesical chemotherapy in intermediate-risk NMIBC (61% vs. 60%), with a higher risk of treatment discontinuation (59% vs. 89% of completed planned treatments) [318]. 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 [319].

In a pilot phase II RCT on 50 high-risk NMIBCs, HIVEC™ MMC showed early outcomes comparable to BCG (24 months RFS, 86.5% with HIVEC™ and 71.8% with BCG, p = 0.184) [320]. 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 [321]. The definitive conclusion, however, needs further confirmation. For application of device-assisted instillations in patients recurring after BCG treatment, see Section 7.9.3.

7.4.2.4 Summary of evidence - intravesical chemotherapy

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

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

7.4.3.1 Efficacy of BCG

7.4.3.1.1 Recurrence rate

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC [300, 322-325]. Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (INF) [326], MMC [327], or epirubicin alone [301] and have confirmed the superiority of BCG for prevention of tumour recurrence. The effect is long-lasting [301, 327] and was also observed in a separate analysis of patients with intermediate-risk tumours [301]. One meta-analysis [300] has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC vs. BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance. A Cochrane systematic review confirmed that BCG is more effective in reducing the recurrence rate over MMC [328].

7.4.3.1.2 Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [298, 299, 325]. A meta-analysis carried out by the EORTC GUCG has evaluated data from 4,863 patients enrolled in 24 RCTs. In 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, tumours progressed in 9.8% of the patients treated with BCG compared to 13.8% in the control groups (TURB alone, TURB and intravesical chemotherapy, or TURB with the addition of other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [299]. A RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [301]. In contrast, an individual patient data meta-analysis and Cochrane review were not able to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [300, 328].

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

7.4.3.1.3 Influence of further factors

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [329]. In the individual patient data meta-analysis, however, BCG maintenance was more effective than MMC in reduction of recurrence rate, both in patients previously treated and not previously treated with chemotherapy [300]. 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 [330]. 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 [331].

7.4.3.2 BCG strain

Although smaller studies without maintenance demonstrated some differences between strains [331-333], 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 [334].

Similarly, a meta-analysis of prospective RCTs [299], published data from a prospective registry [335] as well as from a *post-hoc* analysis of a large phase II prospective trial assessing BCG and INF-α in both BCG-naive and BCG-failure patients did not suggest any clear difference in efficacy between the different BCG strains [336]. However, the quality of data does not allow definitive conclusions.

7.4.3.3 BCG toxicity

Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [299, 328]. However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [337]. The incidence of BCG infections after BCG instillations was 1% in a registry-based cohort analysis [338]. 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 women had a lower incidence than man [339]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [337]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [340]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [341]. No significant difference in toxicity between different BCG strains was demonstrated [335]. Symptoms may be the result of side effects of the BCG treatment or caused by bladder disease (widespread CIS) itself. Consequently, the burden of symptoms is reduced after completion of the treatment in a significant number of patients albeit delayed hypersensitivity to BCG may rarely present even years after completion of treatment [342].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected. The presence of leukocyturia, nonvisible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [132, 343]. Three RCTs showed reduced side effects by administering different quinolones in conjunction with the BCG-instillations [344-346]. The latter, by using two doses of levofloxacin (at six and twelve hours after first voiding) in conjunction with each BCG-instillation, reduced the proportion of patients with high-grade side effects, both local (pollakisuria) and systemic (fever), without improving the

completion rate of the maintenance regimen or the risk of severe BCG related adverse events [346].

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients. Immunosuppression, for example human immunodeficiency virus (HIV) infection, poses relative contraindications [347], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients. The role of prophylactic anti-tuberculosis medication in these patients remains unclear [348-350]. Kidney transplant recipients can be safely treated with BCG [351].

The management of side effects after BCG should reflect their type and grade according to the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [352, 353] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [353-356]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs).
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation. b. Perform a urine culture. c. Start empirical antibiotic treatment.
	If symptoms persist even with antibiotic treatment: a. With positive culture: adjust antibiotic treatment according to sensitivity. b. With negative culture: quinolones* and potentially analgesic anti-inflammatory instillations once daily for five days (repeat cycle if necessary) [354].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for three months.
	Cessation of intravesical therapy.
Epididymo-orchitis [355]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.
Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Reactive arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs [340].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.

BCG sepsis	Prevention: initiate BCG at least two weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin, and ethambutol 1.2 g daily for 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.

** Persistent severe cystitis symptoms associated with BCG use have a high risk to underlie a complicated UTI (even in the absence of a positive culture) and thus no restriction applies to the empirical use of quinolones by the Pharmacovigilance Risk Assessment Committee of the EMA [357, 358].*

7.4.3.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales *et al.*, [359]. For optimal efficacy, BCG must be given in a maintenance schedule [298-300, 325]. Many different maintenance schedules have been used, ranging from a total of ten instillations given in 18 to 27 weeks over three years [360]. The optimal three years maintenance schedule is outlined in recommendation Table 7.10.

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

The optimal number of induction instillations and frequency of maintenance instillations were evaluated by NIMBUS, a prospective phase III RCT. Safety analysis after 345 randomised patients demonstrated that a reduced number of instillations (three instillations in induction and two instillations at three, six and twelve months) proved inferior to the standard schedule (six instillation in induction and three instillations at three, six and twelvemonths) regarding the time to first recurrence [361]. In a 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 [362].

7.4.3.4.2 Optimal length of maintenance

In their meta-analysis, Böhle *et al.*, concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [298].

In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, three years' maintenance (three-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS. However, in the three-year arm 36.1% of patients did not complete the three-year schedule [363]. The main reason why these patients stopped treatment was treatment inefficacy, not toxicity.

7.4.3.5 Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [364, 365]. 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 [366]. 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 [340, 363]. In a recent 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 recurrences [367].

7.4.3.6 BCG shortage

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

7.4.3.7 Summary of evidence - BCG treatment

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical BCG after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule. A complete BCG schedule comprises an induction phase of 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***

7.4.4.1 *Intravesical BCG plus chemotherapy versus BCG alone*

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing the risk of disease recurrence while increasing toxicity compared to BCG monotherapy. Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by an added MMC instillation [368]. In a RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [321, 369]. Two meta-analyses demonstrated improved disease-free survival (DFS), but no benefit in PFS in patients treated with combination treatment comparing to BCG monotherapy [369, 370].

7.4.4.2 *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 [371]. 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 [372]. Additionally, a RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and INF for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [373].

7.4.4.3 *Sequential chemotherapy instillations*

Preclinical data suggest that the efficacy of intravesical chemotherapy instillations can be improved by combinations compared to the administration of single agents only [374]. Sequential (immediate) instillations of gemcitabine and docetaxel was initially reported in 2015 in the wake of BCG-shortage but also at times of limited access to mitomycin [375]. Subsequently other sequential chemotherapy combinations such as valrubicin and docetaxel have been suggested [376]. Over time, additional retrospective data have accumulated where sequential gemcitabine and docetaxel instillations were used in patients recurring after induction BCG and BCG-unresponsive disease [377]; in patients with recurrence after BCG-induction but not fulfilling the criteria for BCG-unresponsive disease [378]; and also in BCG-naïve high-risk patients [379]. Thus, in patients with BCG-unresponsive disease when the treatment standard (radical cystectomy) is not feasible due to age and/or comorbidity or when patients are unwilling to accept radical surgery, sequential instillations with gemcitabine and docetaxel is an emerging treatment concept awaiting further prospective scientific evaluation.

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

7.4.5.1 *Treatment strategy*

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [229, 231]. In this case further treatment according to the criteria summarised in Sections 7.4.2, 7.4.3 and 7.9 is mandatory. Carcinoma *in situ* cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC. Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [240].

7.4.5.2 *Cohort studies on intravesical BCG or chemotherapy*

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72–93% with BCG [232-235, 356]. Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [243, 291, 360, 380].

7.4.5.3 *Prospective randomised trials on intravesical BCG or chemotherapy*

Unfortunately, there have been few RCTs in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [381].

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 [299]. The combination of BCG and MMC was not superior to BCG alone [382]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression.

7.4.5.4 Treatment of CIS in the prostatic urethra and upper urinary tract

Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra. Solsona *et al.*, found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [383]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [383]. In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [384]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours) and for which immediate radical cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [140, 385]. However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement there are promising results of BCG, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [385, 386].

7.4.5.5 Summary of evidence - treatment of carcinoma in situ

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

7.5 Intravesical chemoablation and neoadjuvant treatment

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

Neoadjuvant

Hypothesis-generating findings from an older RCT comparing immediate pre-operative device-assisted (EMDA) MMC with post-operative SI with MMC and TURB only, showed improved long-term RFS among patients treated prior to TURB [387], and thus even suggest a long-term effect after neoadjuvant instillations. While this has not been reproduced by other groups, two recent small neoadjuvant RCTs have reported conflicting results on the ability of neoadjuvant administration of MMC to improve outcomes over the standard approach [388, 389].

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 [390]; therefore, making it possible to avoid TURB. In recurrent low-grade [391] and recurrent Ta tumours [392], 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 TURB, the twelve-month RFS was 36% in the chemoablation group vs. 43% in the TURB group, with no statistical significant difference [392]. UGN-102, a mitomycin-containing reverse thermal gel, followed or not by TURB was compared to TURB alone in a randomised, phase III trial, including 282 patients with low-grade intermediate-risk NMIBC [393]. Notably, three month complete response was similar between UGN-102 (once weekly for six weeks) and TURB (65% vs. 64%). In an ongoing phase III single arm study, the same treatment schedule achieved a 79% complete response rate at three months in 240 recurrent low grade intermediate-risk NMIBC, which was maintained in 82% at one year [394]. Despite the lack of long-term outcomes, chemoablation appears to be a promising treatment option for well-selected NMIBC patients and can potentially help avoid unnecessary TURB, specifically in some elderly patients with intermediate-risk NMIBC [395].

7.6 Radical cystectomy for non-muscle-invasive bladder cancer

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

- The staging accuracy for T1 tumours by TURB is low with 27–51% of patients being upstaged to muscle-invasive tumour at RC [186, 396-400].
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
- Patients who experience disease progression to muscle-invasive stage have a worse prognosis than those who present with 'primary' muscle-invasive disease [401, 402].

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) [78, 183, 229, 231, 403].

Early RC is strongly recommended in patients with BCG-unresponsive tumours and should be considered in BCG relapsing HG tumours as mentioned in Section 7.9 and Table 7.3. A delay in RC may lead to decreased disease-specific survival [404].

In patients in whom RC is performed before progression to MIBC, the five-year DFS rate exceeds 80% [405-407].

7.7 Primary treatment by disease type

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

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

- Treatment of intermediate-risk disease
  Patients in the intermediate-risk group have a relatively low risk of disease progression (7.4 and 8.5% after ten years according to the 2021 EAU NMIBC scoring model). In these patients induction chemotherapy with or without maintenance for a maximum of one year is a reasonable first-line option in the majority of patients [408]. One-year full-dose BCG treatment (induction plus three-weekly instillations at three, six and twelve 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. 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 [252, 253].

- 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. Because of the high risk of progression, immediate RC may also be discussed with the patient. Radical cystectomy is the safest approach from an oncological point of view, it is, however, associated with the risk of complications and QoL impairment and represents over-treatment in some patients.

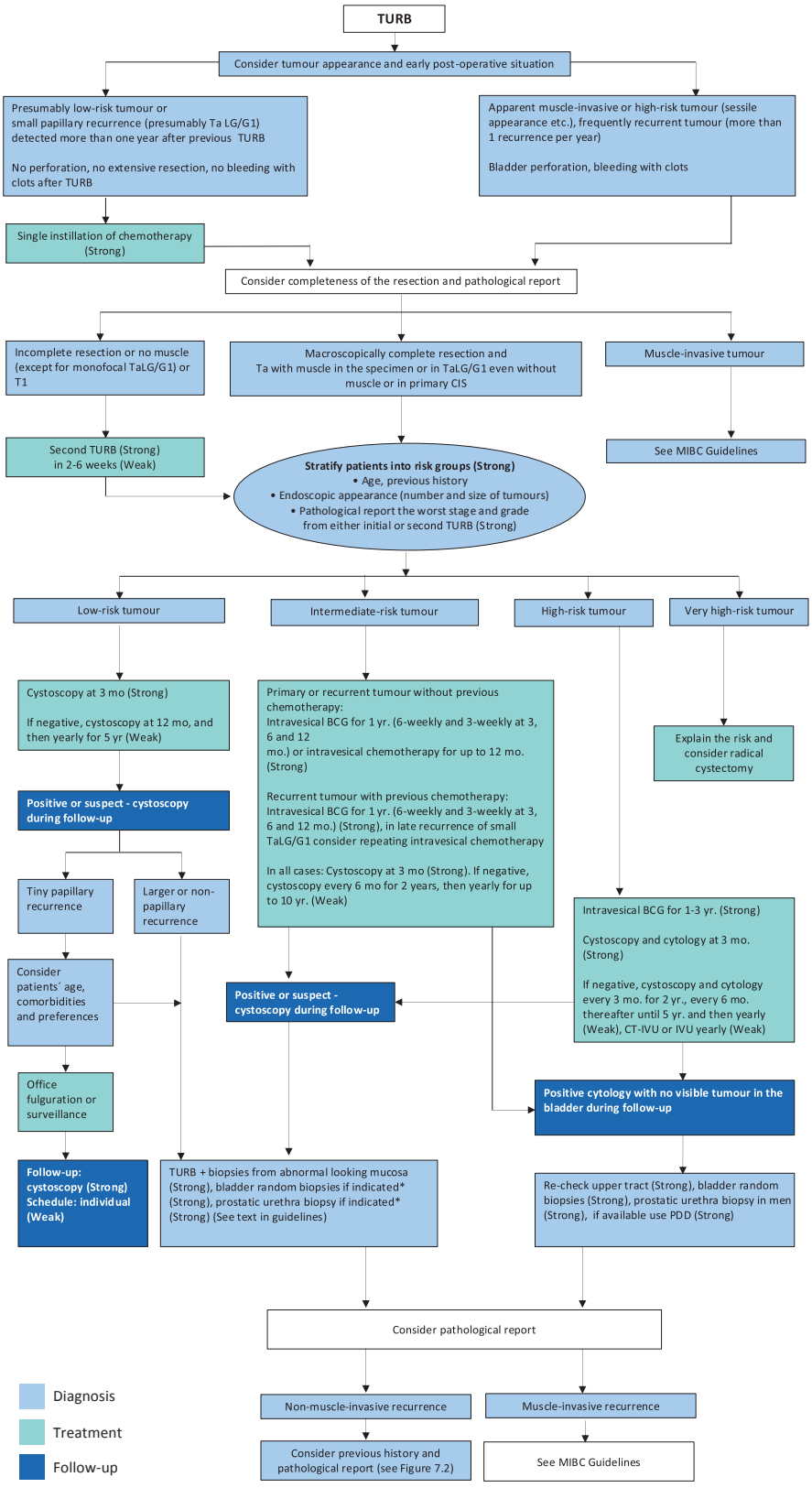
- Treatment of very high-risk disease
  Patients in the very high-risk group have an extremely high risk of tumour progression (53.1 and 58.6% after ten years according to the 2021 EAU NMIBC scoring model). Immediate RC should be discussed with these patients. In case RC is not feasible or refused by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

- Treatment of carcinoma *in situ*
  Patients with carcinoma *in situ* cannot be managed by an endoscopic procedure alone and should be offered either intravesical BCG instillations or RC. BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression. In comparison, immediate RC for CIS results in excellent tumour-specific survival rates although a large proportion of patients might be over-treated [240].

7.8 Multi-disciplinary tumour board

A multi-disciplinary tumour board (MDT) approach including reassessment of radiology and pathology is associated with a changed treatment plan in up to 44% of BC patients [409-412], such as refraining from or recommending cystectomy in 7% of stage T1 patients [410-412], often as a result of the pathologic review [72, 411]. Thus, patients with high-risk and very high-risk NMIBC will especially benefit from MDT discussion and such an approach is recommended for these patients. Figure 7.1 presents a treatment flow chart based on risk category, which may guide management of an individual patient.

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



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

7.9 Treatment of failure of intravesical therapy

7.9.1 Recurrence during or after intravesical chemotherapy

Patients with NMIBC recurrence during or after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillations [300].

7.9.2 Recurrence during or after intravesical BCG therapy

7.9.2.1 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 [413].

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 [244, 414]. The category of BCG-unresponsive tumours comprises BCG-refractory and some of BCG-relapsing tumours (see Table 7.2) [415]. The definition was developed in consultation with the U.S. Food and Drug Administration (FDA), in particular to promote single-arm trials to provide primary evidence of effectiveness in this setting [416]. Patients who experience recurrence with high-grade NMIBC after BCG without meeting BCG-unresponsive criteria may benefit from additional BCG therapy. This category of high risk patients that lies between BCG-naïve and BCG-unresponsive NMIBC is termed **BCG-exposed** [417, 418], and includes:

1. BCG-resistant: persistent or recurrent Ta HG and/or CIS disease at three months following at least five of six doses of induction BCG. According to the definition of adequate BCG (table 7.2), these patients have received inadequate BCG.
2. Delayed relapse after inadequate BCG: to indicate Ta/T1 HG or CIS patients found disease free at the three-months evaluation that recur in between 6 and 24 months without receiving more than an induction course.
3. Delayed relapse after adequate BCG: to indicate patients that are disease free after adequate BCG, but subsequently experience a high-grade recurrence outside of the BCG-unresponsive window (> 6 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 3 months [244, 414, 419]. 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [384]. 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [69, 380, 384]. 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 [420].
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [415].

BCG-exposed tumour [417, 418]
1. If Ta HG/G3 or CIS is present at three months evaluation after induction BCG only. 2. Delayed relapse after adequate or inadequate BCG.
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [353].

** 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.*

7.9.2.2 Treatment of BCG-unresponsive tumours

7.9.2.2.1 Introduction

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Currently, several bladder preservation strategies are being investigated such as cytotoxic intravesical therapies [421-423], device assisted instillations [424-426], intravesical immunotherapy [427, 428], systemic immunotherapy [429], gene therapy [430-432] as well as various combinations of chemotherapies, intravesical or systemic immunotherapies [418, 419] or novel intravesical delivery systems of cytotoxic agents [433].

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 [434]. 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 twelve-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 complete response rate of 17% at one year with a median progression-free rate of 95% at a median follow-up of twelve months), highlighting potential biological differences between these two tumour entities which should be analysed separately when reporting results of clinical trials [435].

7.9.2.2.2 Intravesical device assisted and combination chemotherapies

A phase III RCT including predominantly high-risk NMIBC patients failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia provided 35% overall DFS at two years as compared to 41% in the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at the discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave-induced thermotherapy showed lower response rates in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [426]. 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-year follow-up, demonstrated DFRs of 75, 71.4, 50 and 25%, for TaG3, T1G3, Cis, Ta/T1G3 + CIS, respectively [425]. As outlined in Section 7.4.4.3, sequential intravesical administration of gemcitabine and docetaxel is an emerging treatment option in patients failing BCG.

7.9.2.2.3 New Immunotherapies

Promising data on BCG-unresponsive cohorts of patients with CIS alone or concomitant to papillary tumours were recently reported following new immunotherapies. Systemic pembrolizumab achieved a 40% complete response rate in a prospective phase II study which was maintained in 48% of patients for up to twelve months (n=101), resulting in FDA approval of the study drug for this patient population [436]. Contrary to this in another phase II trial, systemic Atezolizumab achieved a 27% CR at six months in a cohort of 74 patients with CIS, with a median duration of response of 17 months. Among 55 patients with papillary disease only (Ta/T1), the 18-months actuarial EFS rate was 49% [433].

Nadofaragene firadenovec has also obtained FDA approval for BCG-unresponsive CIS following the results of 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 [437]. A secondary analysis indicates that a combination of post- treatment titres of serum anti–human adenovirus type-5 antibody and fold change from baseline can predict treatment efficacy [438].

The QUILT 3032 trial has evaluated the potential of the IL-15 superagonist Nagopendekin alfa-inbakicept (NAI) in BCG-unresponsive HG NMIBC, demonstrating three-, six- and twelve month CR rates 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 [439, 440].

The THOR2 trial compared oral Erdafitinib to investigator's choice of intravesical chemotherapy in patients with Ta/T1 HG recurrent, BCG-treated, and select FGFR alterations refusing or unfit for radical cystectomy. With a median follow-up for RFS of 13.4 months, 73 patients were randomised 2:1 to erdafitinib and chemotherapy. 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 [441].

7.9.2.2.4 Radical cystectomy

At the present time, treatments other than RC are considered oncologically inferior in patients with BCG-unresponsive disease [244, 414, 419].

7.9.2.3 Treatment of BCG-exposed tumours, BCG relapses and LG recurrences after BCG

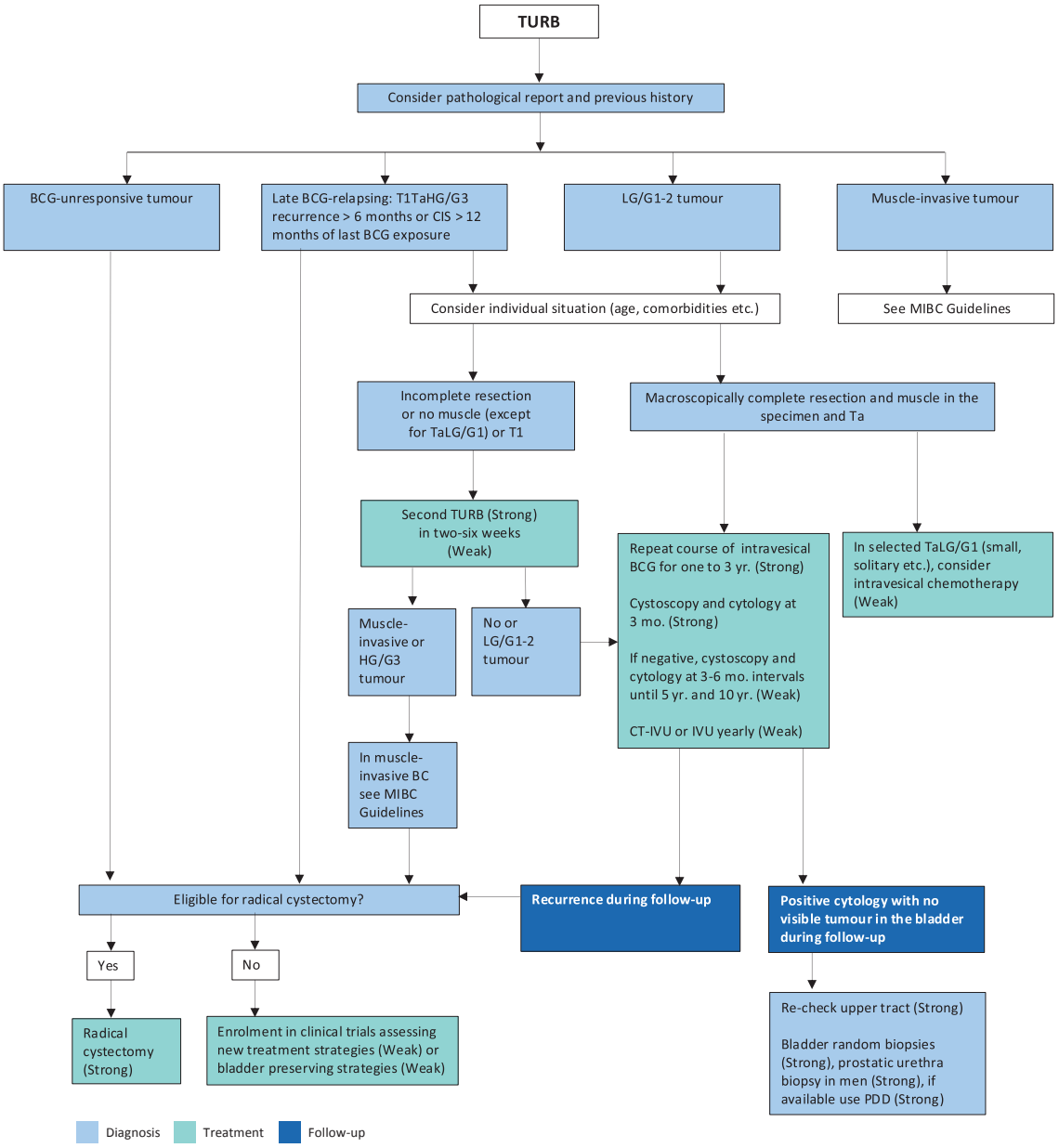
Various studies suggest that repeat-BCG therapy is appropriate for non-HG and even for some HG recurrent tumours; namely those relapsing beyond one year after BCG exposure (cases which do not meet the criteria of BCG-unresponsive disease) [418, 442]. Bacillus Calmette-Guérin exposed patients and late BCG relapses (beyond 24 months) are likely to benefit from further BCG [417, 418].

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

*7.9.3 **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

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



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

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

General recommendations	Strength rating
Counsel smokers to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Section 6.3 and Table 6.2. For determination of a patient's risk group use the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, offer one immediate single chemotherapy instillation.	Strong
Offer post-operative saline or water continuous irrigation of the bladder to patients who cannot receive a single instillation of chemotherapy.	Strong

Patients with small recurrent low-grade Ta tumours can be effectively and safely offered office fulguration.	Strong
Offer active surveillance and/or chemoablation to selected patients with presumed low-grade tumours as an alternative to endoscopic ablation.	Weak
In patients with intermediate-risk tumours (with or without immediate instillation), offer instillations of chemotherapy (the optimal schedule is not known) or one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months). Chemotherapy is a reasonable first option in the majority of cases; however, the final choice should be made in a shared decision-making process with the patient, reflecting his/her risk of recurrence and progression, as well as the efficacy and side effects of each treatment modality.	Strong
In patients with high-risk tumours, 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 access to BCG. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
Discuss immediate RC in patients with very high-risk tumours. Intravesical full-dose BCG instillations for one to three years remains an option for selected patients, particularly those who decline or are unfit for RC.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra if a bladder sparing strategy is considered.	Weak
Cautiously offer quinolones to treat BCG-related side effects*.	Weak
The definition of 'BCG-unresponsive' should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations.	Strong
Offer a RC to patients with BCG-unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak
Discuss high-risk and very high-risk patients within a multidisciplinary board, when possible.	Weak
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be a minimum of one, and up to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

**The side-effect profile of quinolones and fluoroquinolones resulted in the adoption of European regulations restricting their use [357].*

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

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

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

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC). 2. Enrolment in clinical trials assessing new treatment strategies. 3. Other bladder-preserving strategies in patients ineligible for or refusing RC.
Late BCG relapsing: TaT1 HG recurrence > 6 months or CIS > 12 months since 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.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

Due to the risk of recurrence and progression, patients with NMIBC need follow-up after treatment. The first cystoscopy after TURB at three months is an important prognostic indicator for recurrence and progression [238, 243, 265, 268, 443]. Therefore, the first cystoscopy should always be performed three months after TURB in all patients with TaT1 tumours and CIS. The subsequent frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk. This can be defined by using the EAU NMIBC prognostic factor risk groups (Section 6.3, Tables 6.1 and 6.2) or further prognostic models for specific patient populations (Section 6) which predict, the short- and long- term risks of recurrence and progression in individual patients (Section 8.1) [229, 231]. However, recommendations for follow-up are mainly based on retrospective data and there is a lack of RCTs investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

8.1 Intravesical surveillance during follow-up

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

Low-risk group is nearly always low stage and LG/G1. Small, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [267, 444]. In addition, recurrence after five recurrence-free years is low [268]. Therefore, in low-risk tumours, after five years of follow-up, discontinuation of cystoscopy or its replacement with less invasive methods should be considered [443, 445]. A recent 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 [446].

*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-riskcategories [235]; therefore, the intensity of any follow-up scheme could be adapted in line with this. Based on the safety of a reduced intensity follow-up scheme compared to high-risk NMIBC, in a small RCT on multiple and/or recurrent grade 1 and 2 tumours [447], 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 [448]. Due to lack of data supporting the safety of a reduced scheme in the subgroup of high-grade intermediate-risk NMIBC the Panel recommend this group be followed-up in the same way of high-risk NMIBC.

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

In tumours originally, high-risk, or very high-risk treated conservatively, the prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial and the percentage of tumours missed should be as low as possible because a delay in diagnosis and therapy can be life-threatening. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and voided urine cytology. Recurrences after ten years tumour-free are not unusual [449]. Therefore, the optimal surveillance strategy for these patients includes initial frequent cystoscopy and voided urine cytology and life-long follow-up [443].

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

The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders). This risk becomes significant for both sites in high-risk tumours [100], with ten-year tumour rates in UUT varying between 2.8% in CIS [450] and 25% in patients with multiple and recurrent high-risk NMIBC [451]. 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***

8.1.5.1 Enhanced visualisation

There may be a role for newer methods of tumour visualisation in follow-up cystoscopy. In two prospective studies of blue light flexible cystoscopy (BLFC) for surveillance of NMIBC, BLFC allowed identification of 4 to 5.7% of recurrences that would have been missed in case of WL cystoscopy alone [452, 453]. On the other hand, a prospective study of NBI for NMIBC surveillance failed to show any benefit for NBI over WL cystoscopy alone [454].

8.1.5.2 Ultrasound

In patients initially diagnosed with Ta LG/G1–2 BC, US of the bladder and/or a urinary marker may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [134, 455, 456].

8.1.5.3 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 high-grade/G3 UC (Malignant) were 40%, 81%, and 91%, respectively [457].

8.1.5.4 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 risk groups. However, the reported low sensitivity for LG recurrences limits their utility in this group [131, 458] although more recent studies have shown reasonable sensitivity of 40–65% in detecting low grade recurrences [459, 460].

For clinical implementation of urinary molecular markers for NMIBC surveillance some key issues are relevant [133]:

- Inflated 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 where 15% recur will display a 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). Furthermore, 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 [461].
- Cost-effectiveness: Needs to be shown prior to implementation, i.e. to calculate quality-adjusted life-years (QALY), total costs, and incremental cost effectiveness ratios (ICER) for different follow-up scenarios.

In the current absence of randomised trials investigating marker guided use of urinary molecular markers with non-inferiority design in predefined NMIBC risk groups, high-level evidence for clinical implementation is currently lacking. Consequently, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion. Nonetheless, 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 [460, 462-464] (Table 8.1). 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 [124]	5 mRNAs	52-91	79-100	41-91	76-91	11 studies 2,800 pts
EpiCheck™ [123]	15 DNA methylations	62-90	78-95	82-88		6 studies 2,236 pts
CX BLADDER [465]	5mRNAs	93	95	61	-	1 study 763 pts
UROMONITOR [466]	DNA mutations FDFGR3+TERT+K ras	49-93	-	86-99	-	5 studies 1,190 pts
Galeas Bladder [467]	Multiple DNA mutations (n= 443 in 23 genes)	86	100	63	-	1 study 293 pts

HG = high grade; n = number

** 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	CT annually up to 5 years Then CT every 2 years up to 10 years	Life long

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

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

Summary of evidence	LE
The first cystoscopy after transurethral resection of the bladder at 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 intermediate-risk that are high-grade should be followed up as high-risk.	Weak
Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then annually lifelong.	Weak
Take regular and long-term upper tract imaging (computed tomography urography) for high-risk and very high-risk tumours.	Weak
Perform endoscopy under anaesthesia and bladder biopsies when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong

9. PATIENT REPORTED OUTCOME MEASURES AND QUALITY INDICATORS FOR NMIBC

9.1 PROMS and PREMS in NMIBC

As NMIBC is associated with a significant number of hospital visits and interventions (TURB, re-TURB, surveillance cystoscopy, intravesical instillations) survivorship has a significant effect on patient QoL [468, 469]. 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 [470]. Regardless, in order to provide the best possible care, clinicians should always be cognisant of the impact of disease and treatment (including surveillance) on their patients' QoL. The use of PROMs is an important endpoint for quality metrics and RCTs should systematically incorporate PROs for patient-centred research design.

9.2 Quality Indicators (QI) in Bladder Cancer

Evidence based Quality Indicators (QIs) and Quality Performance Indicators (QPIs) are designed to be surrogates of good practice and consequently, outcomes. They allow for the gap between efficacy and effectiveness to be narrowed, i.e. being able to bring research evidence and guideline recommendations into real world practice by improving compliance to them [471]. They also permit objective monitoring of the quality of care and thus facilitate quality control as well as service and process improvements.

Several QIs for bladder cancer have been suggested [472-475]. The table below represents the general and NMIBC related QIs adapted from Leow *et al.*, [474] and the Scottish Quality Performance Indicator (QPI) programme [475]. Quality indicators and QPIs should be SMART (Specific, Measurable, Achievable, Relevant, Trainable) [471]. Scotland introduced such a programme for Bladder Cancer in 2014 [475], and have been an exemplar by being able to demonstrate high levels of compliance to QPIs while reducing practice variation across country whilst also demonstrating the clinical value of such a programme [166], including development of prognostic models [448].

Successful implementation of a QI programme has the potential to inspire and catalyse clinical excellence in contemporary Bladder Cancer practice [471].

Table 9.1: Quality Indicators for general aspects of bladder cancer and NMIBC care adapted from [474, 475]**.**

General aspects of bladder cancer care	**Recommended Quality Indicators**
Appropriate imaging for patients newly diagnosed with bladder cancer	Newly diagnosed bladder cancer patients who have cross-sectional imaging of UUT (eg, CT, MRI, or US) - as recommended in Section 5.4.
Participation in clinical trials	Availability of clinical trials to bladder cancer patients who are treated at a particular health care facility.
Aspects of NMIBC care	**Recommended Quality Indicators**
Pre-operative:	
Counselling	At the time of diagnosis, patients should be counselled to discontinue tobacco smoking.
Intra-operative:	
Tumour/patient history	Use of an Intra-operative checklist (as recommended in Table 5.1).
Conduct of TURB	Patients with muscle present in specimen from initial TURB (excluding TaLG disease).
	Use of a Bladder Diagram (as per Figure 5.1).
Re-staging TURB	Restaging TURB should be performed within 2–6 wk of the initial TURB and include resection of the primary tumour site as per recommendations in Section 5.13.

Post-operative:	
Risk stratification and surveillance counselling for patients with NMIBC	Use the EAU 2021 Risk Stratification for progression and the 2006 EORTC scoring model for recurrence to counsel patients with NMIBC on treatment and surveillance.
Intravesical therapy	Patients who received immediate post-TURBT instillation of intravesical chemotherapy, excluding those with contraindications (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 bladder cancer	Appropriate intervals between cystoscopic surveillance as per Table 8.2.
	Appropriate assessment of the UUT in high-risk patients.

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 [476].

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 [415].

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 [477]. A multi-disciplinary oversight with expert clinician involvement is essential to making this work, and 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 low grade Ta NMIBC – Section 5.10
2. The single post-TURB chemotherapy instillation (SI-IVC) is very effective in reducing recurrence in patients with low grade Ta NMIBC. Cystoscopic prediction of this group of patients will allow for selective utilisation of SI-IVC – Section 7.4.2.1.
3. Selective re-TURB in high-risk NMIBC – Section 5.13
4. Active Surveillance in recurrent LGTa – Section 7.3 and/or Office fulguration for recurrent LGTa – Section 7.2 and/or Chemo-ablation in recurrence LGTa – Section 7.5
5. BCG 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 [478].
6. Bladder preservation options for BCG un-responsive disease – Section 7.9.2.

7. Reduced frequency/intensity of surveillance (cystoscopy and CTU) 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.

11. REFERENCES

1. Masson-Lecomte, A., *et al.* EAU Guidelines on Urothelial Carcinomas of the Upper Urinary Tract. 2025. Edn. presented at the 40th EAU Annual Congress Madrid 2025. https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma
2. van der Heijden, A.G., *et al.* EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. 2025. Edn. presented at the 40th EAU Annual Congress Madrid 2025. https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer
3. Neuzillet, Y., *et al.* EAU Guidelines on Primary Urethral Carcinoma. 2025. Edn. presented at the 40th EAU Annual Congress Madrid 2025. https://uroweb.org/guidelines/primary-urethral-carcinoma
4. Gontero, P., *et al.* European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma *In Situ*)-A Summary of the 2024 Guidelines Update. Eur Urol, 2024. https://www.ncbi.nlm.nih.gov/pubmed/39155194
5. Phillips, B. Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidencemarch-2009/
6. Guyatt, G.H., *et al.* Going from evidence to recommendations. BMJ, 2008. 336: 1049. https://www.ncbi.nlm.nih.gov/pubmed/18467413
7. International Agency for Research on Cancer. Estimated number of new cases in 2020, worldwide, both sexes, all ages. World Health Organization. 2021. https://shorturl.at/bvfpj
8. Burger, M., *et al.* Epidemiology and risk factors of urothelial bladder cancer. Eur Urol, 2013. 63: 234. https://www.ncbi.nlm.nih.gov/pubmed/22877502
9. Teoh, J.Y., *et al.* Global Trends of Bladder Cancer Incidence and Mortality, and Their Associations with Tobacco Use and Gross Domestic Product Per Capita. Eur Urol, 2020. 78: 893. https://www.ncbi.nlm.nih.gov/pubmed/32972792
10. Comperat, E., *et al.* Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. Virchows Arch, 2015. 466: 589. https://www.ncbi.nlm.nih.gov/pubmed/25697540
11. Freedman, N.D., *et al.* Association between smoking and risk of bladder cancer among men and women. JAMA, 2011. 306: 737. https://www.ncbi.nlm.nih.gov/pubmed/21846855
12. Laaksonen, M.A., *et al.* The future burden of kidney and bladder cancers preventable by behavior modification in Australia: A pooled cohort study. Int J Cancer, 2020. 146: 874. https://www.ncbi.nlm.nih.gov/pubmed/31107541
13. van Osch, F.H., *et al.* Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. Int J Epidemiol, 2016. 45: 857. https://www.ncbi.nlm.nih.gov/pubmed/27097748
14. Bjurlin, M.A., *et al.* Carcinogen Biomarkers in the Urine of Electronic Cigarette Users and Implications for the Development of Bladder Cancer: A Systematic Review. Eur Urol Oncol, 2021. 4: 766. https://www.ncbi.nlm.nih.gov/pubmed/32192941
15. Colt, J.S., *et al.* A case-control study of occupational exposure to metalworking fluids and bladder cancer risk among men. Occup Environ Med, 2014. 71: 667. https://www.ncbi.nlm.nih.gov/pubmed/25201311
16. Pesch, B., *et al.* Screening for bladder cancer with urinary tumor markers in chemical workers with exposure to aromatic amines. Int Arch Occup Environ Health, 2014. 87: 715. https://www.ncbi.nlm.nih.gov/pubmed/24129706
17. Koutros, S., *et al.* Diesel exhaust and bladder cancer risk by pathologic stage and grade subtypes. Environ Int, 2020. 135: 105346. https://www.ncbi.nlm.nih.gov/pubmed/31864026

18. Kayyal-Tarabeia, I., *et al.* Residence near industrial complex and cancer incidence: A registry-based cohort of 1,022,637 participants with a follow-up of 21 years, Israel. Environ Res, 2023. 216: 114471. https://www.ncbi.nlm.nih.gov/pubmed/36208787
19. Egbers, L., *et al.* The prognostic value of family history among patients with urinary bladder cancer. Int J Cancer, 2015. 136: 1117. https://www.ncbi.nlm.nih.gov/pubmed/24978702
20. Kim, H.J., *et al.* Familial Risk and Interaction With Smoking and Alcohol Consumption in Bladder Cancer: A Population-Based Cohort Study. World J Oncol, 2023. 14: 382. https://www.ncbi.nlm.nih.gov/pubmed/37869241
21. Corral, R., *et al.* Comprehensive analyses of DNA repair pathways, smoking and bladder cancer risk in Los Angeles and Shanghai. Int J Cancer, 2014. 135: 335. https://www.ncbi.nlm.nih.gov/pubmed/24382701
22. Figueroa, J.D., *et al.* Identification of a novel susceptibility locus at 13q34 and refinement of the 20p12.2 region as a multi-signal locus associated with bladder cancer risk in individuals of European ancestry. Hum Mol Genet, 2016. 25: 1203. https://www.ncbi.nlm.nih.gov/pubmed/26732427
23. Zhong, J.H., *et al.* Association between APE1 Asp148Glu polymorphism and the risk of urinary cancers: a meta-analysis of 18 case-control studies. Onco Targets Ther, 2016. 9: 1499. https://www.ncbi.nlm.nih.gov/pubmed/27042118
24. Al-Zalabani, A.H., *et al.* Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses. Eur J Epidemiol, 2016. 31: 811. https://www.ncbi.nlm.nih.gov/pubmed/27000312
25. Wu, J., *et al.* A Functional rs353293 Polymorphism in the Promoter of miR-143/145 Is Associated with a Reduced Risk of Bladder Cancer. PLoS One, 2016. 11: e0159115. https://www.ncbi.nlm.nih.gov/pubmed/27438131
26. Martin, C., *et al.* Familial Cancer Clustering in Urothelial Cancer: A Population-Based Case-Control Study. J Natl Cancer Inst, 2018. 110: 527. https://www.ncbi.nlm.nih.gov/pubmed/29228305
27. Yu, E.Y., *et al.* Family History and Risk of Bladder Cancer: An Analysis Accounting for First- and Second-degree Relatives. Cancer Prev Res (Phila), 2022. 15: 319. https://www.ncbi.nlm.nih.gov/pubmed/35027464
28. Lenfant, L., *et al.* Genetic variability in 13q33 and 9q34 is linked to aggressiveness patterns and a higher risk of progression of non-muscle-invasive bladder cancer at the time of diagnosis. BJU Int, 2021. 127: 375. https://www.ncbi.nlm.nih.gov/pubmed/32975901
29. Rossi, M., *et al.* Flavonoids and bladder cancer risk. Cancer Causes Control, 2019. 30: 527. https://www.ncbi.nlm.nih.gov/pubmed/30903485
30. Buckland, G., *et al.* Adherence to the Mediterranean diet and risk of bladder cancer in the EPIC cohort study. Int J Cancer, 2014. 134: 2504. https://www.ncbi.nlm.nih.gov/pubmed/24226765
31. Liu, H., *et al.* Fruit and vegetable consumption and risk of bladder cancer: an updated meta-analysis of observational studies. Eur J Cancer Prev, 2015. 24: 508. https://www.ncbi.nlm.nih.gov/pubmed/25642791
32. Vieira, A.R., *et al.* Fruits, vegetables, and bladder cancer risk: a systematic review and meta-analysis. Cancer Med, 2015. 4: 136. https://www.ncbi.nlm.nih.gov/pubmed/25461441
33. Zhao, L., *et al.* Association of body mass index with bladder cancer risk: a dose-response meta-analysis of prospective cohort studies. Oncotarget, 2017. 8: 33990. https://www.ncbi.nlm.nih.gov/pubmed/28389625
34. Witlox, W.J.A., *et al.* An inverse association between the Mediterranean diet and bladder cancer risk: a pooled analysis of 13 cohort studies. Eur J Nutr, 2020. 59: 287. https://www.ncbi.nlm.nih.gov/pubmed/30737562
35. Dianatinasab, M., *et al.* Dietary fats and their sources in association with the risk of bladder cancer: A pooled analysis of 11 prospective cohort studies. Int J Cancer, 2022. 151: 44. https://www.ncbi.nlm.nih.gov/pubmed/35182086
36. Dianatinasab, M., *et al.* The association between meat and fish consumption and bladder cancer risk: a pooled analysis of 11 cohort studies. Eur J Epidemiol, 2021. 36: 781. https://www.ncbi.nlm.nih.gov/pubmed/34036467

37. Jochems, S.H.J., *et al.* Fruit consumption and the risk of bladder cancer: A pooled analysis by the Bladder Cancer Epidemiology and Nutritional Determinants Study. Int J Cancer, 2020. 147: 2091.
https://www.ncbi.nlm.nih.gov/pubmed/32285440
38. Boot, I.W.A., *et al.* Dietary B group vitamin intake and the bladder cancer risk: a pooled analysis of prospective cohort studies. Eur J Nutr, 2022. 61: 2397.
https://www.ncbi.nlm.nih.gov/pubmed/35129646
39. Al-Zalabani, A.H., *et al.* Tea consumption and risk of bladder cancer in the Bladder Cancer Epidemiology and Nutritional Determinants (BLEND) Study: Pooled analysis of 12 international cohort studies. Clin Nutr, 2022. 41: 1122.
https://www.ncbi.nlm.nih.gov/pubmed/35413574
40. Bryan, R.T., *et al.* Selenium and Vitamin E for Prevention of Non-Muscle-Invasive Bladder Cancer Recurrence and Progression: A Randomized Clinical Trial. JAMA Netw Open, 2023. 6: e2337494.
https://www.ncbi.nlm.nih.gov/pubmed/37847504
41. Wang, Z., *et al.* Associations of dietary isothiocyanate exposure from cruciferous vegetable consumption with recurrence and progression of non-muscle-invasive bladder cancer: findings from the Be-Well Study. Am J Clin Nutr, 2023. 117: 1110.
https://www.ncbi.nlm.nih.gov/pubmed/37044209
42. Steinmaus, C., *et al.* Increased lung and bladder cancer incidence in adults after in utero and early-life arsenic exposure. Cancer Epidemiol Biomarkers Prev, 2014. 23: 1529.
https://www.ncbi.nlm.nih.gov/pubmed/24859871
43. Koutros, S., *et al.* Potential effect modifiers of the arsenic-bladder cancer risk relationship. Int J Cancer, 2018. 143: 2640.
https://www.ncbi.nlm.nih.gov/pubmed/29981168
44. Arafa, A., *et al.* Chronic exposure to nitrate in drinking water and the risk of bladder cancer: a meta-analysis of epidemiological evidence. Public Health, 2022. 203: 123.
https://www.ncbi.nlm.nih.gov/pubmed/35063929
45. Zhang, Y., *et al.* Personal use of permanent hair dyes and cancer risk and mortality in US women: prospective cohort study. BMJ, 2020. 370: m2942.
https://www.ncbi.nlm.nih.gov/pubmed/32878860
46. Moschini, M., *et al.* External Beam Radiotherapy Increases the Risk of Bladder Cancer When Compared with Radical Prostatectomy in Patients Affected by Prostate Cancer: A Population-based Analysis. Eur Urol, 2019. 75: 319.
https://www.ncbi.nlm.nih.gov/pubmed/30293908
47. Minami, T., *et al.* External beam radiotherapy combination is a risk factor for bladder cancer in patients with prostate cancer treated with brachytherapy. World J Urol, 2023. 41: 1317.
https://www.ncbi.nlm.nih.gov/pubmed/37024557
48. Teleka, S., *et al.* Risk of bladder cancer by disease severity in relation to metabolic factors and smoking: A prospective pooled cohort study of 800,000 men and women. Int J Cancer, 2018. 143: 3071.
https://www.ncbi.nlm.nih.gov/pubmed/29756343
49. Hektoen, H.H., *et al.* Vitamin D and Vitamin D-binding protein and risk of bladder cancer: A nested case-control study in the Norwegian Janus Serum Bank Cohort. Cancer Med, 2021. 10: 4107.
https://www.ncbi.nlm.nih.gov/pubmed/34080787
50. An, H., *et al.* Physical Activity and Bladder Cancer Risk: Findings of the Japan Collaborative Cohort Study. Cancer Res Treat, 2024. 56: 616.
https://www.ncbi.nlm.nih.gov/pubmed/37817564
51. Tuccori, M., *et al.* Pioglitazone use and risk of bladder cancer: population based cohort study. BMJ, 2016. 352: i1541.
https://www.ncbi.nlm.nih.gov/pubmed/27029385
52. Otto, W., *et al.* WHO 1973 grade 3 and infiltrative growth pattern proved, aberrant E-cadherin expression tends to be of predictive value for progression in a series of stage T1 high-grade bladder cancer after organ-sparing approach. Int Urol Nephrol, 2017. 49: 431.
https://www.ncbi.nlm.nih.gov/pubmed/28035618
53. van Rhijn, B.W., *et al.* A new and highly prognostic system to discern T1 bladder cancer substage. Eur Urol, 2012. 61: 378.
https://www.ncbi.nlm.nih.gov/pubmed/22036775
54. Comperat, E., *et al.* What's new in WHO fifth edition - urinary tract. Histopathology, 2022. 81: 439.
https://www.ncbi.nlm.nih.gov/pubmed/35942645

55. WHO Classification of Tumours Editorial Board. WHO Classification of Tumours. Urinary and male genital tumours. International Agency for Research on Cancer 5th Edn.; Vol 8. 2022. https://publications.iarc.fr/610
56. Moch, H., *et al.* WHO Classification of Tumours of the Urinary System and Male Genital Organs. International Agency for Research on Cancer 4th Edn. 2016. www.iarc.fr
57. Comperat, E., *et al.* The Genitourinary Pathology Society Update on Classification of Variant Histologies, T1 Substaging, Molecular Taxonomy, and Immunotherapy and PD-L1 Testing Implications of Urothelial Cancers. Adv Anat Pathol, 2021. 28: 196. https://www.ncbi.nlm.nih.gov/pubmed/34128484
58. Kim, H.S., *et al.* Presence of lymphovascular invasion in urothelial bladder cancer specimens after transurethral resections correlates with risk of upstaging and survival: a systematic review and meta-analysis. Urol Oncol, 2014. 32: 1191. https://www.ncbi.nlm.nih.gov/pubmed/24954108
59. Tilki, D., *et al.* Lymphovascular invasion is independently associated with bladder cancer recurrence and survival in patients with final stage T1 disease and negative lymph nodes after radical cystectomy. BJU Int, 2013. 111: 1215. https://www.ncbi.nlm.nih.gov/pubmed/23181623
60. Martin-Doyle, W., *et al.* Improving selection criteria for early cystectomy in high-grade t1 bladder cancer: a meta-analysis of 15,215 patients. J Clin Oncol, 2015. 33: 643. https://www.ncbi.nlm.nih.gov/pubmed/25559810
61. Mari, A., *et al.* A systematic review and meta-analysis of the impact of lymphovascular invasion in bladder cancer transurethral resection specimens. BJU Int, 2019. 123: 11. https://www.ncbi.nlm.nih.gov/pubmed/29807387
62. D, D.A., *et al.* Accurate prediction of progression to muscle-invasive disease in patients with pT1G3 bladder cancer: A clinical decision-making tool. Urol Oncol, 2018. 36: 239 e1. https://www.ncbi.nlm.nih.gov/pubmed/29506941
63. Sauter G, A.F., Amin M, *et al.* . Tumours of the urinary system: non-invasive urothelial neoplasias. In: WHO classification of classification of tumours of the urinary system and male genital organs. IARCC Press, 2004: 29. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHOClassification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organ
64. Soukup, V., *et al.* Prognostic Performance and Reproducibility of the 1973 and 2004/2016 World Health Organization Grading Classification Systems in Non-muscle-invasive Bladder Cancer: A European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel Systematic Review. Eur Urol, 2017. 72: 801. https://www.ncbi.nlm.nih.gov/pubmed/28457661
65. Mariappan, P., *et al.* Combining two grading systems: the clinical validity and inter-observer variability of the 1973 and 2004 WHO bladder cancer classification systems assessed in a UK cohort with 15 years of prospective follow-up. World J Urol, 2021. 39: 425. https://www.ncbi.nlm.nih.gov/pubmed/32266509
66. Hentschel, A.E., *et al.* Papillary urothelial neoplasm of low malignant potential (PUN-LMP): Still a meaningful histo-pathological grade category for Ta, noninvasive bladder tumors in 2019? Urol Oncol, 2020. 38: 440. https://www.ncbi.nlm.nih.gov/pubmed/31704141
67. van Rhijn, B.W.G., *et al.* Prognostic Value of the WHO1973 and WHO2004/2016 Classification Systems for Grade in Primary Ta/T1 Non-muscle-invasive Bladder Cancer: A Multicenter European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel Study. Eur Urol Oncol, 2021. 4: 182. https://www.ncbi.nlm.nih.gov/pubmed/33423944
68. Andersson, M., *et al.* The diagnostic challenge of suspicious or positive malignant urine cytology findings when cystoscopy findings are normal: an outpatient blue-light flexible cystoscopy may solve the problem. Scand J Urol, 2021. 55: 263. https://www.ncbi.nlm.nih.gov/pubmed/34037496
69. Lamm, D., *et al.* Updated concepts and treatment of carcinoma *in situ*. Urol Oncol, 1998. 4: 130. https://www.ncbi.nlm.nih.gov/pubmed/21227218
70. Witjes, J.A., *et al.* Review pathology in a diagnostic bladder cancer trial: effect of patient risk category. Urology, 2006. 67: 751. https://www.ncbi.nlm.nih.gov/pubmed/16566990

71. May, M., *et al.* Prognostic accuracy of individual uropathologists in noninvasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation classifications. Eur Urol, 2010. 57: 850.
https://www.ncbi.nlm.nih.gov/pubmed/19346063
72. van Rhijn, B.W., *et al.* Pathological stage review is indicated in primary pT1 bladder cancer. BJU Int, 2010. 106: 206.
https://www.ncbi.nlm.nih.gov/pubmed/20002439
73. Comperat, E., *et al.* An interobserver reproducibility study on invasiveness of bladder cancer using virtual microscopy and heatmaps. Histopathology, 2013. 63: 756.
https://www.ncbi.nlm.nih.gov/pubmed/24102813
74. Mangrud, O.M., *et al.* Reproducibility and prognostic value of WHO1973 and WHO2004 grading systems in TaT1 urothelial carcinoma of the urinary bladder. PLoS One, 2014. 9: e83192.
https://www.ncbi.nlm.nih.gov/pubmed/24409280
75. Veskimae, E., *et al.* What Is the Prognostic and Clinical Importance of Urothelial and Nonurothelial Histological Variants of Bladder Cancer in Predicting Oncological Outcomes in Patients with Muscle-invasive and Metastatic Bladder Cancer? A European Association of Urology Muscle Invasive and Metastatic Bladder Cancer Guidelines Panel Systematic Review. Eur Urol Oncol, 2019. 2: 625.
https://www.ncbi.nlm.nih.gov/pubmed/31601522
76. Comperat, E.M., *et al.* Grading of Urothelial Carcinoma and The New "World Health Organisation Classification of Tumours of the Urinary System and Male Genital Organs 2016". Eur Urol Focus, 2019. 5: 457.
https://www.ncbi.nlm.nih.gov/pubmed/29366854
77. Lonati, C., *et al.* Accuracy of Transurethral Resection of the Bladder in Detecting Variant Histology of Bladder Cancer Compared with Radical Cystectomy. Eur Urol Focus, 2022. 8: 457.
https://www.ncbi.nlm.nih.gov/pubmed/33867307
78. Willis, D.L., *et al.* Clinical outcomes of cT1 micropapillary bladder cancer. J Urol, 2015. 193: 1129.
https://www.ncbi.nlm.nih.gov/pubmed/25254936
79. Comperat, E., *et al.* Micropapillary urothelial carcinoma of the urinary bladder: a clinicopathological analysis of 72 cases. Pathology, 2010. 42: 650.
https://www.ncbi.nlm.nih.gov/pubmed/21080874
80. Kaimakliotis, H.Z., *et al.* Plasmacytoid variant urothelial bladder cancer: is it time to update the treatment paradigm? Urol Oncol, 2014. 32: 833.
https://www.ncbi.nlm.nih.gov/pubmed/24954925
81. Willis, D.L., *et al.* Micropapillary bladder cancer: current treatment patterns and review of the literature. Urol Oncol, 2014. 32: 826.
https://www.ncbi.nlm.nih.gov/pubmed/24931270
82. Beltran, A.L., *et al.* Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. Virchows Arch, 2014. 465: 199.
https://www.ncbi.nlm.nih.gov/pubmed/24878757
83. Soave, A., *et al.* Does the extent of variant histology affect oncological outcomes in patients with urothelial carcinoma of the bladder treated with radical cystectomy? Urol Oncol, 2015. 33: 21 e1.
https://www.ncbi.nlm.nih.gov/pubmed/25465301
84. Masson-Lecomte, A., *et al.* Oncological outcomes of advanced muscle-invasive bladder cancer with a micropapillary variant after radical cystectomy and adjuvant platinum-based chemotherapy. World J Urol, 2015. 33: 1087.
https://www.ncbi.nlm.nih.gov/pubmed/25179011
85. Seisen, T., *et al.* Impact of histological variants on the outcomes of nonmuscle invasive bladder cancer after transurethral resection. Curr Opin Urol, 2014. 24: 524.
https://www.ncbi.nlm.nih.gov/pubmed/25051021
86. Burger, M., *et al.* Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. Eur Urol, 2008. 54: 835.
https://www.ncbi.nlm.nih.gov/pubmed/18166262
87. Fristrup, N., *et al.* Cathepsin E, maspin, Plk1, and survivin are promising prognostic protein markers for progression in non-muscle invasive bladder cancer. Am J Pathol, 2012. 180: 1824.
https://www.ncbi.nlm.nih.gov/pubmed/22449953
88. Palou, J., *et al.* Protein expression patterns of ezrin are predictors of progression in T1G3 bladder tumours treated with nonmaintenance bacillus Calmette-Guerin. Eur Urol, 2009. 56: 829.
https://www.ncbi.nlm.nih.gov/pubmed/18926620

89. van Rhijn, B.W., *et al.* The FGFR3 mutation is related to favorable pT1 bladder cancer. J Urol, 2012. 187: 310.
https://www.ncbi.nlm.nih.gov/pubmed/22099989
90. Remy, E., *et al.* A Modeling Approach to Explain Mutually Exclusive and Co-Occurring Genetic Alterations in Bladder Tumorigenesis. Cancer Res, 2015. 75: 4042.
https://www.ncbi.nlm.nih.gov/pubmed/26238783
91. Dyrskjot, L., *et al.* Prognostic Impact of a 12-gene Progression Score in Non-muscle-invasive Bladder Cancer: A Prospective Multicentre Validation Study. Eur Urol, 2017. 72: 461.
https://www.ncbi.nlm.nih.gov/pubmed/28583312
92. Marzouka, N.A., *et al.* The Lund Molecular Taxonomy Applied to Non-Muscle-Invasive Urothelial Carcinoma. J Mol Diagn, 2022. 24: 992.
https://www.ncbi.nlm.nih.gov/pubmed/35853574
93. Ramirez, D., *et al.* Microscopic haematuria at time of diagnosis is associated with lower disease stage in patients with newly diagnosed bladder cancer. BJU Int, 2016. 117: 783.
https://www.ncbi.nlm.nih.gov/pubmed/26435378
94. Trinh, T.W., *et al.* Bladder cancer diagnosis with CT urography: test characteristics and reasons for false-positive and false-negative results. Abdom Radiol (NY), 2018. 43: 663.
https://www.ncbi.nlm.nih.gov/pubmed/28677000
95. Waisbrod, S., *et al.* Assessment of Diagnostic Yield of Cystoscopy and Computed Tomographic Urography for Urinary Tract Cancers in Patients Evaluated for Microhematuria: A Systematic Review and Meta-analysis. JAMA Netw Open, 2021. 4: e218409.
https://www.ncbi.nlm.nih.gov/pubmed/33970257
96. Nolte-Ernsting, C., *et al.* Understanding multislice CT urography techniques: Many roads lead to Rome. Eur Radiol, 2006. 16: 2670.
https://www.ncbi.nlm.nih.gov/pubmed/16953373
97. Goessl, C., *et al.* Is routine excretory urography necessary at first diagnosis of bladder cancer? J Urol, 1997. 157: 480.
https://www.ncbi.nlm.nih.gov/pubmed/8996338
98. Palou, J., *et al.* Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. J Urol, 2005. 174: 859.
https://www.ncbi.nlm.nih.gov/pubmed/16093970
99. Holmang, S., *et al.* Long-term followup of a bladder carcinoma cohort: routine followup urography is not necessary. J Urol, 1998. 160: 45.
https://www.ncbi.nlm.nih.gov/pubmed/9628602
100. Millan-Rodriguez, F., *et al.* Upper urinary tract tumors after primary superficial bladder tumors: prognostic factors and risk groups. J Urol, 2000. 164: 1183.
https://www.ncbi.nlm.nih.gov/pubmed/10992362
101. Tan, W.S., *et al.* Can Renal and Bladder Ultrasound Replace Computerized Tomography Urogram in Patients Investigated for Microscopic Hematuria? J Urol, 2018. 200: 973.
https://www.ncbi.nlm.nih.gov/pubmed/29702097
102. Hilton, S., *et al.* Recent advances in imaging cancer of the kidney and urinary tract. Surg Oncol Clin N Am, 2014. 23: 863.
https://www.ncbi.nlm.nih.gov/pubmed/25246053
103. Panebianco, V., *et al.* Multiparametric Magnetic Resonance Imaging for Bladder Cancer: Development of VI-RADS (Vesical Imaging-Reporting And Data System). Eur Urol, 2018. 74: 294.
https://www.ncbi.nlm.nih.gov/pubmed/29755006
104. Del Giudice, F., *et al.* The accuracy of Vesical Imaging-Reporting and Data System (VI-RADS): an updated comprehensive multi-institutional, multi-readers systematic review and meta-analysis from diagnostic evidence into future clinical recommendations. World J Urol, 2022. 40: 1617.
https://www.ncbi.nlm.nih.gov/pubmed/35294583
105. Yafi, F.A., *et al.* Prospective analysis of sensitivity and specificity of urinary cytology and other urinary biomarkers for bladder cancer. Urol Oncol, 2015. 33: 66 e25.
https://www.ncbi.nlm.nih.gov/pubmed/25037483
106. Tetu, B. Diagnosis of urothelial carcinoma from urine. Mod Pathol, 2009. 22 Suppl 2: S53.
https://www.ncbi.nlm.nih.gov/pubmed/19494853
107. Lobo, J., *et al.* Evaluation of the Implementation and Diagnostic Accuracy of the Paris Classification for Reporting Urinary Cytology in Voided Urine Specimens: A Cyto-Histological Correlation Study in a Cancer Center. Pathobiology, 2023. 90: 233.
https://www.ncbi.nlm.nih.gov/pubmed/36574757

108. Raitanen, M.P., *et al.* Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol, 2002. 41: 284.
https://www.ncbi.nlm.nih.gov/pubmed/12180229
109. Karakiewicz, P.I., *et al.* Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. BJU Int, 2006. 97: 997.
https://www.ncbi.nlm.nih.gov/pubmed/16542342
110. Tian, W., *et al.* Significant reduction of indeterminate (atypical) diagnosis after implementation of The Paris System for Reporting Urinary Cytology: A single-institution study of more than 27,000 cases. Cancer Cytopathol, 2021. 129: 114.
https://www.ncbi.nlm.nih.gov/pubmed/32931158
111. Lebret, T., *et al.* Artificial intelligence to improve cytology performances in bladder carcinoma detection: results of the VisioCyt test. BJU Int, 2022. 129: 356.
https://www.ncbi.nlm.nih.gov/pubmed/33751774
112. Wojcik, E.M., Kurtycz, D.F.I., Rosenthal, D.L., The Paris System for Reporting Urinary Cytology, ed. E.M. Wojcik, Kurtycz, DFI, Rosenthal, D.L., Eds. Vol. 2nd Edn. . 2022.
https://link.springer.com/book/10.1007/978-3-030-88686-8
113. Pastorello, R.G., *et al.* Experience on the use of The Paris System for Reporting Urinary Cytopathology: review of the published literature. J Am Soc Cytopathol, 2021. 10: 79.
https://www.ncbi.nlm.nih.gov/pubmed/33160893
114. Meilleroux, J., *et al.* One year of experience using the Paris System for Reporting Urinary Cytology. Cancer Cytopathol, 2018. 126: 430.
https://www.ncbi.nlm.nih.gov/pubmed/29663682
115. Gomez Del Canizo, C., *et al.* Voided urine cytology is a useful tool predicting non-muscle-invasive bladder cancer risk before surgery. Urol Oncol, 2024. 42: 246 e15.
https://www.ncbi.nlm.nih.gov/pubmed/38664179
116. Nabi, G., *et al.* Suspicious urinary cytology with negative evaluation for malignancy in the diagnostic investigation of haematuria: how to follow up? J Clin Pathol, 2004. 57: 365.
https://www.ncbi.nlm.nih.gov/pubmed/15047737
117. Soria, F., *et al.* An up-to-date catalog of available urinary biomarkers for the surveillance of non-muscle invasive bladder cancer. World J Urol, 2018. 36: 1981.
https://www.ncbi.nlm.nih.gov/pubmed/29931526
118. Heard, J.R., *et al.* Noninvasive Tests for Bladder Cancer Detection and Surveillance: A Systematic Review of Commercially Available Assays. Bladder Cancer, 2024. 10: 71.
https://www.ncbi.nlm.nih.gov/pubmed/38993533
119. Moulavasilis, N., *et al.* The Paris system classification for urinary cytology in patients under bacillus Calmette-Guerin treatment. Diagn Cytopathol, 2022. 50: 289.
https://www.ncbi.nlm.nih.gov/pubmed/35262275
120. D'Andrea, D., *et al.* Diagnostic accuracy, clinical utility and influence on decision-making of a methylation urine biomarker test in the surveillance of non-muscle-invasive bladder cancer. BJU Int, 2019. 123: 959.
https://www.ncbi.nlm.nih.gov/pubmed/30653818
121. Ribal, M.J., *et al.* Gene expression test for the non-invasive diagnosis of bladder cancer: A prospective, blinded, international and multicenter validation study. Eur J Cancer, 2016. 54: 131.
https://www.ncbi.nlm.nih.gov/pubmed/26761785
122. Wolff, I., *et al.* Real-world performance of Uromonitor(R) in urothelial bladder cancer detection: a multicentric trial. BJU Int, 2024.
https://www.ncbi.nlm.nih.gov/pubmed/38923777
123. Fiorentino, V., *et al.* Bladder Epicheck Test: A Novel Tool to Support Urothelial Carcinoma Diagnosis in Urine Samples. Int J Mol Sci, 2023. 24.
https://www.ncbi.nlm.nih.gov/pubmed/37569864
124. Sharma, G., *et al.* Xpert bladder cancer monitor in surveillance of bladder cancer: Systematic review and meta-analysis. Urol Oncol, 2022. 40: 163 e1.
https://www.ncbi.nlm.nih.gov/pubmed/34535354
125. van der Aa, M.N., *et al.* Microsatellite analysis of voided-urine samples for surveillance of low-grade non-muscle-invasive urothelial carcinoma: feasibility and clinical utility in a prospective multicenter study (Cost-Effectiveness of Follow-Up of Urinary Bladder Cancer trial [CEFUB]). Eur Urol, 2009. 55: 659.
https://www.ncbi.nlm.nih.gov/pubmed/18501499

126. Roupret, M., *et al.* A comparison of the performance of microsatellite and methylation urine analysis for predicting the recurrence of urothelial cell carcinoma, and definition of a set of markers by Bayesian network analysis. BJU Int, 2008. 101: 1448.
https://www.ncbi.nlm.nih.gov/pubmed/18325051
127. Todenhofer, T., *et al.* Prognostic relevance of positive urine markers in patients with negative cystoscopy during surveillance of bladder cancer. BMC Cancer, 2015. 15: 155.
https://www.ncbi.nlm.nih.gov/pubmed/25884545
128. Grossman, H.B., *et al.* Detection of bladder cancer using a point-of-care proteomic assay. JAMA, 2005. 293: 810.
https://www.ncbi.nlm.nih.gov/pubmed/15713770
129. Kim, P.H., *et al.* Reflex fluorescence *in situ* hybridization assay for suspicious urinary cytology in patients with bladder cancer with negative surveillance cystoscopy. BJU Int, 2014. 114: 354.
https://www.ncbi.nlm.nih.gov/pubmed/24128299
130. Palou, J., *et al.* Management of Patients with Normal Cystoscopy but Positive Cytology or Urine Markers. Eur Urol Oncol, 2020. 3: 548.
https://www.ncbi.nlm.nih.gov/pubmed/31331861
131. Beukers, W., *et al.* FGFR3, TERT and OTX1 as a Urinary Biomarker Combination for Surveillance of Patients with Bladder Cancer in a Large Prospective Multicenter Study. J Urol, 2017. 197: 1410.
https://www.ncbi.nlm.nih.gov/pubmed/28049011
132. Critelli, R., *et al.* Detection of multiple mutations in urinary exfoliated cells from male bladder cancer patients at diagnosis and during follow-up. Oncotarget, 2016. 7: 67435.
https://www.ncbi.nlm.nih.gov/pubmed/27611947
133. Liedberg, F., *et al.* Clinical Implementation of Urinary Biomarkers for Surveillance of Non-muscle-invasive Bladder Cancer (NMIBC): Considerations from the European Association of Urology NMIBC Guideline Panel. Eur Urol Oncol, 2024.
https://www.ncbi.nlm.nih.gov/pubmed/39343636
134. Roobol, M.J., *et al.* Feasibility study of screening for bladder cancer with urinary molecular markers (the BLU-P project). Urol Oncol, 2010. 28: 686.
https://www.ncbi.nlm.nih.gov/pubmed/21062653
135. Starke, N., *et al.* Long-term outcomes in a high-risk bladder cancer screening cohort. BJU Int, 2016. 117: 611.
https://www.ncbi.nlm.nih.gov/pubmed/25891519
136. Shang, D., *et al.* Diagnostic value comparison of CellDetect, fluorescent *in situ* hybridization (FISH), and cytology in urothelial carcinoma. Cancer Cell Int, 2021. 21: 465.
https://www.ncbi.nlm.nih.gov/pubmed/34488763
137. Valenberg, F., *et al.* Validation of an mRNA-based Urine Test for the Detection of Bladder Cancer in Patients with Haematuria. Eur Urol Oncol, 2021. 4: 93.
https://www.ncbi.nlm.nih.gov/pubmed/33004290
138. Kurth, K.H., *et al.* Current methods of assessing and treating carcinoma *in situ* of the bladder with or without involvement of the prostatic urethra. Int J Urol, 1995. 2 Suppl 2: 8.
https://www.ncbi.nlm.nih.gov/pubmed/7553309
139. Krajewski, W., *et al.* How different cystoscopy methods influence patient sexual satisfaction, anxiety, and depression levels: a randomized prospective trial. Qual Life Res, 2017. 26: 625.
https://www.ncbi.nlm.nih.gov/pubmed/28050795
140. Aaronson, D.S., *et al.* Meta-analysis: does lidocaine gel before flexible cystoscopy provide pain relief? BJU Int, 2009. 104: 506.
https://www.ncbi.nlm.nih.gov/pubmed/19239453
141. Berjaoui, M.B., *et al.* A Prospective Randomized Controlled Trial of Irrigation "Bag Squeeze" to Manage Pain for Patients Undergoing Flexible Cystoscopy. J Urol, 2020. 204: 1012.
https://www.ncbi.nlm.nih.gov/pubmed/32396409
142. Gunendran, T., *et al.* Does increasing hydrostatic pressure ("bag squeeze") during flexible cystoscopy improve patient comfort: a randomized, controlled study. Urology, 2008. 72: 255.
https://www.ncbi.nlm.nih.gov/pubmed/18554699
143. Suarez-Ibarrola, R., *et al.* Surgical checklist impact on recurrence-free survival of patients with non-muscle-invasive bladder cancer undergoing transurethral resection of bladder tumour. BJU Int, 2019. 123: 646.
https://www.ncbi.nlm.nih.gov/pubmed/30248235

144. Teoh, J.Y., *et al.* An International Collaborative Consensus Statement on *En Bloc* Resection of Bladder Tumour Incorporating Two Systematic Reviews, a Two-round Delphi Survey, and a Consensus Meeting. Eur Urol, 2020. 78: 546.
https://www.ncbi.nlm.nih.gov/pubmed/32389447
145. Anderson, C., *et al.* A 10-Item Checklist Improves Reporting of Critical Procedural Elements during Transurethral Resection of Bladder Tumor. J Urol, 2016. 196: 1014.
https://www.ncbi.nlm.nih.gov/pubmed/27044571
146. Mariappan, P., *et al.* Predicting Grade and Stage at Cystoscopy in Newly Presenting Bladder Cancers-a Prospective Double-Blind Clinical Study. Urology, 2017. 109: 134.
https://www.ncbi.nlm.nih.gov/pubmed/28818537
147. Breda, A., *et al.* The DEpth of Endoscopic Perforation scale to assess intraoperative perforations during transurethral resection of bladder tumor: subgroup analysis of a randomized controlled trial. World J Urol, 2023. 41: 2583.
https://www.ncbi.nlm.nih.gov/pubmed/35665840
148. Brausi, M., *et al.* Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol, 2002. 41: 523.
https://www.ncbi.nlm.nih.gov/pubmed/12074794
149. Richterstetter, M., *et al.* The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. BJU Int, 2012. 110: E76.
https://www.ncbi.nlm.nih.gov/pubmed/22313727
150. Chai, Y.-M.e.a. The efficacy and safety of thulium laser resection of bladder tumor versus standard transurethral resection in patients with non muscle-invasive bladder cancer: a systematic review and meta-analysis. Journal of Men's Health, 2021.
151. Yanagisawa, T., *et al. En Bloc* Resection for Bladder Tumors: An Updated Systematic Review and Meta-Analysis of Its Differential Effect on Safety, Recurrence and Histopathology. J Urol, 2022. 207: 754.
https://www.ncbi.nlm.nih.gov/pubmed/35060770
152. Kramer, M.W., *et al. En bloc* resection of urothelium carcinoma of the bladder (EBRUC): a European multicenter study to compare safety, efficacy, and outcome of laser and electrical *en bloc* transurethral resection of bladder tumor. World J Urol, 2015. 33: 1937.
https://www.ncbi.nlm.nih.gov/pubmed/25910478
153. Hurle, R., *et al.* "*En Bloc*" Resection of Nonmuscle Invasive Bladder Cancer: A Prospective Single-center Study. Urology, 2016. 90: 126.
https://www.ncbi.nlm.nih.gov/pubmed/26776561
154. Migliari, R., *et al.* Thulium Laser Endoscopic *En Bloc* Enucleation of Nonmuscle-Invasive Bladder Cancer. J Endourol, 2015. 29: 1258.
https://www.ncbi.nlm.nih.gov/pubmed/26102556
155. Zhang, X.R., *et al.* Two Micrometer Continuous-Wave Thulium Laser Treating Primary Non-Muscle-Invasive Bladder Cancer: Is It Feasible? A Randomized Prospective Study. Photomed Laser Surg, 2015. 33: 517.
https://www.ncbi.nlm.nih.gov/pubmed/26397029
156. Hashem, A., *et al.* Holmium Laser En-bloc Resection Versus Conventional Transurethral Resection of Bladder Tumors for Treatment of Non-muscle-invasive Bladder Cancer: A Randomized Clinical Trial. Eur Urol Focus, 2021. 7: 1035.
https://www.ncbi.nlm.nih.gov/pubmed/33386289
157. Fan, J., *et al.* Green-light laser *en bloc* resection versus conventional transurethral resection for initial non-muscle-invasive bladder cancer: A randomized controlled trial. Int J Urol, 2021. 28: 855.
https://www.ncbi.nlm.nih.gov/pubmed/34013615
158. Badawy, A., *et al.* Thulium laser *en bloc* resection versus conventional transurethral resection of urinary bladder tumor: A comparative prospective study. Urol Ann, 2023. 15: 88.
https://www.ncbi.nlm.nih.gov/pubmed/37006212
159. Gallioli, A., *et al. En Bloc* Versus Conventional Transurethral Resection of Bladder Tumors: A Single-center Prospective Randomized Noninferiority Trial. Eur Urol Oncol, 2022. 5: 440.
https://www.ncbi.nlm.nih.gov/pubmed/35618567
160. D'Andrea, D., *et al. En Bloc* Versus Conventional Resection of Primary Bladder Tumor (eBLOC): A Prospective, Multicenter, Open-label, Phase 3 Randomized Controlled Trial. Eur Urol Oncol, 2023. 6: 508.
https://www.ncbi.nlm.nih.gov/pubmed/37543464

161. Li, Z., *et al.* Systematic review and meta-analysis of randomized controlled trials of perioperative outcomes and prognosis of transurethral en-bloc resection vs. conventional transurethral resection for non-muscle-invasive bladder cancer. Int J Surg, 2022. 104: 106777.
https://www.ncbi.nlm.nih.gov/pubmed/35850465
162. Yuen-Chun Teoh, J., *et al.* Transurethral *En Bloc* Resection Versus Standard Resection of Bladder Tumour: A Randomised, Multicentre, Phase 3 Trial. Eur Urol, 2024. 86: 103.
https://www.ncbi.nlm.nih.gov/pubmed/38692956
163. Teoh, J.Y., *et al.* En-bloc resection of bladder tumour as primary treatment for patients with non-muscle-invasive bladder cancer: routine implementation in a multi-centre setting. World J Urol, 2021. 39: 3353.
https://www.ncbi.nlm.nih.gov/pubmed/33774705
164. Mariappan, P., *et al.* Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. Eur Urol, 2010. 57: 843.
https://www.ncbi.nlm.nih.gov/pubmed/19524354
165. Taoka, R., *et al.* Use of surgical checklist during transurethral resection increases detrusor muscle collection rate and improves recurrence-free survival in patients with non-muscle-invasive bladder cancer. Int J Urol, 2021. 28: 727.
https://www.ncbi.nlm.nih.gov/pubmed/33742465
166. Mariappan, P., *et al.* Enhanced Quality and Effectiveness of Transurethral Resection of Bladder Tumour in Non-muscle-invasive Bladder Cancer: A Multicentre Real-world Experience from Scotland's Quality Performance Indicators Programme. Eur Urol, 2020. 78: 520.
https://www.ncbi.nlm.nih.gov/pubmed/32690321
167. Del Giudice, F., *et al.* Surgical checklist adherence across urology expertise levels impacts transurethral resection of bladder tumour quality indicators. BJU Int, 2023. 131: 712.
https://www.ncbi.nlm.nih.gov/pubmed/36251366
168. Mariappan, P., *et al.* Achieving Benchmarks for National Quality Indicators Reduces Recurrence and Progression in Non-muscle-invasive Bladder Cancer. Eur Urol Oncol, 2024.
https://www.ncbi.nlm.nih.gov/pubmed/38296735
169. Mariappan, P., *et al.* Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU Int, 2012. 109: 1666.
https://www.ncbi.nlm.nih.gov/pubmed/22044434
170. Neumann, E., *et al.* Transurethral Resection of Bladder Tumors: Next-generation Virtual Reality Training for Surgeons. Eur Urol Focus, 2019. 5: 906.
https://www.ncbi.nlm.nih.gov/pubmed/29802051
171. Bebane, S., *et al.* Perioperative outcomes of transurethral resection for t1 bladder tumors: quality evaluation based on patient, tumor and surgeon criteria. World J Urol, 2021. 39: 4159.
https://www.ncbi.nlm.nih.gov/pubmed/34160681
172. Jancke, G., *et al.* Impact of surgical experience on recurrence and progression after transurethral resection of bladder tumour in non-muscle-invasive bladder cancer. Scand J Urol, 2014. 48: 276.
https://www.ncbi.nlm.nih.gov/pubmed/24286506
173. Wettstein, M.S., *et al.* Association between surgical case volume and survival in T1 bladder cancer: A plea for regionalization of care? Canadian Urological Association Journal, 2020. 14: E394.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7492039/
174. Mao, X., *et al.* Outcomes and Complications of Bipolar vs. Monopolar Energy for Transurethral Resection of Bladder Tumors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Surg, 2021. 8: 583806.
https://www.ncbi.nlm.nih.gov/pubmed/34150834
175. Tzelves, L., *et al.* Does bipolar energy provide any advantage over monopolar surgery in transurethral resection of non-muscle invasive bladder tumors? A systematic review and meta-analysis. World J Urol, 2021. 39: 1093.
https://www.ncbi.nlm.nih.gov/pubmed/32591900
176. Xie, K., *et al.* Bipolar versus monopolar transurethral resection of non-muscle-invasive bladder cancer: a systematic review and meta-analysis of randomized controlled trials. World J Urol, 2021. 39: 1177.
https://www.ncbi.nlm.nih.gov/pubmed/32462303

177. Picozzi, S.C., *et al.* Is it oncologically safe performing simultaneous transurethral resection of the bladder and prostate? A meta-analysis on 1,234 patients. Int Urol Nephrol, 2012. 44: 1325. https://www.ncbi.nlm.nih.gov/pubmed/22710969
178. Tsivian, A., *et al.* Simultaneous transurethral resection of bladder tumor and benign prostatic hyperplasia: hazardous or a safe timesaver? J Urol, 2003. 170: 2241. https://www.ncbi.nlm.nih.gov/pubmed/14634388
179. Sari Motlagh, R., *et al.* The recurrence and progression risk after simultaneous endoscopic surgery of urothelial bladder tumour and benign prostatic hyperplasia: a systematic review and meta-analysis. BJU Int, 2021. 127: 143. https://www.ncbi.nlm.nih.gov/pubmed/32564458
180. Laukhtina, E., *et al.* Oncological and safety profiles in patients undergoing simultaneous transurethral resection (TUR) of bladder tumour and TUR of the prostate. BJU Int, 2023. 131: 571. https://www.ncbi.nlm.nih.gov/pubmed/36134575
181. van der Meijden, A., *et al.* Significance of bladder biopsies in Ta,T1 bladder tumors: a report from the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. Eur Urol, 1999. 35: 267. https://www.ncbi.nlm.nih.gov/pubmed/10419345
182. Hara, T., *et al.* Risk of concomitant carcinoma *in situ* determining biopsy candidates among primary non-muscle-invasive bladder cancer patients: retrospective analysis of 173 Japanese cases. Int J Urol, 2009. 16: 293. https://www.ncbi.nlm.nih.gov/pubmed/19207607
183. Palou, J., *et al.* Female gender and carcinoma *in situ* in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guerin. Eur Urol, 2012. 62: 118. https://www.ncbi.nlm.nih.gov/pubmed/22101115
184. Mungan, M.U., *et al.* Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. Eur Urol, 2005. 48: 760. https://www.ncbi.nlm.nih.gov/pubmed/16005563
185. Brant, A., *et al.* Prognostic implications of prostatic urethral involvement in non-muscle-invasive bladder cancer. World J Urol, 2019. 37: 2683. https://www.ncbi.nlm.nih.gov/pubmed/30850856
186. Huguet, J., *et al.* Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. Eur Urol, 2005. 48: 53. https://www.ncbi.nlm.nih.gov/pubmed/15967252
187. Kausch, I., *et al.* Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies. Eur Urol, 2010. 57: 595. https://www.ncbi.nlm.nih.gov/pubmed/20004052
188. Mowatt, G., *et al.* Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: Systematic review and meta-analysis. Int J Technol Assess Health Care, 2011. 27: 3. https://www.ncbi.nlm.nih.gov/pubmed/21262078
189. Neuzillet, Y., *et al.* Assessment of diagnostic gain with hexaminolevulinate (HAL) in the setting of newly diagnosed non-muscle-invasive bladder cancer with positive results on urine cytology. Urol Oncol, 2014. 32: 1135. https://www.ncbi.nlm.nih.gov/pubmed/25023786
190. Draga, R.O., *et al.* Photodynamic diagnosis (5-aminolevulinic acid) of transitional cell carcinoma after bacillus Calmette-Guerin immunotherapy and mitomycin C intravesical therapy. Eur Urol, 2010. 57: 655. https://www.ncbi.nlm.nih.gov/pubmed/19819064
191. Ray, E.R., *et al.* Hexylaminolaevulinate fluorescence cystoscopy in patients previously treated with intravesical bacille Calmette-Guerin. BJU Int, 2010. 105: 789. https://www.ncbi.nlm.nih.gov/pubmed/19832725
192. Chou, R., *et al.* Comparative Effectiveness of Fluorescent Versus White Light Cystoscopy for Initial Diagnosis or Surveillance of Bladder Cancer on Clinical Outcomes: Systematic Review and Meta-Analysis. J Urol, 2017. 197: 548. https://www.ncbi.nlm.nih.gov/pubmed/27780784
193. Veeratterapillay, R., *et al.* Time to Turn on the Blue Lights: A Systematic Review and Meta-analysis of Photodynamic Diagnosis for Bladder Cancer. Eur Urol Open Sci, 2021. 31: 17. https://www.ncbi.nlm.nih.gov/pubmed/34467237

194. Maisch, P., *et al.* Blue vs white light for transurethral resection of non-muscle-invasive bladder cancer: an abridged Cochrane Review. BJU Int, 2022. 130: 730.
https://www.ncbi.nlm.nih.gov/pubmed/35238145
195. Zhao, H., *et al.* Comparison of hexaminolevulinate (HAL) -guided versus white light transurethral resection for NMIBC: A systematic review and meta-analysis of randomized controlled trials. Photodiagnosis Photodyn Ther, 2023. 41: 103220.
https://www.ncbi.nlm.nih.gov/pubmed/36462704
196. Heer, R., *et al.* A Randomized Trial of PHOTOdynamic Surgery in Non–Muscle-Invasive Bladder Cancer. NEJM Evidence, 2022. 1.
197. Zheng, C., *et al.* Narrow band imaging diagnosis of bladder cancer: systematic review and meta-analysis. BJU Int, 2012. 110: E680.
https://www.ncbi.nlm.nih.gov/pubmed/22985502
198. Drejer, D., *et al.* Clinical relevance of narrow-band imaging in flexible cystoscopy: the DaBlaCa-7 study. Scand J Urol, 2017. 51: 120.
https://www.ncbi.nlm.nih.gov/pubmed/28266904
199. Ye, Z., *et al.* A comparison of NBI and WLI cystoscopy in detecting non-muscle-invasive bladder cancer: A prospective, randomized and multi-center study. Sci Rep, 2015. 5: 10905.
https://www.ncbi.nlm.nih.gov/pubmed/26046790
200. Kim, S.B., *et al.* Detection and recurrence rate of transurethral resection of bladder tumors by narrow-band imaging: Prospective, randomized comparison with white light cystoscopy. Investig Clin Urol, 2018. 59: 98.
https://www.ncbi.nlm.nih.gov/pubmed/29520385
201. Naito, S., *et al.* The Clinical Research Office of the Endourological Society (CROES) Multicentre Randomised Trial of Narrow Band Imaging-Assisted Transurethral Resection of Bladder Tumour (TURBT) Versus Conventional White Light Imaging-Assisted TURBT in Primary Non-Muscle-invasive Bladder Cancer Patients: Trial Protocol and 1-year Results. Eur Urol, 2016. 70: 506.
https://www.ncbi.nlm.nih.gov/pubmed/27117749
202. Russo, G.I., *et al.* Performance of Narrow Band Imaging (NBI) and Photodynamic Diagnosis (PDD) Fluorescence Imaging Compared to White Light Cystoscopy (WLC) in Detecting Non-Muscle Invasive Bladder Cancer: A Systematic Review and Lesion-Level Diagnostic Meta-Analysis. Cancers (Basel), 2021. 13.
https://www.ncbi.nlm.nih.gov/pubmed/34503188
203. Li, H., *et al.* Novel Visualization Methods Assisted Transurethral Resection for Bladder Cancer: An Updated Survival-Based Systematic Review and Meta-Analysis. Front Oncol, 2021. 11: 644341.
https://www.ncbi.nlm.nih.gov/pubmed/34327134
204. Sari Motlagh, R., *et al.* Impact of enhanced optical techniques at time of transurethral resection of bladder tumour, with or without single immediate intravesical chemotherapy, on recurrence rate of non-muscle-invasive bladder cancer: a systematic review and network meta-analysis of randomized trials. BJU Int, 2021. 128: 280.
https://www.ncbi.nlm.nih.gov/pubmed/33683778
205. Howard, J.M., *et al.* Enhanced Endoscopy with IMAGE1 S CHROMA Improves Detection of Nonmuscle Invasive Bladder Cancer During Transurethral Resection. J Endourol, 2021. 35: 647.
https://www.ncbi.nlm.nih.gov/pubmed/33176470
206. Mulawkar, P., *et al.* Evaluation of Spectra A and B Modes in Diagnosis of Suspicious Bladder Lesions. J Endourol, 2021. 35: 1184.
https://www.ncbi.nlm.nih.gov/pubmed/33446044
207. de la Rosette, J., *et al.* Conventional white light imaging-assisted transurethral resection of bladder tumour (TURBT) versus IMAGE1S-assisted TURBT in non-muscle-invasive bladder cancer patients: trial protocol and 18 months results. World J Urol, 2022. 40: 727.
https://www.ncbi.nlm.nih.gov/pubmed/34741631
208. Trelles Guzman, C.R., *et al.* Randomized clinical trial on the use of IMAGE1 S LIGHT (SPIES) vs. white light in the prevention of recurrence during transurethral resection of bladder tumors: Analysis after 12-month follow-up. Actas Urol Esp (Engl Ed), 2024. 48: 512.
https://www.ncbi.nlm.nih.gov/pubmed/38159804
209. Liem, E., *et al.* Validation of Confocal Laser Endomicroscopy Features of Bladder Cancer: The Next Step Towards Real-time Histologic Grading. Eur Urol Focus, 2020. 6: 81.
https://www.ncbi.nlm.nih.gov/pubmed/30033066

210. Cumberbatch, M.G.K., *et al.* Repeat Transurethral Resection in Non-muscle-invasive Bladder Cancer: A Systematic Review. Eur Urol, 2018. 73: 925.
https://www.ncbi.nlm.nih.gov/pubmed/29523366
211. Yanagisawa, T., *et al.* Repeat Transurethral Resection for Non-muscle-invasive Bladder Cancer: An Updated Systematic Review and Meta-analysis in the Contemporary Era. Eur Urol Focus, 2024. 10: 41.
https://www.ncbi.nlm.nih.gov/pubmed/37495458
212. Naselli, A., *et al.* Role of Restaging Transurethral Resection for T1 Non-muscle invasive Bladder Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus, 2018. 4: 558.
https://www.ncbi.nlm.nih.gov/pubmed/28753839
213. Elsawy, A.A., *et al.* Diagnostic performance and predictive capacity of early urine cytology after transurethral resection of nonmuscle invasive bladder cancer: A prospective study. Urol Oncol, 2020. 38: 935 e1.
https://www.ncbi.nlm.nih.gov/pubmed/32654947
214. Elsawy, A.A., *et al.* Can repeat biopsy be skipped after initial complete resection of T1 bladder cancer? The role of a novel urinary mRNA biomarker. Urol Oncol, 2021. 39: 437 e11.
https://www.ncbi.nlm.nih.gov/pubmed/33785220
215. Grimm, M.O., *et al.* Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol, 2003. 170: 433.
https://www.ncbi.nlm.nih.gov/pubmed/12853793
216. Eroglu, A., *et al.* The prognostic value of routine second transurethral resection in patients with newly diagnosed stage pT1 non-muscle-invasive bladder cancer: results from randomized 10-year extension trial. Int J Clin Oncol, 2020. 25: 698.
https://www.ncbi.nlm.nih.gov/pubmed/31760524
217. Lee, K., *et al.* Evaluating the efficacy of secondary transurethral resection of the bladder for high-grade Ta tumors. Investig Clin Urol, 2022. 63: 14.
https://www.ncbi.nlm.nih.gov/pubmed/34983118
218. Gordon, P.C., *et al.* Long-term Outcomes from Re-resection for High-risk Non-muscle-invasive Bladder Cancer: A Potential to Rationalize Use. Eur Urol Focus, 2019. 5: 650.
https://www.ncbi.nlm.nih.gov/pubmed/29089252
219. Hashine, K., *et al.* Results of second transurethral resection for high-grade T1 bladder cancer. Urol Ann, 2016. 8: 10.
https://www.ncbi.nlm.nih.gov/pubmed/26834394
220. Dalbagni, G., *et al.* Clinical outcome in a contemporary series of restaged patients with clinical T1 bladder cancer. Eur Urol, 2009. 56: 903.
https://www.ncbi.nlm.nih.gov/pubmed/19632765
221. Bishr, M., *et al.* Tumour stage on re-staging transurethral resection predicts recurrence and progression-free survival of patients with high-risk non-muscle invasive bladder cancer. Can Urol Assoc J, 2014. 8: E306.
https://www.ncbi.nlm.nih.gov/pubmed/24940455
222. Palou, J., *et al.* Recurrence, progression and cancer-specific mortality according to stage at re-TUR in T1G3 bladder cancer patients treated with BCG: not as bad as previously thought. World J Urol, 2018. 36: 1621.
https://www.ncbi.nlm.nih.gov/pubmed/29721611
223. Gontero, P., *et al.* The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette-Guerin. BJU Int, 2016. 118: 44.
https://www.ncbi.nlm.nih.gov/pubmed/26469362
224. Hensley, P.J., *et al.* Implications of Guideline-based, Risk-stratified Restaging Transurethral Resection of High-grade Ta Urothelial Carcinoma on Bacillus Calmette-Guerin Therapy Outcomes. Eur Urol Oncol, 2022. 5: 347.
https://www.ncbi.nlm.nih.gov/pubmed/33935020
225. Baltaci, S., *et al.* Significance of the interval between first and second transurethral resection on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer treated with maintenance intravesical Bacillus Calmette-Guerin. BJU Int, 2015. 116: 721.
https://www.ncbi.nlm.nih.gov/pubmed/25715815
226. Paner, G.P., *et al.* Challenges in Pathologic Staging of Bladder Cancer: Proposals for Fresh Approaches of Assessing Pathologic Stage in Light of Recent Studies and Observations Pertaining to Bladder Histoanatomic Variances. Adv Anat Pathol, 2017. 24: 113.
https://www.ncbi.nlm.nih.gov/pubmed/28398951

227. ICCR. Urinary Tract Carcinoma Biopsy and Transurethral Resection Specimen (TNM8). 2019. 2022. http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/ut-biopsy-and-tr
228. Mostafid, H., *et al.* Best Practices to Optimise Quality and Outcomes of Transurethral Resection of Bladder Tumours. Eur Urol Oncol, 2021. 4: 12. https://www.ncbi.nlm.nih.gov/pubmed/32684515
229. Sylvester, R.J., *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol, 2006. 49: 466. https://www.ncbi.nlm.nih.gov/pubmed/16442208
230. Lammers, R.J., *et al.* Prediction model for recurrence probabilities after intravesical chemotherapy in patients with intermediate-risk non-muscle-invasive bladder cancer, including external validation. World J Urol, 2016. 34: 173. https://www.ncbi.nlm.nih.gov/pubmed/26025189
231. Fernandez-Gomez, J., *et al.* Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol, 2009. 182: 2195. https://www.ncbi.nlm.nih.gov/pubmed/19758621
232. Fernandez-Gomez, J., *et al.* The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: external validation of the EORTC risk tables. Eur Urol, 2011. 60: 423. https://www.ncbi.nlm.nih.gov/pubmed/21621906
233. van Rhijn, B.W., *et al.* Molecular grade (FGFR3/MIB-1) and EORTC risk scores are predictive in primary non-muscle-invasive bladder cancer. Eur Urol, 2010. 58: 433. https://www.ncbi.nlm.nih.gov/pubmed/20646825
234. Cambier, S., *et al.* EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. Eur Urol, 2016. 69: 60. https://www.ncbi.nlm.nih.gov/pubmed/26210894
235. Sylvester, R.J., *et al.* European Association of Urology (EAU) Prognostic Factor Risk Groups for Non-muscle-invasive Bladder Cancer (NMIBC) Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An Update from the EAU NMIBC Guidelines Panel. Eur Urol, 2021. 79: 480. https://www.ncbi.nlm.nih.gov/pubmed/33419683
236. Gontero, P., *et al.* Prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with Bacillus Calmette-Guerin: results of a retrospective multicenter study of 2451 patients. Eur Urol, 2015. 67: 74. https://www.ncbi.nlm.nih.gov/pubmed/25043942
237. Voskuilen, C.S., *et al.* Urothelial Carcinoma in Bladder Diverticula: A Multicenter Analysis of Characteristics and Clinical Outcomes. Eur Urol Focus, 2020. 6: 1226. https://www.ncbi.nlm.nih.gov/pubmed/30559065
238. Palou, J., *et al.* Recurrence at three months and high-grade recurrence as prognostic factor of progression in multivariate analysis of T1G2 bladder tumors. Urology, 2009. 73: 1313. https://www.ncbi.nlm.nih.gov/pubmed/19362341
239. Alkhateeb, S.S., *et al.* Long-term prognostic value of the combination of EORTC risk group calculator and molecular markers in non-muscle-invasive bladder cancer patients treated with intravesical Bacille Calmette-Guerin. Urol Ann, 2011. 3: 119. https://www.ncbi.nlm.nih.gov/pubmed/21976923
240. Lamm, D.L. Carcinoma *in situ*. Urol Clin North Am, 1992. 19: 499. https://www.ncbi.nlm.nih.gov/pubmed/1636234
241. Losa, A., *et al.* Low dose bacillus Calmette-Guerin for carcinoma *in situ* of the bladder: long-term results. J Urol, 2000. 163: 68. https://www.ncbi.nlm.nih.gov/pubmed/10604316
242. Griffiths, T.R., *et al.* Treatment of carcinoma *in situ* with intravesical bacillus Calmette-Guerin without maintenance. J Urol, 2002. 167: 2408. https://www.ncbi.nlm.nih.gov/pubmed/11992047
243. Takenaka, A., *et al.* Clinical outcomes of bacillus Calmette-Guerin instillation therapy for carcinoma *in situ* of urinary bladder. Int J Urol, 2008. 15: 309. https://www.ncbi.nlm.nih.gov/pubmed/18380817

244. Solsona, E., *et al.* The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol, 2000. 164: 685. https://www.ncbi.nlm.nih.gov/pubmed/10953125
245. van Gils-Gielen, R.J., *et al.* Risk factors in carcinoma *in situ* of the urinary bladder. Dutch South East Cooperative Urological Group. Urology, 1995. 45: 581. https://www.ncbi.nlm.nih.gov/pubmed/7716838
246. Deuker, M., *et al.* Bladder Cancer: A Comparison Between Non-urothelial Variant Histology and Urothelial Carcinoma Across All Stages and Treatment Modalities. Clin Genitourin Cancer, 2021. 19: 60. https://www.ncbi.nlm.nih.gov/pubmed/32782133
247. Dursun, F., *et al.* Histological variants of non-muscle invasive bladder cancer: Survival outcomes of radical cystectomy vs. bladder preservation therapy. Urol Oncol, 2022. 40: 275 e1. https://www.ncbi.nlm.nih.gov/pubmed/35351370
248. Sood, A., *et al.* Long-Term Oncological Outcomes in Patients Diagnosed With Nonmetastatic Plasmacytoid Variant of Bladder Cancer: A 20-Year University of Texas MD Anderson Cancer Center Experience. J Urol, 2024. 211: 241. https://www.ncbi.nlm.nih.gov/pubmed/37922370
249. Lonati, C., *et al.* Survival Outcomes After Immediate Radical Cystectomy Versus Conservative Management with Bacillus Calmette-Guerin Among T1 High-grade Micropapillary Bladder Cancer Patients: Results from a Multicentre Collaboration. Eur Urol Focus, 2022. 8: 1270. https://www.ncbi.nlm.nih.gov/pubmed/34419381
250. McFadden, J., *et al.* Impact of variant histology on upstaging and survival in patients with nonmuscle invasive bladder cancer undergoing radical cystectomy. Urol Oncol, 2024. 42: 69 e11. https://www.ncbi.nlm.nih.gov/pubmed/38267301
251. Lobo, N., *et al.* Updated European Association of Urology (EAU) Prognostic Factor Risk Groups Overestimate the Risk of Progression in Patients with Non-muscle-invasive Bladder Cancer Treated with Bacillus Calmette-Guerin. Eur Urol Oncol, 2022. 5: 84. https://www.ncbi.nlm.nih.gov/pubmed/34920986
252. Tan, W.S., *et al.* Intermediate-risk Non-muscle-invasive Bladder Cancer: Updated Consensus Definition and Management Recommendations from the International Bladder Cancer Group. Eur Urol Oncol, 2022. 5: 505. https://www.ncbi.nlm.nih.gov/pubmed/35718695
253. Soria, F., *et al.* Clinical Validation of the Intermediate-risk Non-muscle-invasive Bladder Cancer Scoring System and Substratification Model Proposed by the International Bladder Cancer Group: A Multicenter Young Academic Urologists Urothelial Working Group Collaboration. Eur Urol Oncol, 2024. https://www.ncbi.nlm.nih.gov/pubmed/38906794
254. Lammers, R.J., *et al.* Smoking status is a risk factor for recurrence after transurethral resection of non-muscle-invasive bladder cancer. Eur Urol, 2011. 60: 713. https://www.ncbi.nlm.nih.gov/pubmed/21794974
255. Rink, M., *et al.* Smoking reduces the efficacy of intravesical bacillus Calmette-Guerin immunotherapy in non-muscle-invasive bladder cancer. Eur Urol, 2012. 62: 1204. https://www.ncbi.nlm.nih.gov/pubmed/22980442
256. Slusarczyk, A., *et al.* The impact of smoking on recurrence and progression of non-muscle invasive bladder cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol, 2023. 149: 2673. https://www.ncbi.nlm.nih.gov/pubmed/36404390
257. Ho, C.-H., *et al.* Association between Smoking and Overall and Specific Mortality in Patients with Bladder Cancer: A Population-based Study. Bladder Cancer, 2022. 8: 129. http://www.iospress.nl/journal/bladder-cancer/ http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed23&NEWS=N&AN=638216135
258. Rink, M., *et al.* Impact of smoking on outcomes of patients with a history of recurrent nonmuscle invasive bladder cancer. J Urol, 2012. 188: 2120. https://www.ncbi.nlm.nih.gov/pubmed/23083868
259. Crivelli, J.J., *et al.* Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. Eur Urol, 2014. 65: 742. https://www.ncbi.nlm.nih.gov/pubmed/23810104
260. Muller, J., *et al.* Trends in the risk of second primary cancer among bladder cancer survivors: a population-based cohort of 10 047 patients. BJU Int, 2016. 118: 53. https://www.ncbi.nlm.nih.gov/pubmed/26469096

261. Xu, Y., *et al.* Comparing the treatment outcomes of potassium-titanyl-phosphate laser vaporization and transurethral electroresection for primary nonmuscle-invasive bladder cancer: A prospective, randomized study. Lasers Surg Med, 2015. 47: 306.
https://www.ncbi.nlm.nih.gov/pubmed/25864416
262. Planelles Gomez, J., *et al.* Holmium YAG Photocoagulation: Safe and Economical Alternative to Transurethral Resection in Small Nonmuscle-Invasive Bladder Tumors. J Endourol, 2017. 31: 674.
https://www.ncbi.nlm.nih.gov/pubmed/28462594
263. Pedersen, G.L., *et al.* Outpatient Photodynamic Diagnosis-guided Laser Destruction of Bladder Tumors Is as Good as Conventional Inpatient Photodynamic Diagnosis-guided Transurethral Tumor Resection in Patients with Recurrent Intermediate-risk Low-grade Ta Bladder Tumors. A Prospective Randomized Noninferiority Clinical Trial. Eur Urol, 2023. 83: 125.
https://www.ncbi.nlm.nih.gov/pubmed/36058804
264. Holmang, S., *et al.* Recurrence and progression in low grade papillary urothelial tumors. J Urol, 1999. 162: 702.
https://www.ncbi.nlm.nih.gov/pubmed/10458347
265. Holmang, S., *et al.* Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. J Urol, 2002. 167: 1634.
https://www.ncbi.nlm.nih.gov/pubmed/11912378
266. Mariappan, P., *et al.* Pattern of recurrence changes in noninvasive bladder tumors observed during 2 decades. J Urol, 2007. 177: 867.
https://www.ncbi.nlm.nih.gov/pubmed/17296362
267. Holmang, S., *et al.* Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol, 2001. 165: 1124.
https://www.ncbi.nlm.nih.gov/pubmed/11257652
268. Mariappan, P., *et al.* A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on a 25-year prospective database. J Urol, 2005. 173: 1108.
https://www.ncbi.nlm.nih.gov/pubmed/15758711
269. Millan-Rodriguez, F. Millan-Rodriguez F, *et al.* Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol. 2000. 164: 680.
https://pubmed.ncbi.nlm.nih.gov/10954628/
270. Soloway, M.S., *et al.* Expectant management of small, recurrent, noninvasive papillary bladder tumors. J Urol, 2003. 170: 438.
https://www.ncbi.nlm.nih.gov/pubmed/12853794
271. Miyake, M., *et al.* Active surveillance for nonmuscle invasive bladder cancer. Investig Clin Urol, 2016. 57 Suppl 1: S4.
https://www.ncbi.nlm.nih.gov/pubmed/27326406
272. Marcq, G., *et al.* Active surveillance for non-muscle invasive bladder cancer. Transl Androl Urol, 2019. 8: 54.
https://www.ncbi.nlm.nih.gov/pubmed/30976569
273. Contieri, R., *et al.* Long-term Follow-up and Factors Associated with Active Surveillance Failure for Patients with Non-muscle-invasive Bladder Cancer: The Bladder Cancer Italian Active Surveillance (BIAS) Experience. Eur Urol Oncol, 2022. 5: 251.
https://www.ncbi.nlm.nih.gov/pubmed/34059485
274. Hurle, R., *et al.* Active surveillance for low-risk non-muscle-invasive bladder cancer: mid-term results from the Bladder cancer Italian Active Surveillance (BIAS) project. BJU Int, 2016. 118: 935.
https://www.ncbi.nlm.nih.gov/pubmed/27207387
275. Tan, W.S., *et al.* International Bladder Cancer Group Intermediate-risk Nonmuscle-invasive Bladder Cancer Scoring System Predicts Outcomes of Patients on Active Surveillance. J Urol, 2023. 210: 763.
https://www.ncbi.nlm.nih.gov/pubmed/37535836
276. Li, M., *et al.* Continuous bladder irrigation after transurethral resection of non-muscle invasive bladder cancer for prevention of tumour recurrence: a systematic review. ANZ J Surg, 2021. 91: 2592.
https://www.ncbi.nlm.nih.gov/pubmed/33890701
277. Mahran, A., *et al.* Bladder irrigation after transurethral resection of superficial bladder cancer: a systematic review of the literature. Can J Urol, 2018. 25: 9579.
https://www.ncbi.nlm.nih.gov/pubmed/30553282

278. Zhou, Z., *et al.* Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors. World J Urol, 2019. 37: 1075.
https://www.ncbi.nlm.nih.gov/pubmed/30612154
279. Soloway, M.S., *et al.* Urothelial susceptibility to tumor cell implantation: influence of cauterization. Cancer, 1980. 46: 1158.
https://www.ncbi.nlm.nih.gov/pubmed/7214299
280. Pan, J.S., *et al.* Inhibition of implantation of murine bladder tumor by thiotepa in cauterized bladder. J Urol, 1989. 142: 1589.
https://www.ncbi.nlm.nih.gov/pubmed/2511340
281. Brocks, C.P., *et al.* Inhibition of tumor implantation by intravesical gemcitabine in a murine model of superficial bladder cancer. J Urol, 2005. 174: 1115.
https://www.ncbi.nlm.nih.gov/pubmed/16094076
282. Oosterlinck, W., *et al.* A prospective European Organization for Research and Treatment of Cancer Genitourinary Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. J Urol, 1993. 149: 749.
https://www.ncbi.nlm.nih.gov/pubmed/8455236
283. Sylvester, R.J., *et al.* Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? Eur Urol, 2016. 69: 231.
https://www.ncbi.nlm.nih.gov/pubmed/26091833
284. Sylvester, R.J., *et al.* A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol, 2004. 171: 2186.
https://www.ncbi.nlm.nih.gov/pubmed/15126782
285. Abern, M.R., *et al.* Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. J Natl Compr Canc Netw, 2013. 11: 477.
https://www.ncbi.nlm.nih.gov/pubmed/23584348
286. Perlis, N., *et al.* Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. Eur Urol, 2013. 64: 421.
https://www.ncbi.nlm.nih.gov/pubmed/23830475
287. Messing, E.M., *et al.* Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non-Muscle-Invasive Bladder Cancer on Tumor Recurrence: SWOG S0337 Randomized Clinical Trial. JAMA, 2018. 319: 1880.
https://www.ncbi.nlm.nih.gov/pubmed/29801011
288. Bohle, A., *et al.* Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. Eur Urol, 2009. 56: 495.
https://www.ncbi.nlm.nih.gov/pubmed/19560257
289. Pode, D., *et al.* The mechanism of human bladder tumor implantation in an in vitro model. J Urol, 1986. 136: 482.
https://www.ncbi.nlm.nih.gov/pubmed/3525861
290. Bohle, A., *et al.* Inhibition of bladder carcinoma cell adhesion by oligopeptide combinations in vitro and *in vivo*. J Urol, 2002. 167: 357.
https://www.ncbi.nlm.nih.gov/pubmed/11743356
291. Gofrit, O.N., *et al.* The natural history of bladder carcinoma *in situ* after initial response to bacillus Calmette-Guerin immunotherapy. Urol Oncol, 2009. 27: 258.
https://www.ncbi.nlm.nih.gov/pubmed/18440839
292. Karsh, L., *et al.* Double-Blind, Randomized, Placebo-controlled Studies Evaluating Apaziquone (E09, Qapzola) Intravesical Instillation Post Transurethral Resection of Bladder Tumors for the Treatment of Low-risk Non-Muscle Invasive Bladder Cancer. Bladder Cancer, 2018. 4: 293.
https://www.ncbi.nlm.nih.gov/pubmed/30112440
293. Oddens, J.R., *et al.* One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? Eur Urol, 2004. 46: 336.
https://www.ncbi.nlm.nih.gov/pubmed/15306104

294. Elmamoun, M.H., *et al.* Destruction of the bladder by single dose Mitomycin C for low-stage transitional cell carcinoma (TCC)--avoidance, recognition, management and consent. BJU Int, 2014. 113: E34.
https://www.ncbi.nlm.nih.gov/pubmed/24053461
295. Dunsmore, J., *et al.* What influences adherence to guidance for postoperative instillation of intravesical chemotherapy to patients with bladder cancer? BJU Int, 2021. 128: 225.
https://www.ncbi.nlm.nih.gov/pubmed/33450116
296. Tolley, D.A., *et al.* The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. J Urol, 1996. 155: 1233.
https://www.ncbi.nlm.nih.gov/pubmed/8632538
297. Huncharek, M., *et al.* Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res, 2001. 21: 765.
https://www.ncbi.nlm.nih.gov/pubmed/11299841
298. Bohle, A., *et al.* Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology, 2004. 63: 682.
https://www.ncbi.nlm.nih.gov/pubmed/15072879
299. Sylvester, R.J., *et al.* Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol, 2002. 168: 1964.
https://www.ncbi.nlm.nih.gov/pubmed/12394686
300. Malmstrom, P.U., *et al.* An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol, 2009. 56: 247.
https://www.ncbi.nlm.nih.gov/pubmed/19409692
301. Sylvester, R.J., *et al.* Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol, 2010. 57: 766.
https://www.ncbi.nlm.nih.gov/pubmed/20034729
302. Shang, P.F., *et al.* Intravesical Bacillus Calmette-Guerin versus epirubicin for Ta and T1 bladder cancer. Cochrane Database Syst Rev, 2011: CD006885.
https://www.ncbi.nlm.nih.gov/pubmed/21563157
303. Bosschieter, J., *et al.* Value of an Immediate Intravesical Instillation of Mitomycin C in Patients with Non-muscle-invasive Bladder Cancer: A Prospective Multicentre Randomised Study in 2243 patients. Eur Urol, 2018. 73: 226.
https://www.ncbi.nlm.nih.gov/pubmed/28705539
304. Bouffioux, C., *et al.* Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol, 1995. 153: 934.
https://www.ncbi.nlm.nih.gov/pubmed/7853578
305. Kaasinen, E., *et al.* Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol, 2002. 42: 167.
https://www.ncbi.nlm.nih.gov/pubmed/12160589
306. Sylvester, R.J., *et al.* The schedule and duration of intravesical chemotherapy in patients with non-muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. Eur Urol, 2008. 53: 709.
https://www.ncbi.nlm.nih.gov/pubmed/18207317
307. Bosschieter, J., *et al.* An immediate, single intravesical instillation of mitomycin C is of benefit in patients with non-muscle-invasive bladder cancer irrespective of prognostic risk groups. Urol Oncol, 2018. 36: 400 e7.
https://www.ncbi.nlm.nih.gov/pubmed/30064935
308. Elsawy, A.A., *et al.* The value of immediate postoperative intravesical epirubicin instillation as an adjunct to standard adjuvant treatment in intermediate and high-risk non-muscle-invasive bladder cancer: A preliminary results of randomized controlled trial. Urol Oncol, 2019. 37: 179 e9.
https://www.ncbi.nlm.nih.gov/pubmed/30448030

309. Tabayoyong, W.B., *et al.* Systematic Review on the Utilization of Maintenance Intravesical Chemotherapy in the Management of Non-muscle-invasive Bladder Cancer. Eur Urol Focus, 2018. 4: 512.
https://www.ncbi.nlm.nih.gov/pubmed/30190111
310. Au, J.L., *et al.* Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst, 2001. 93: 597.
https://www.ncbi.nlm.nih.gov/pubmed/11309436
311. Miyata, Y., *et al.* Intravesical mitomycin C (MMC) and MMC + cytosine arabinoside for non-muscle-invasive bladder cancer: a randomised clinical trial. BJU Int, 2022. 129: 534.
https://www.ncbi.nlm.nih.gov/pubmed/34383381
312. Myers, A.L., *et al.* Solubilization and Stability of Mitomycin C Solutions Prepared for Intravesical Administration. Drugs R D, 2017. 17: 297.
https://www.ncbi.nlm.nih.gov/pubmed/28470465
313. Giesbers, A.A., *et al.* Recurrence of superficial bladder carcinoma after intravesical instillation of mitomycin-C. Comparison of exposure times. Br J Urol, 1989. 63: 176.
https://www.ncbi.nlm.nih.gov/pubmed/2495144
314. Kuroda, M., *et al.* Effect of prophylactic treatment with intravesical epirubicin on recurrence of superficial bladder cancer--The 6th Trial of the Japanese Urological Cancer Research Group (JUCRG): a randomized trial of intravesical epirubicin at dose of 20mg/40ml, 30mg/40ml, 40mg/40ml. Eur Urol, 2004. 45: 600.
https://www.ncbi.nlm.nih.gov/pubmed/15082202
315. Zhao, H., *et al.* Intravesical Chemohyperthermia vs. Bacillus Calmette-Guerin Instillation for Intermediate- and High-Risk Non-muscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. Front Surg, 2021. 8: 775527.
https://www.ncbi.nlm.nih.gov/pubmed/34888347
316. Arends, T.J., *et al.* Combined chemohyperthermia: 10-year single center experience in 160 patients with nonmuscle invasive bladder cancer. J Urol, 2014. 192: 708.
https://www.ncbi.nlm.nih.gov/pubmed/24704017
317. Arends, T.J., *et al.* Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guerin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer. Eur Urol, 2016. 69: 1046.
https://www.ncbi.nlm.nih.gov/pubmed/26803476
318. Tan, W.S., *et al.* Adjuvant Intravesical Chemohyperthermia Versus Passive Chemotherapy in Patients with Intermediate-risk Non-muscle-invasive Bladder Cancer (HIVEC-II): A Phase 2, Open-label, Randomised Controlled Trial. Eur Urol, 2023. 83: 497.
https://www.ncbi.nlm.nih.gov/pubmed/35999119
319. Angulo, J.C., *et al.* Hyperthermic Mitomycin C in Intermediate-risk Non-muscle-invasive Bladder Cancer: Results of the HIVEC-1 Trial. Eur Urol Oncol, 2023. 6: 58.
https://www.ncbi.nlm.nih.gov/pubmed/36435738
320. Guerrero-Ramos, F., *et al.* Recirculating hyperthermic intravesical chemotherapy with mitomycin C (HIVEC) versus BCG in high-risk non-muscle-invasive bladder cancer: results of the HIVEC-HR randomized clinical trial. World J Urol, 2022. 40: 999.
https://www.ncbi.nlm.nih.gov/pubmed/35037963
321. Di Stasi, S.M., *et al.* Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. Lancet Oncol, 2006. 7: 43.
https://www.ncbi.nlm.nih.gov/pubmed/16389183
322. Shelley, M.D., *et al.* A systematic review of intravesical bacillus Calmette-Guerin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int, 2001. 88: 209.
https://www.ncbi.nlm.nih.gov/pubmed/11488731
323. Han, R.F., *et al.* Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urology, 2006. 67: 1216.
https://www.ncbi.nlm.nih.gov/pubmed/16765182
324. Shelley, M.D., *et al.* Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int, 2004. 93: 485.
https://www.ncbi.nlm.nih.gov/pubmed/15008714

325. Bohle, A., *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol, 2003. 169: 90.
https://www.ncbi.nlm.nih.gov/pubmed/12478111
326. Duchek, M., *et al.* Bacillus Calmette-Guerin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. Eur Urol, 2010. 57: 25.
https://www.ncbi.nlm.nih.gov/pubmed/19819617
327. Jarvinen, R., *et al.* Long-term efficacy of maintenance bacillus Calmette-Guerin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma *in situ*: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. Eur Urol, 2009. 56: 260.
https://www.ncbi.nlm.nih.gov/pubmed/19395154
328. Schmidt, S., *et al.* Intravesical Bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev, 2020. 1: CD011935.
https://www.ncbi.nlm.nih.gov/pubmed/31912907
329. Huncharek, M., *et al.* The influence of intravesical therapy on progression of superficial transitional cell carcinoma of the bladder: a metaanalytic comparison of chemotherapy versus bacilli Calmette-Guerin immunotherapy. Am J Clin Oncol, 2004. 27: 522.
https://www.ncbi.nlm.nih.gov/pubmed/15596924
330. Oddens, J.R., *et al.* The effect of age on the efficacy of maintenance bacillus Calmette-Guerin relative to maintenance epirubicin in patients with stage Ta T1 urothelial bladder cancer: results from EORTC genito-urinary group study 30911. Eur Urol, 2014. 66: 694.
https://www.ncbi.nlm.nih.gov/pubmed/24948466
331. Miyake, M., *et al.* Outcomes of subsequent non-muscle-invasive bladder cancer treated with intravesical Bacillus Calmette-Guerin after radical nephroureterectomy for upper urinary tract urothelial carcinoma. BJU Int, 2018. 121: 764.
https://www.ncbi.nlm.nih.gov/pubmed/29281857
332. Rentsch, C.A., *et al.* Bacillus Calmette-Guerin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. Eur Urol, 2014. 66: 677.
https://www.ncbi.nlm.nih.gov/pubmed/24674149
333. Sengiku, A., *et al.* A prospective comparative study of intravesical bacillus Calmette-Guerin therapy with the Tokyo or Connaught strain for nonmuscle invasive bladder cancer. J Urol, 2013. 190: 50.
https://www.ncbi.nlm.nih.gov/pubmed/23376145
334. Boehm, B.E., *et al.* Efficacy of bacillus Calmette-Guerin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis. J Urol, 2017. 198: 503.
https://www.ncbi.nlm.nih.gov/pubmed/28286068
335. Unda-Urzaiz, M., *et al.* Safety and efficacy of various strains of bacille Calmette-Guerin in the treatment of bladder tumours in standard clinical practice. Actas Urol Esp (Engl Ed), 2018. 42: 238.
https://www.ncbi.nlm.nih.gov/pubmed/29295749
336. Steinberg, R.L., *et al.* Bacillus Calmette-Guerin strain may not effect recurrence-free survival when used intravesically with interferon-alpha2b for non-muscle-invasive bladder cancer. Urol Oncol, 2017. 35: 201.
https://www.ncbi.nlm.nih.gov/pubmed/28041998
337. van der Meijden, A.P., *et al.* Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. Eur Urol, 2003. 44: 429.
https://www.ncbi.nlm.nih.gov/pubmed/14499676
338. Larsen, E.S., *et al.* The epidemiology of bacille Calmette-Guerin infections after bladder instillation from 2002 through 2017: a nationwide retrospective cohort study. BJU Int, 2019. 124: 910.
https://www.ncbi.nlm.nih.gov/pubmed/31054198
339. Holmberg, L., *et al.* Cumulative incidence of and risk factors for BCG infection after adjuvant BCG instillations. BJU Int, 2024. 134: 229.
https://www.ncbi.nlm.nih.gov/pubmed/38403809
340. Brausi, M., *et al.* Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol, 2014. 65: 69.
https://www.ncbi.nlm.nih.gov/pubmed/23910233

341. Oddens, J.R., *et al.* Increasing age is not associated with toxicity leading to discontinuation of treatment in patients with urothelial non-muscle-invasive bladder cancer randomised to receive 3 years of maintenance bacille Calmette-Guerin: results from European Organisation for Research and Treatment of Cancer Genito-Urinary Group study 30911. BJU Int, 2016. 118: 423. https://www.ncbi.nlm.nih.gov/pubmed/26945890
342. Danielsson, G., *et al.* Bladder health in patients treated with BCG instillations for T1G2-G3 bladder cancer - a follow-up five years after the start of treatment. Scand J Urol, 2018. 52: 377. https://www.ncbi.nlm.nih.gov/pubmed/30616479
343. Herr, H.W. Intravesical bacillus Calmette-Guerin outcomes in patients with bladder cancer and asymptomatic bacteriuria. J Urol, 2012. 187: 435. https://www.ncbi.nlm.nih.gov/pubmed/22177154
344. Colombel, M., *et al.* The effect of ofloxacin on bacillus calmette-guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. J Urol, 2006. 176: 935. https://www.ncbi.nlm.nih.gov/pubmed/16890660
345. Damiano, R., *et al.* Short-term administration of prulifloxacin in patients with nonmuscle-invasive bladder cancer: an effective option for the prevention of bacillus Calmette-Guerin-induced toxicity? BJU Int, 2009. 104: 633. https://www.ncbi.nlm.nih.gov/pubmed/19298412
346. Numakura, K., *et al.* Effect of Levofloxacin on the Efficacy and Adverse Events in Intravesical Bacillus Calmette-Guerin Treatment for Bladder Cancer: Results of a Randomized, Prospective, Multicenter Study. Eur Urol Focus, 2022. 8: 1666. https://www.ncbi.nlm.nih.gov/pubmed/35717522
347. Lamm, D.L., *et al.* Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol, 1992. 147: 596. https://www.ncbi.nlm.nih.gov/pubmed/1538436
348. Palou, J., *et al.* Intravesical bacillus Calmette-Guerin for the treatment of superficial bladder cancer in renal transplant patients. Transplantation, 2003. 76: 1514. https://www.ncbi.nlm.nih.gov/pubmed/14657696
349. Yossepowitch, O., *et al.* Safety and efficacy of intravesical bacillus Calmette-Guerin instillations in steroid treated and immunocompromised patients. J Urol, 2006. 176: 482. https://www.ncbi.nlm.nih.gov/pubmed/16813873
350. Roumeguere, T., *et al.* Bacillus Calmette-Guerin therapy in non-muscle-invasive bladder carcinoma after renal transplantation for end-stage aristolochic acid nephropathy. Transpl Int, 2015. 28: 199. https://www.ncbi.nlm.nih.gov/pubmed/25377421
351. Jue, J.S., *et al.* Risk factors, management, and survival of bladder cancer after kidney transplantation. Actas Urol Esp (Engl Ed), 2021. 45: 427. https://www.ncbi.nlm.nih.gov/pubmed/34147429
352. Rodriguez, F., *et al.* [Practical guideline for the management of adverse events associated with BCG installations]. Arch Esp Urol, 2008. 61: 591. https://www.ncbi.nlm.nih.gov/pubmed/18709813
353. Witjes JA, P.J., Soloway M, *et al.* . Clinical practice recommendations for the prevention and management of intravesical therapy-associated adverse events. Eur Urol Suppl, 2008. 7: 667. http://www.europeanurology.com/article/S1569-9056(08)00110-3/abstract
354. Palou, J., *et al.* Intravesical treatment of severe bacillus Calmette-Guerin cystitis. Int Urol Nephrol, 2001. 33: 485. https://www.ncbi.nlm.nih.gov/pubmed/12230277
355. Falkensammer, C., *et al.* Late occurrence of bilateral tuberculous-like epididymo-orchitis after intravesical bacille Calmette-Guerin therapy for superficial bladder carcinoma. Urology, 2005. 65: 175. https://www.ncbi.nlm.nih.gov/pubmed/15667898
356. Tinazzi, E., *et al.* Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. Rheumatol Int, 2006. 26: 481. https://www.ncbi.nlm.nih.gov/pubmed/16220289
357. European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. 2019. 2022. https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products

358. Bonkat, G., *et al.* EAU Guidelines on Urological Infections 2025. Edn. presented at the 40th EAU Annual Congress Madrid 2025.
https://uroweb.org/guidelines/urological-infections
359. Morales, A., *et al.* Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol, 1976. 116: 180.
https://www.ncbi.nlm.nih.gov/pubmed/820877
360. Lamm, D.L., *et al.* Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma *in situ* transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol, 2000. 163: 1124.
https://www.ncbi.nlm.nih.gov/pubmed/10737480
361. Grimm, M.O., *et al.* Treatment of High-grade Non-muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS". Eur Urol, 2020. 78: 690.
https://www.ncbi.nlm.nih.gov/pubmed/32446864
362. Martinez-Pineiro, L., *et al.* Maintenance Therapy with 3-monthly Bacillus Calmette-Guerin for 3 Years is Not Superior to Standard Induction Therapy in High-risk Non-muscle-invasive Urothelial Bladder Carcinoma: Final Results of Randomised CUETO Study 98013. Eur Urol, 2015. 68: 256.
https://www.ncbi.nlm.nih.gov/pubmed/25794457
363. Oddens, J., *et al.* Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol, 2013. 63: 462.
https://www.ncbi.nlm.nih.gov/pubmed/23141049
364. Martinez-Pineiro, J.A., *et al.* Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guerin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int, 2002. 89: 671.
https://www.ncbi.nlm.nih.gov/pubmed/11966623
365. Martinez-Pineiro, J.A., *et al.* Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol, 2005. 174: 1242.
https://www.ncbi.nlm.nih.gov/pubmed/16145378
366. Ojea, A., *et al.* A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. Eur Urol, 2007. 52: 1398.
https://www.ncbi.nlm.nih.gov/pubmed/17485161
367. Choi, S.Y., *et al.* Low-dose versus standard-dose bacille Calmette-Guerin for non-muscle-invasive bladder cancer: Systematic review and meta-analysis of randomized controlled trials. Investig Clin Urol, 2022. 63: 140.
https://www.ncbi.nlm.nih.gov/pubmed/35244987
368. Solsona, E., *et al.* Sequential combination of mitomycin C plus bacillus Calmette-Guerin (BCG) is more effective but more toxic than BCG alone in patients with non-muscle-invasive bladder cancer in intermediate- and high-risk patients: final outcome of CUETO 93009, a randomized prospective trial. Eur Urol, 2015. 67: 508.
https://www.ncbi.nlm.nih.gov/pubmed/25301758
369. Cui, J., *et al.* Combination of Intravesical Chemotherapy and Bacillus Calmette-Guerin Versus Bacillus Calmette-Guerin Monotherapy in Intermediate- and High-risk Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-analysis. Medicine (Baltimore), 2016. 95: e2572.
https://www.ncbi.nlm.nih.gov/pubmed/26817914
370. Huang, D., *et al.* Combination of Intravesical Bacille Calmette-Guerin and Chemotherapy vs. Bacille Calmette-Guerin Alone in Non-muscle Invasive Bladder Cancer: A Meta-Analysis. Front Oncol, 2019. 9: 121.
https://www.ncbi.nlm.nih.gov/pubmed/30881921
371. Shepherd, A.R., *et al.* Intravesical Bacillus Calmette-Guerin with interferon-alpha versus intravesical Bacillus Calmette-Guerin for treating non-muscle-invasive bladder cancer. Cochrane Database Syst Rev, 2017. 3: CD012112.
https://www.ncbi.nlm.nih.gov/pubmed/28268259

372. Jarvinen, R., *et al.* Long-term outcome of patients with frequently recurrent non-muscle-invasive bladder carcinoma treated with one perioperative plus four weekly instillations of mitomycin C followed by monthly bacillus Calmette-Guerin (BCG) or alternating BCG and interferon-alpha2b instillations: prospective randomised FinnBladder-4 study. Eur Urol, 2015. 68: 611.
https://www.ncbi.nlm.nih.gov/pubmed/25748117
373. Marttila, T., *et al.* Intravesical Bacillus Calmette-Guerin Versus Combination of Epirubicin and Interferon-alpha2a in Reducing Recurrence of Non-Muscle-invasive Bladder Carcinoma: FinnBladder-6 Study. Eur Urol, 2016. 70: 341.
https://www.ncbi.nlm.nih.gov/pubmed/27085624
374. Delto, J., *et al.* Preclinical analyses of intravesical chemotherapy for prevention of bladder cancer. Oncotarget, 2013. 4: 269
https://pubmed.ncbi.nlm.nih.gov/23563166/
375. Steinberg, R.L., *et al.* Sequential Intravesical Gemcitabine and Docetaxel for the Salvage Treatment of Non-Muscle Invasive Bladder Cancer. Bladder Cancer, 2015. 1: 65.
https://www.ncbi.nlm.nih.gov/pubmed/30561441
376. McElree, I.M., *et al.* Sequential Intravesical Valrubicin and Docetaxel for the Salvage Treatment of Non-Muscle-Invasive Bladder Cancer. J Urol, 2022. 208: 969.
https://www.ncbi.nlm.nih.gov/pubmed/35830552
377. Steinberg, R.L., *et al.* Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer. J Urol, 2020. 203: 902.
https://www.ncbi.nlm.nih.gov/pubmed/31821066
378. Steinberg, R.L., *et al.* Intravesical sequential gemcitabine and docetaxel versus bacillus calmette-guerin (BCG) plus interferon in patients with recurrent non-muscle invasive bladder cancer following a single induction course of BCG. Urol Oncol, 2022. 40: 9 e1.
https://www.ncbi.nlm.nih.gov/pubmed/34092482
379. McElree, I.M., *et al.* Sequential Intravesical Gemcitabine and Docetaxel for bacillus Calmette-Guerin-Naive High-Risk Nonmuscle-Invasive Bladder Cancer. J Urol, 2022. 208: 589.
https://www.ncbi.nlm.nih.gov/pubmed/35892270
380. Jakse, G., *et al.* Intravesical BCG in patients with carcinoma *in situ* of the urinary bladder: long-term results of EORTC GU Group phase II protocol 30861. Eur Urol, 2001. 40: 144.
https://www.ncbi.nlm.nih.gov/pubmed/11528191
381. Sylvester, R.J., *et al.* Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma *in situ* of the bladder: a meta-analysis of the published results of randomized clinical trials. J Urol, 2005. 174: 86.
https://www.ncbi.nlm.nih.gov/pubmed/15947584
382. Kaasinen, E., *et al.* Seventeen-year follow-up of the prospective randomized Nordic CIS study: BCG monotherapy versus alternating therapy with mitomycin C and BCG in patients with carcinoma *in situ* of the urinary bladder. Scand J Urol, 2016. 50: 360.
https://www.ncbi.nlm.nih.gov/pubmed/27603424
383. Solsona, E., *et al.* Extravesical involvement in patients with bladder carcinoma *in situ*: biological and therapy implications. J Urol, 1996. 155: 895.
https://www.ncbi.nlm.nih.gov/pubmed/8583601
384. Sylvester, R.J., *et al.* High-grade Ta urothelial carcinoma and carcinoma *in situ* of the bladder. Urology, 2005. 66: 90.
https://www.ncbi.nlm.nih.gov/pubmed/16399418
385. Palou, J., *et al.* Urothelial carcinoma of the prostate. Urology, 2007. 69: 50.
https://www.ncbi.nlm.nih.gov/pubmed/17280908
386. Palou Redorta, J., *et al.* Intravesical instillations with bacillus calmette-guerin for the treatment of carcinoma *in situ* involving prostatic ducts. Eur Urol, 2006. 49: 834.
https://www.ncbi.nlm.nih.gov/pubmed/16426729
387. Di Stasi, S.M., *et al.* Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial. Lancet Oncol, 2011. 12: 871.
https://www.ncbi.nlm.nih.gov/pubmed/21831711
388. Carrion, D.M., *et al.* The benefit of a neoadjuvant instillation of chemotherapy in non-muscle invasive bladder cancer: Interim analysis of the PRECAVE randomized clinical trial. Arch Esp Urol, 2021. 74: 883.
https://www.ncbi.nlm.nih.gov/pubmed/34726625

389. Lee, H.W., *et al.* Clinical Efficacy of Neoadjuvant Intravesical Mitomycin-C Therapy Immediately Before Transurethral Resection of Bladder Tumor in Patients With Nonmuscle-invasive Bladder Cancer: Preliminary Results of a Prospective, Randomized Phase II Study. J Urol, 2023. 209: 131. https://www.ncbi.nlm.nih.gov/pubmed/36250938
390. Popert, R.J., *et al.* Superficial bladder cancer: the response of a marker tumour to a single intravesical instillation of epirubicin. Br J Urol, 1994. 74: 195. https://www.ncbi.nlm.nih.gov/pubmed/7921938
391. Mostafid, A.H., *et al.* CALIBER: a phase II randomized feasibility trial of chemoablation with mitomycin-C vs surgical management in low-risk non-muscle-invasive bladder cancer. BJU Int, 2020. 125: 817. https://www.ncbi.nlm.nih.gov/pubmed/32124514
392. Lindgren, M.S., *et al.* DaBlaCa-13 Study: Oncological Outcome of Short-Term, Intensive Chemoresection With Mitomycin in Nonmuscle Invasive Bladder Cancer: Primary Outcome of a Randomized Controlled Trial. J Clin Oncol, 2023. 41: 206. https://www.ncbi.nlm.nih.gov/pubmed/36223555
393. Prasad, S.M., *et al.* Treatment of Low-grade Intermediate-risk Nonmuscle-invasive Bladder Cancer With UGN-102 +/- Transurethral Resection of Bladder Tumor Compared to Transurethral Resection of Bladder Tumor Monotherapy: A Randomized, Controlled, Phase 3 Trial (ATLAS). J Urol, 2023. 210: 619. https://www.ncbi.nlm.nih.gov/pubmed/37548555
394. Prasad, S.M., *et al.* Primary Chemoablation of Recurrent Low-Grade Intermediate-Risk Nonmuscle-Invasive Bladder Cancer With UGN-102: A Single-Arm, Open-Label, Phase 3 Trial (ENVISION). J Urol, 2024: 101097JU0000000000004296. https://www.ncbi.nlm.nih.gov/pubmed/39446087
395. Yanagisawa, T., *et al.* A Systematic Review and Meta-analysis of Chemoablation for Non-muscle-invasive Bladder Cancer. Eur Urol Focus, 2023. 9: 463. https://www.ncbi.nlm.nih.gov/pubmed/36517409
396. Fritsche, H.M., *et al.* Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. Eur Urol, 2010. 57: 300. https://www.ncbi.nlm.nih.gov/pubmed/19766384
397. Turker, P., *et al.* Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome. BJU Int, 2012. 110: 804. https://www.ncbi.nlm.nih.gov/pubmed/22321341
398. May, M., *et al.* Pathological upstaging detected in radical cystectomy procedures is associated with a significantly worse tumour-specific survival rate for patients with clinical T1 urothelial carcinoma of the urinary bladder. Scand J Urol Nephrol, 2011. 45: 251. https://www.ncbi.nlm.nih.gov/pubmed/21388337
399. Svatek, R.S., *et al.* Discrepancy between clinical and pathological stage: external validation of the impact on prognosis in an international radical cystectomy cohort. BJU Int, 2011. 107: 898. https://www.ncbi.nlm.nih.gov/pubmed/21244604
400. Shariat, S.F., *et al.* Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. Eur Urol, 2007. 51: 137. https://www.ncbi.nlm.nih.gov/pubmed/16793197
401. Moschini, M., *et al.* Comparing long-term outcomes of primary and progressive carcinoma invading bladder muscle after radical cystectomy. BJU Int, 2016. 117: 604. https://www.ncbi.nlm.nih.gov/pubmed/25851271
402. Schrier, B.P., *et al.* Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. Eur Urol, 2004. 45: 292. https://www.ncbi.nlm.nih.gov/pubmed/15036673
403. Kamat, A.M., *et al.* The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. J Urol, 2006. 175: 881. https://www.ncbi.nlm.nih.gov/pubmed/16469571
404. Raj, G.V., *et al.* Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. J Urol, 2007. 177: 1283. https://www.ncbi.nlm.nih.gov/pubmed/17382713
405. Stein, J.P., *et al.* Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol, 2001. 19: 666. https://www.ncbi.nlm.nih.gov/pubmed/11157016

406. Hautmann, R.E., *et al.* Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol, 2012. 61: 1039. https://www.ncbi.nlm.nih.gov/pubmed/22381169
407. Shariat, S.F., *et al.* Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol, 2006. 176: 2414. https://www.ncbi.nlm.nih.gov/pubmed/17085118
408. Scilipoti, P., *et al.* The Role of Mitomycin C in Intermediate-risk Non-muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis. Eur Urol Oncol, 2024. https://www.ncbi.nlm.nih.gov/pubmed/38902138
409. Kurpad, R., *et al.* A multidisciplinary approach to the management of urologic malignancies: does it influence diagnostic and treatment decisions? Urol Oncol, 2011. 29: 378. https://www.ncbi.nlm.nih.gov/pubmed/19576797
410. Wayment, R.O., *et al.* Second opinion pathology in tertiary care of patients with urologic malignancies. Urol Oncol, 2011. 29: 194. https://www.ncbi.nlm.nih.gov/pubmed/19523859
411. Traboulsi, S.L., *et al.* Pathology review impacts clinical management of patients with T1-T2 bladder cancer. Can Urol Assoc J, 2017. 11: 188. https://www.ncbi.nlm.nih.gov/pubmed/28652877
412. Luchey, A.M., *et al.* Change in Management Based on Pathologic Second Opinion Among Bladder Cancer Patients Presenting to a Comprehensive Cancer Center: Implications for Clinical Practice. Urology, 2016. 93: 130. https://www.ncbi.nlm.nih.gov/pubmed/27041469
413. Herr, H.W., *et al.* BCG-refractory vs. BCG-relapsing non-muscle-invasive bladder cancer: a prospective cohort outcomes study. Urol Oncol, 2015. 33: 108 e1. https://www.ncbi.nlm.nih.gov/pubmed/25813144
414. Lerner, S.P., *et al.* Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non-muscle invasive bladder cancer. Urol Oncol, 2009. 27: 155. https://www.ncbi.nlm.nih.gov/pubmed/18367117
415. Kamat, A.M., *et al.* Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. J Clin Oncol, 2016. 34: 1935. https://www.ncbi.nlm.nih.gov/pubmed/26811532
416. U.S. Department of Health and Human Services Food and Drug Administration. BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER), 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM529600.pdf
417. Roumiguie, M., *et al.* International Bladder Cancer Group Consensus Statement on Clinical Trial Design for Patients with Bacillus Calmette-Guerin-exposed High-risk Non-muscle-invasive Bladder Cancer. Eur Urol, 2022. 82: 34. https://www.ncbi.nlm.nih.gov/pubmed/34955291
418. Gallagher, B.L., *et al.* Impact of previous bacille Calmette-Guerin failure pattern on subsequent response to bacille Calmette-Guerin plus interferon intravesical therapy. Urology, 2008. 71: 297. https://www.ncbi.nlm.nih.gov/pubmed/18308107
419. Herr, H.W., *et al.* Defining bacillus Calmette-Guerin refractory superficial bladder tumors. J Urol, 2003. 169: 1706. https://www.ncbi.nlm.nih.gov/pubmed/12686813
420. van den Bosch, S., *et al.* Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. Eur Urol, 2011. 60: 493. https://www.ncbi.nlm.nih.gov/pubmed/21664041
421. Cockerill, P.A., *et al.* Intravesical gemcitabine in combination with mitomycin C as salvage treatment in recurrent non-muscle-invasive bladder cancer. BJU Int, 2016. 117: 456. https://www.ncbi.nlm.nih.gov/pubmed/25682834
422. Barlow, L., *et al.* A single-institution experience with induction and maintenance intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to bacille Calmette-Guerin therapy. BJU Int, 2009. 104: 1098. https://www.ncbi.nlm.nih.gov/pubmed/19389012

423. Jones, G., *et al.* Intravesical gemcitabine for non-muscle invasive bladder cancer. Cochrane Database Syst Rev, 2012. 1: CD009294.
https://www.ncbi.nlm.nih.gov/pubmed/22259002
424. Nativ, O., *et al.* Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guerin. J Urol, 2009. 182: 1313.
https://www.ncbi.nlm.nih.gov/pubmed/19683278
425. Racioppi, M., *et al.* ElectroMotive drug administration (EMDA) of Mitomycin C as first-line salvage therapy in high risk "BCG failure" non muscle invasive bladder cancer: 3 years follow-up outcomes. BMC Cancer, 2018. 18: 1224.
https://www.ncbi.nlm.nih.gov/pubmed/30522445
426. Tan, W.S., *et al.* Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guerin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guerin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial. Eur Urol, 2019. 75: 63.
https://www.ncbi.nlm.nih.gov/pubmed/30274699
427. Morales, A., *et al.* Efficacy and safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression after failed treatment with bacillus Calmette-Guerin. J Urol, 2015. 193: 1135.
https://www.ncbi.nlm.nih.gov/pubmed/25286009
428. Joudi, F.N., *et al.* Final results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. Urol Oncol, 2006. 24: 344.
https://www.ncbi.nlm.nih.gov/pubmed/16818189
429. Wright, K.M. FDA Approves Pembrolizumab for BCG-Unresponsive NMIBC. Oncology (Williston Park), 2020. 34: 44.
https://www.ncbi.nlm.nih.gov/pubmed/32645193
430. Shore, N.D., *et al.* Intravesical rAd-IFNalpha/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin-Refractory or Relapsed Non-Muscle-Invasive Bladder Cancer: A Phase II Randomized Study. J Clin Oncol, 2017. 35: 3410.
https://www.ncbi.nlm.nih.gov/pubmed/28834453
431. Packiam, V.T., *et al.* An open label, single-arm, phase II multicenter study of the safety and efficacy of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non-muscle-invasive bladder cancer: Interim results. Urol Oncol, 2018. 36: 440.
https://www.ncbi.nlm.nih.gov/pubmed/28755959
432. Hassler, M.R., *et al.* Salvage therapeutic strategies for bacillus Calmette-Guerin failure. Curr Opin Urol, 2019. 29: 239.
https://www.ncbi.nlm.nih.gov/pubmed/30762670
433. Black, P.C., *et al.* Phase 2 Trial of Atezolizumab in Bacillus Calmette-Guerin-unresponsive High-risk Non-muscle-invasive Bladder Cancer: SWOG S1605. Eur Urol, 2023. 84: 536.
https://www.ncbi.nlm.nih.gov/pubmed/37596191
434. Kamat, A.M., *et al.* Evidence-based Assessment of Current and Emerging Bladder-sparing Therapies for Non-muscle-invasive Bladder Cancer After Bacillus Calmette-Guerin Therapy: A Systematic Review and Meta-analysis. Eur Urol Oncol, 2020. 3: 318.
https://www.ncbi.nlm.nih.gov/pubmed/32201133
435. Li, R., *et al.* Systematic Review of the Therapeutic Efficacy of Bladder-preserving Treatments for Non-muscle-invasive Bladder Cancer Following Intravesical Bacillus Calmette-Guerin. Eur Urol, 2020. 78: 387.
https://www.ncbi.nlm.nih.gov/pubmed/32143924
436. Balar, A.V., *et al.* Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol, 2021. 22: 919.
https://www.ncbi.nlm.nih.gov/pubmed/34051177
437. Boorjian, S.A., *et al.* Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. Lancet Oncol, 2021. 22: 107.
https://www.ncbi.nlm.nih.gov/pubmed/33253641
438. Mitra, A.P., *et al.* Antiadenovirus Antibodies Predict Response Durability to Nadofaragene Firadenovec Therapy in BCG-unresponsive Non-muscle-invasive Bladder Cancer: Secondary Analysis of a Phase 3 Clinical Trial. Eur Urol, 2022. 81: 223.
https://www.ncbi.nlm.nih.gov/pubmed/34933753

439. Chamie, K., *et al.* IL-15 Superagonist NAI in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer. NEJM Evid, 2023. 2: EVIDoa2200167.
https://www.ncbi.nlm.nih.gov/pubmed/38320011
440. Chamie, K., *et al.* Quality of Life in the Phase 2/3 Trial of N-803 Plus Bacillus Calmette-Guerin in Bacillus Calmette-Guerin–Unresponsive Nonmuscle-Invasive Bladder Cancer. Urol Pract, 2024. 11: 367.
https://www.ncbi.nlm.nih.gov/pubmed/38226931
441. Catto, J.W.F., *et al.* Erdafitinib in BCG-treated high-risk non-muscle-invasive bladder cancer. Ann Oncol, 2024. 35: 98.
https://www.ncbi.nlm.nih.gov/pubmed/37871701
442. Rosevear, H.M., *et al.* Factors affecting response to bacillus Calmette-Guerin plus interferon for urothelial carcinoma *in situ*. J Urol, 2011. 186: 817.
https://www.ncbi.nlm.nih.gov/pubmed/21788050
443. Soukup, V., *et al.* Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. Eur Urol, 2012. 62: 290.
https://www.ncbi.nlm.nih.gov/pubmed/22609313
444. Gofrit, O.N., *et al.* Watchful waiting policy in recurrent Ta G1 bladder tumors. Eur Urol, 2006. 49: 303.
https://www.ncbi.nlm.nih.gov/pubmed/16413659
445. Ma, J., *et al.* Long-term Recurrence Rates of Low-risk Non-muscle-invasive Bladder Cancer-How Long Is Cystoscopic Surveillance Necessary? Eur Urol Focus, 2024. 10: 189.
https://www.ncbi.nlm.nih.gov/pubmed/37442722
446. Shah, C.P., *et al.* The Value of Negative Urinary Dipstick Tests for Haematuria in Patients Undergoing Surveillance for Low-grade Ta Urothelial Cancer: A Two-stage Prospective Clinical Study in 524 Patients. Eur Urol Open Sci, 2024. 60: 24.
https://www.ncbi.nlm.nih.gov/pubmed/38375346
447. Olsen, L.H., *et al.* Prolonging follow-up intervals for non-invasive bladder tumors: a randomized controlled trial. Scand J Urol Nephrol Suppl, 1995. 172: 33.
https://www.ncbi.nlm.nih.gov/pubmed/8578253
448. Mariappan, P., *et al.* The Scottish Bladder Cancer Quality Performance Indicators Influencing Outcomes, Prognosis, and Surveillance (Scot BC Quality OPS) Clinical Project. Eur Urol Focus, 2021. 7: 905.
https://www.ncbi.nlm.nih.gov/pubmed/34419380
449. Holmang, S., *et al.* Should follow-up cystoscopy in bacillus Calmette-Guerin-treated patients continue after five tumour-free years? Eur Urol, 2012. 61: 503.
https://www.ncbi.nlm.nih.gov/pubmed/22119022
450. Subiela, J.D., *et al.* Long-term Recurrence and Progression Patterns in a Contemporary Series of Patients with Carcinoma *In Situ* of the Bladder With or Without Associated Ta/T1 Disease Treated with Bacillus Calmette-Guerin: Implications for Risk-adapted Follow-up. Eur Urol Focus, 2023. 9: 325.
https://www.ncbi.nlm.nih.gov/pubmed/36163105
451. Herr, H.W. Extravesical tumor relapse in patients with superficial bladder tumors. J Clin Oncol, 1998. 16: 1099.
https://www.ncbi.nlm.nih.gov/pubmed/9508196
452. Lotan, Y., *et al.* Prospective evaluation of blue-light flexible cystoscopy with hexaminolevulinate in non-muscle-invasive bladder cancer. BJU Int, 2021. 127: 108.
https://www.ncbi.nlm.nih.gov/pubmed/32648957
453. Chappidi, M.R., *et al.* Utility of Blue Light Cystoscopy for Post-bacillus Calmette-Guerin Bladder Cancer Recurrence Detection: Implications for Clinical Trial Recruitment and Study Comparisons. J Urol, 2022. 207: 534.
https://www.ncbi.nlm.nih.gov/pubmed/34694916
454. Tschirdewahn, S., *et al.* Narrow-band imaging assisted cystoscopy in the follow-up of patients with transitional cell carcinoma of the bladder: a randomized study in comparison with white light cystoscopy. World J Urol, 2020. 38: 1509.
https://www.ncbi.nlm.nih.gov/pubmed/31471739
455. Babjuk, M., *et al.* Urinary cytology and quantitative BTA and UBC tests in surveillance of patients with pTapT1 bladder urothelial carcinoma. Urology, 2008. 71: 718.
https://www.ncbi.nlm.nih.gov/pubmed/18387400
456. Niwa, N., *et al.* Comparison of outcomes between ultrasonography and cystoscopy in the surveillance of patients with initially diagnosed TaG1-2 bladder cancers: A matched-pair analysis. Urol Oncol, 2015. 33: 386 e15.
https://www.ncbi.nlm.nih.gov/pubmed/26027764

457. Farahani, S.J., *et al.* Impact of implementing the first edition of the Paris system for reporting: A systematic review and meta-analysis. Cytopathology, 2024. 35: 616.
https://www.ncbi.nlm.nih.gov/pubmed/38934101
458. van Rhijn, B.W., *et al.* Urine markers for bladder cancer surveillance: a systematic review. Eur Urol, 2005. 47: 736.
https://www.ncbi.nlm.nih.gov/pubmed/15925067
459. Cancel-Tassin, G., *et al.* Assessment of Xpert Bladder Cancer Monitor test performance for the detection of recurrence during non-muscle invasive bladder cancer follow-up. World J Urol, 2021. 39: 3329.
https://www.ncbi.nlm.nih.gov/pubmed/33770241
460. Cowan, B., *et al.* Longitudinal follow-up and performance validation of an mRNA-based urine test (Xpert((R)) Bladder Cancer Monitor) for surveillance in patients with non-muscle-invasive bladder cancer. BJU Int, 2021. 128: 713.
https://www.ncbi.nlm.nih.gov/pubmed/33793062
461. van Osch, F.H.M., *et al.* Patients choose certainty over burden in bladder cancer surveillance. World J Urol, 2019. 37: 2747.
https://www.ncbi.nlm.nih.gov/pubmed/30903352
462. Roupret, M., *et al.* Reducing the Frequency of Follow-up Cystoscopy in Low-grade pTa Non-muscle-invasive Bladder Cancer Using the ADXBLADDER Biomarker. Eur Urol Focus, 2022. 8: 1643.
https://www.ncbi.nlm.nih.gov/pubmed/35300937
463. Fasulo, V., *et al.* Xpert Bladder Cancer Monitor May Avoid Cystoscopies in Patients Under "Active Surveillance" for Recurrent Bladder Cancer (BIAS Project): Longitudinal Cohort Study. Front Oncol, 2022. 12: 832835.
https://www.ncbi.nlm.nih.gov/pubmed/35155263
464. Pierconti, F., *et al.* The bladder epicheck test and cytology in the follow-up of patients with non-muscle-invasive high grade bladder carcinoma. Urol Oncol, 2022. 40: 108 e19.
https://www.ncbi.nlm.nih.gov/pubmed/34903453
465. Kavalieris, L., *et al.* Performance Characteristics of a Multigene Urine Biomarker Test for Monitoring for Recurrent Urothelial Carcinoma in a Multicenter Study. J Urol, 2017. 197: 1419.
https://www.ncbi.nlm.nih.gov/pubmed/27986532
466. Kravchuk, A.P., *et al.* Urine-Based Biomarker Test Uromonitor((R)) in the Detection and Disease Monitoring of Non-Muscle-Invasive Bladder Cancer-A Systematic Review and Meta-Analysis of Diagnostic Test Performance. Cancers (Basel), 2024. 16.
https://www.ncbi.nlm.nih.gov/pubmed/38398144
467. Ward, D.G., *et al.* Highly Sensitive and Specific Detection of Bladder Cancer via Targeted Ultra-deep Sequencing of Urinary DNA. Eur Urol Oncol, 2023. 6: 67.
https://www.ncbi.nlm.nih.gov/pubmed/35410825
468. Nayak, A., *et al.* Quality of life in patients undergoing surveillance for non-muscle invasive bladder cancer-a systematic review. Transl Androl Urol, 2021. 10: 2737.
https://www.ncbi.nlm.nih.gov/pubmed/34295759
469. Public Health England. Living with and beyond bladder cancer - A descriptive summary of responses to a pilot of Patient Reported Outcome Measures for bladder cancer. 2015.
https://www.england.nhs.uk/wp-content/uploads/2015/10/proms-bladder-cancer.pdf
470. Mason, S.J., *et al.* Evaluating patient-reported outcome measures (PROMs) for bladder cancer: a systematic review using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. BJU Int, 2018. 122: 760.
https://www.ncbi.nlm.nih.gov/pubmed/29726085
471. Mariappan, P. Propensity for Quality: No Longer a Tenuous Proposition in Bladder Cancer. Eur Urol, 2020. 78: 60.
https://www.ncbi.nlm.nih.gov/pubmed/32444262
472. Akand, M., *et al.* Quality Control Indicators for Transurethral Resection of Non-Muscle-Invasive Bladder Cancer. Clin Genitourin Cancer, 2019. 17: e784.
https://www.ncbi.nlm.nih.gov/pubmed/31097388
473. Khare, S.R., *et al.* Quality indicators in the management of bladder cancer: A modified Delphi study. Urol Oncol, 2017. 35: 328.
https://www.ncbi.nlm.nih.gov/pubmed/28065393
474. Leow, J.J., *et al.* Quality Indicators for Bladder Cancer Services: A Collaborative Review. Eur Urol, 2020. 78: 43.
https://www.ncbi.nlm.nih.gov/pubmed/31563501

475. NHS National Services Scotland. Bladder Cancer Quality Performance Indicators - Patients diagnosed between April 2014 and March 2017. 2018. https://www.isdscotland.org/Health-Topics/Quality-Indicators/Publications/2018-08-28/2018-08-28-Bladder-QPI-Report.pdf?774782897]
476. Garg, T., *et al.* "Faith and a sunny day": Association of patient frailty with strain experienced by informal caregivers of older adults with non-muscle-invasive bladder cancer. J Geriatr Oncol, 2024. 15: 102060. https://www.ncbi.nlm.nih.gov/pubmed/39244892
477. Fenning, S.J., *et al.* Realistic Medicine: Changing culture and practice in the delivery of health and social care. Patient Educ Couns, 2019. 102: 1751. https://www.ncbi.nlm.nih.gov/pubmed/31301921
478. Contieri, R., *et al.* Oncological Outcomes for Patients with European Association of Urology Very High-risk Non-muscle-Invasive Bladder Cancer Treated with Bacillus Calmette-Guerin or Early Radical Cystectomy. Eur Urol Oncol, 2023. 6: 590. https://www.ncbi.nlm.nih.gov/pubmed/37558542

12. CONFLICT OF INTEREST

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

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

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.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Madrid 2025. ISBN 978-94-92671-29-5.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands.

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

14. COPYRIGHT AND TERMS OF USE