Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1 and CIS)

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and scope

This overview represents the updated European Association of Urology (EAU) guidelines for Non-muscle-invasive Bladder Cancer (NMIBC) Ta, T1 and CIS. The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical guidance on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

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

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring bladder cancer.

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the NMIBC Guidelines. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available, as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents can be accessed through the EAU website Uroweb: http://www.uroweb.org/guidelines/online-guidelines/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The first EAU Guidelines on Bladder Cancer were published in 2000. This 2015 MIBC guidelines document presents a limited update of the 2014 full text document.

*1.4.2 **Summary of changes***

Key changes for this 2015 print:

- The literature for the complete document has been assessed and updated, whenever relevant.
- A new section on resection techniques has been added, also expanding on the significance of biopsy for bladder cancer pathology.
- The sections on the role of imaging for initial diagnosis and follow-up have been updated.
- The sections on stratification of patients into risk groups and high-risk disease have been enlarged.
- A new section on Bacillus Calmette-Guérin (BCG) is included and the section on intravesical BCG and immunotherapy schedule has been expanded in this 2015 version of the NMIBC Guidelines.

Recommendations have been rephrased and added to throughout the current document, not resulting in a change in the grade of recommendation (GR). New recommendations have been included in sections:

*5.14 **Guidelines for TURB and/or biopsies, tumour classification and pathology report***

	GR
Avoid cauterization as much as possible during TURB to avoid tissue deterioration.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC, CIS in the bladder (random biopsies or PDD targeted biopsies) and tumour in prostatic urethra (prostatic urethra biopsy).	C
If indicated, perform a second TURB within 2-6 weeks after initial resection. It should include resection of the primary tumour site.	C
Classification and pathological report	
Do not use the term “Superficial BC”.	A
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

CIS = carcinoma in situ; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

*6.3.1 **Recommendations for stratification of NMIBC***

	GR
In patients treated with BCG, use CUETO risk tables for individual prediction of the risk of tumour recurrence and progression.	B

7.5 Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS

	GR
In patients with intermediate-risk tumours, one immediate instillation of chemotherapy should be followed by 1-year full-dose BCG treatment, or by further instillations of chemotherapy for a maximum of 1 year. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconvenience.	A
Intravesical chemotherapy	
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C

8.1 Guidelines for follow-up in patients after TURB of NMIBC

	GR
Consider R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 months) in patients with CIS.	C

2. METHODS

2.1 Data Identification

For the current update, all articles published in 2014 and 2015 on NMIBC were considered. A systematic literature search for each section of the NMIBC Guidelines was performed by the Panel members. For identification of original and review articles, Medline, Web of Science, and Embase databases were used. These literature searches focused on identification of all level 1 scientific papers (randomized controlled trials [RCTs], systematic reviews [SRs], and meta-analyses of RCTs).

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the 11th most commonly diagnosed cancer in the world [4]. The worldwide age-standardised incidence rate (per 100,000 person-years) is 8.9 for men and 2.2 for women (2008 data) [4]. In the European Union (EU), the age-standardised incidence rate is 27 for men and six for women [4]. In Europe, the highest age-standardised incidence rate has been reported in Spain (41.5 in men and 4.8 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [4].

Worldwide, BC is the 14th leading cause of cancer deaths, age-standardised mortality rate (per 100.000 person-years) was 3.3 for men versus 0.9 for women in 2008 [4]. In the EU, the age-standardised mortality rate was 8 for men and 3 for women, respectively [4].

BC incidence and mortality rates vary across the countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are however partly caused by the different methodology and quality of data collection [5, 6].

The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [6, 7].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). They have a high prevalence due to long-term survival in many cases and lower risk of cancer specific mortality compared to T2-4 tumours [5, 8].

3.2 Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [5, 9-11] (LE: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants processing paint, dye, metal and petroleum products [5, 12-14]. In developed industrial settings, these risks have been reduced by work safety guidelines so that chemical workers no longer have a higher incidence of BC compared to the general population [15].

Genetic predisposition has an influence on the incidence of BC, especially via its impact on susceptibility to other risk factors [5, 16].

Although the significance of the amount of fluid intake is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, while exposure to arsenic in drinking water increases risk [5, 8, 17] (LE: 3). The association between personal hair dye use and risk remains uncertain; an increased risk has been suggested in users of permanent hair dyes with an NAT2 slow acetylation phenotype [18, 19].

Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [5, 8] (LE: 3). Schistosomiasis, a chronic endemic cystitis, based on recurrent infection with a parasitic trematode, is also a cause of BC [5] (LE: 3).

3.3 Pathology

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

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis). These tumours can be treated by transurethral resection of the bladder (TURB) and/or intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. However, molecular biology techniques and clinical experience have demonstrated the highly malignant potential of CIS and T1 lesions. The terms “NMIBC” and older one “superficial BC” are therefore suboptimal descriptions.

4.2 Tumour, Node, Metastasis Classification (TNM)

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) was updated in 2009 (7th version), but it had no changes for bladder tumours (Table 4.1) [20].

Table 4.1: 2009 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, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N - 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 lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	

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

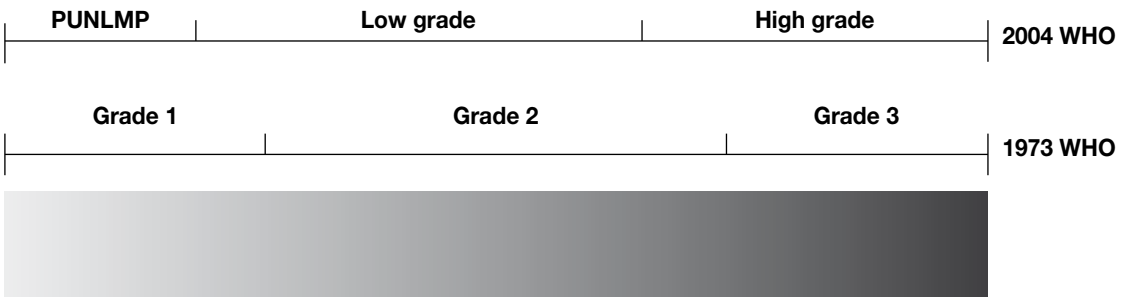
In 2004, the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [21, 22] (Tables 4.2, 4.3, Fig 4.1). A website (www.pathology.jhu.edu/bladder) that illustrates examples of the various grades has been developed to further improve accuracy in using the system.

Table 4.2: WHO grading in 1973 and in 2004 [21, 22]

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading system [papillary lesions]
Urothelial papilloma (completely benign lesion)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

The prognostic value of both WHO 1973 and 2004 grading systems has been confirmed. Attempts to demonstrate better prognostic value of one of them, however, have yielded controversial results [23-28] (LE: 2a). Moreover the WHO 2004 system has not been fully incorporated into prognostic models yet. Most clinical trials published to date on Ta, T1 bladder tumours have been performed using the 1973 WHO classification, and the following guidelines are therefore based on this version.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications [23]*



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

PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organization.

4.4 CIS and its classification

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma. It can be missed at cystoscopy or be considered as an inflammatory lesion if it is not biopsied. CIS is often multifocal and can occur in the bladder, but also in the upper urinary tract, prostatic ducts, and prostatic urethra [29].

Classification of CIS into clinical type [30]:

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

Table 4.3: WHO 2004 grading system

WHO 2004 grading system (flat lesions):
• Hyperplasia (flat lesion without atypia or papillary aspects)
• Reactive atypia (flat lesion with atypia)
• Atypia of unknown significance
• Urothelial dysplasia
• Urothelial CIS is always high-grade

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

There is significant variability among pathologists for diagnosis of CIS, for which agreement is achieved in only 70-78% of cases [31, 32] (LE: 2a). There is also interobserver variability in the classification of stage T1 versus Ta tumours and tumour grading in both 1997 and 2004 classifications. The general conformity in staging and grading is between 50% and 60% [27, 31-36] (LE: 2a). The published comparisons have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification [24, 27].

4.6 Further promising pathology parameters

Some novel parameters based on pathological investigation of resected tissue have been considered for subclassification and prognostic purposes.

In T1 tumours, the depth and extent of invasion into the lamina propria (T1 substaging) can be evaluated. The prognostic value of this evaluation has been demonstrated by some retrospective cohort studies [37-40] (LE: 3); nevertheless, it is not recommended in the WHO classification.

According to a meta-analysis of retrospective trials, the presence of lymphovascular invasion (LVI) in TURB specimens was connected with increased risk of pathological upstaging [41] (LE: 3). Lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours [42] (LE: 3).

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, nested, sarcomatoid, squamous and adeno variants of urothelial carcinoma etc.), have a poor prognosis [43-47] (LE: 3).

Molecular markers, particularly FGFR3 mutation status, are promising but need further evaluation [25, 40, 48-50].

4.7 Recommendations

The recommendations for BC classification can be found in section 5.14.

5. DIAGNOSIS

5.1 Patient history

A comprehensive patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Ta, T1 tumours do not cause bladder pain and rarely present with lower urinary tract symptoms. CIS might be suspected in patients who do complain of these symptoms, particularly if they are refractory to symptomatic treatment.

5.3 Physical examination

Physical examination does not reveal NMIBC.

5.4 Imaging

*5.4.1 **Computed tomography urography and intravenous urography***

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

Intravenous urography (IVU) can be an alternative if CT is not available [51] (LE: 3), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography gives more information than IVU does (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography or IVU once a bladder tumour has been detected is questioned because of the low incidence of significant findings obtained [52-54] (LE: 2a). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [53] (LE: 2b). The risk of UTUC during follow-up increases in patients with multiple- and high-risk tumours [55] (LE: 3).

*5.4.2 **Ultrasound (US)***

Transabdominal US permits characterization of renal masses, detection of hydronephrosis, and visualization of intraluminal masses in the bladder. It is as accurate as IVU for diagnosis of UTUC [52] (LE: 3). Ultrasound is therefore a useful tool for detection of obstruction in patients with haematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

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

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in G3 tumours, but low sensitivity in G1 tumours. The sensitivity in CIS detection is 28-100% [56] (LE: 2b). Cytology is useful, particularly as an adjunct to cystoscopy, when a G3 malignancy or CIS is present. Positive voided urinary cytology can indicate an urothelial tumour anywhere in the urinary tract; negative cytology, however, does not exclude the presence of a tumour.

Cytological interpretation is user-dependent [57]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, but in experienced hands specificity exceeds 90% [58] (LE: 2b). Urine collection should respect recommendations (see Section 5.9). One cytospin slide from the sample is usually sufficient [59]. In patients with suspect cytology it is reasonable to repeat the investigation [60] (LE: 3).

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests were developed [58, 61-68]. None of these markers have been accepted for diagnosis or follow-up in routine urology or in guidelines. Some urine tests that have been evaluated in several laboratories/centres and with sufficient numbers of patients are listed in Table 5.1.

The following conclusions can be drawn regarding the existing tests.

- Sensitivity is usually higher and at the cost of lower specificity compared to urine cytology [58, 62-72] (LE: 3).
- Benign conditions and BCG influence many urinary marker tests [58, 61-68] (LE: 3).
- Sensitivity and specificity of a urinary marker test depend on the clinical context of the patient

(screening, primary detection, follow-up [high risk, low-/intermediate-risk]) [62-65] (LE: 3).

- Patient selection explains the wide range in performance of the markers listed in Table 5.1.
- Unlike other urine tests, false-positive results of UroVysion and microsatellite analysis can be attributed to occult disease and thus identify patients likely to experience early recurrence [73-77] (LE: 3).

Table 5.1: Summary of main urinary markers

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

BTA = bladder tumour antigen; LE = level of evidence.

5.7 Potential application of urinary cytology and markers

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

*5.7.1 **Screening of the population at risk of BC***

The application of haematuria dipstick, NMP22 or UroVysion in BC screening in high-risk populations has been reported [78, 79]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [65, 77-79]. Routine application of screening is not recommended.

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

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

*5.7.3 **Surveillance of NMIBC***

Research has been carried out into the usefulness of urinary cytology versus markers in the follow-up of NMIBC [65, 67, 80, 81].

5.7.3.1 Follow-up of high-risk NMIBC

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

5.7.3.2 Follow-up of low-/intermediate-risk NMIBC

To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology is its low sensitivity for low-grade recurrences. Several urinary markers are better, but still do not detect half of the low-grade tumours identified by cystoscopy [62, 65] (LE: 3).

According to current knowledge, no urinary marker can replace cystoscopy during follow-up or help to lower cystoscopic frequency in a routine fashion. One prospective randomized study confirmed that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [82] (LE: 1b). It supports the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy [82].

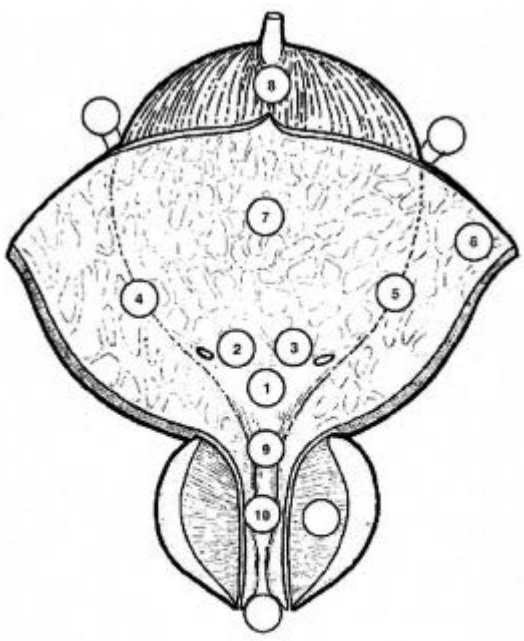
5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. CIS is diagnosed by a combination of cystoscopy, urine cytology, and

histological evaluation of multiple bladder biopsies [83].

Cystoscopy is initially performed in the office. A flexible instrument with topical intra-urethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [84].

Figure 5.1: Bladder diagram



5.9 Guidelines for the primary assessment of NMIBC

	GR
Patient history should be taken.	A
Renal and bladder US may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of NMIBC, CT urography (or IVU) should be performed only in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	B
Cystoscopy is recommended in all patients with symptoms suggestive of BC. It cannot be replaced by cytology or by any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended (Figure 5.1).	C
Voided urine cytology is advocated to predict high-grade tumour before TURB.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C

BC = bladder cancer; CT = computed tomography; GR = grade of recommendation; IVU = intravenous urography; US = ultrasound; NMIBC = non-muscle invasive bladder cancer; TURB = transurethral resection of the bladder.

5.10 Transurethral resection of Ta, T1 bladder tumours

5.10.1 Strategy of the procedure

The goal of TURB in Ta,T1 BC is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of BC. TURB should be performed systematically in individual steps (see Section 5.14). The strategy of resection depends on the size of the lesion (see Section 5.14). Separate resection of larger tumours provides good information about the vertical and horizontal extent of the tumour and helps to improve resection completeness [85, 86] (LE: 3).

Complete and correct TURB is essential to achieve a good prognosis [87]. It has been confirmed that the absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumour understaging [86, 88] (LE: 2b). It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [89].

5.10.2 ***Office-based fulguration***

In patients with a history of small, Ta LG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option [90] (LE: 3).

5.10.3 ***New resection techniques***

Compared to monopolar resection, the bipolar electrocautery system has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and produce better specimens for the pathologist [91] (LE: 3). As yet, the results are controversial [92-94].

5.10.4 ***Bladder and prostatic urethral 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, the strategy of biopsies from abnormal urothelium and biopsies from normal-looking mucosa (random/mapping biopsies) was recommended (see Section 5.14). The indication of random biopsies reflects the fact, that the likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) [95] (LE: 2a). The risk increases in patients with high-risk tumours and with positive cytology [96].

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

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou et al. [97] showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% (LE: 2b). The risk of prostatic urethra- or duct involvement is higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [98] (LE: 3). Based on this observation a biopsy from the prostatic urethra is necessary in some cases. A recommendation is included in Section 5.14 [97, 99].

5.11 New methods of tumour visualization

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

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

Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for detection of malignant tumours, particularly for CIS [100, 101] (LE: 2a). In a systematic review and meta-analysis, PDD had higher sensitivity than white-light endoscopy in the pooled estimates for analyses at both the patient-level (92% versus 71%) and biopsy-level (93% versus 65%) [101].

PDD had lower specificity than white-light endoscopy (63% vs. 81%) [101]. False-positivity can be induced by inflammation or recent TURB and during the first 3 months after BCG instillation [102, 103] (LE: 3). Prospective randomized studies evaluating the impact of ALA fluorescence-guided (FC) TURB on disease recurrence rate provided controversial results [101, 104, 105].

The beneficial effect of HAL FC on recurrence rate in patients with TURB was confirmed by a multicentre, prospective, randomized trial and by raw-data based meta-analysis of controlled trials. A meta-analysis reported in HAL arms an increase in detection of tumour lesions across all risk groups and an absolute reduction of < 10% in recurrence rates within 12 months [106] (LE: 1a). The beneficial effect of HAL FC on recurrence rate in patients with TURB and early intravesical instillation of chemotherapy was not confirmed by a prospective randomized trial [107]. The value of FC for improvement of outcome in relation to progression rate, survival and clinical management remains to be demonstrated.

5.11.2 ***Narrow-band imaging***

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection [108, 109] (LE: 3). The suggested reduction of recurrence rate if NBI is used during TURB has not been fully confirmed yet [110].

5.12 Second resection

The significant risk of residual tumour after initial TURB of Ta, T1 lesions has been demonstrated [87] (LE: 2a).

Persistent disease after resection of T1 tumours has been observed in 33-55% of patients, and after resection of TaG3 tumour in 41.4% [111-115].

Moreover, the tumour is often understaged by initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 4-25%, and it increases to 45% if there was no muscle in the initial resection [86]. This risk has increased up to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [116-118] (LE: 2a). Treatment of a Ta, T1 high-grade tumour and a T2 tumour is completely different; correct staging is therefore important.

It has been demonstrated that a second TURB can increase recurrence-free survival [111, 112] (LE: 2a), improve outcomes after BCG treatment [119] (LE: 3) and provide prognostic information [116, 120] (LE: 3)

Based on these arguments, a second TURB is recommended in selected cases (see Section 5.14).

5.13 Pathology report

Pathology investigation of the specimen obtained by TURB and biopsies is an essential step in the diagnosis and treatment decision-making process for BC. Close co-operation between urologists and pathologists is recommended.

A high quality of resected and submitted tissue is essential for correct pathological assessment. The presence of sufficient muscle is necessary for the correct assignment of T category. To achieve all required information, the specimen collection, handling and evaluation should respect the recommendations provided below (section 5.14) [121].

5.14 Guidelines for TURB and/or biopsies, tumour classification and pathology report

	GR
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • surgical report formulation; • precise description of the specimen for pathology evaluation.	C
Performance of individual steps:	
Perform resection in one piece for small papillary tumours (< 1 cm), including a part from the underlying bladder wall.	B
Perform resection in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area for tumours > 1 cm in diameter.	B
Avoid cauterization as much as possible during TURB to avoid tissue deterioration.	C
Take biopsies from abnormal-looking urothelium.	
Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance).	C
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, the cold-cup biopsy with forceps can be used.	C
If equipment is available, use fluorescence-guided (PDD) biopsy instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion).	B
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC, CIS in the bladder (random biopsies or PDD targeted biopsies) and tumour in the prostatic urethra (prostatic urethra biopsy).	C

Perform a second TURB in the following situations: • after incomplete initial TURB; • if there is no muscle in the specimen after initial resection, with the exception of TaG1 tumours and primary CIS; • in all T1 tumours; • in all G3 tumours, except primary CIS.	A
If indicated, perform a second TURB within 2-6 weeks after initial resection. It should include resection of the primary tumour site.	C
Classification and pathological report	
For classification of the depth of tumour invasion (staging) use the 2009 TNM system.	A
For histological classification, use both the 1973 and 2004 WHO grading.	A
Do not use the term “Superficial BC”.	A
Whenever using the terminology NMIBC, in individual cases, mention the tumour stage and grade.	A
The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathological report should specify the presence of LVI or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

BC = bladder cancer; CIS = carcinoma in situ; CT = computed tomography; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; TNM = Tumour, Node, Metastasis; TURB = transurethral resection of the bladder; WHO = World Health Organisation.

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 Ta, T1 tumours

In order to predict separately the short- and long-term risks of disease recurrence and progression in individual patients, the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancer Group (GUCG) has developed a scoring system and risk tables [122]. The basis for these tables are individual patient data for 2,596 patients diagnosed with Ta, T1 tumours, who were randomized into seven EORTC-GUCG trials. Patients with CIS alone were not included. Seventy-eight percent of patients received intravesical treatment, mostly chemotherapy. However, they did not undergo a second TURB or receive maintenance BCG.

The scoring system is based on the six most significant clinical and pathological factors which are shown in Table 6.1.

It also illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 6.2 shows the total scores stratified, as in the original article [122], into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years (LE: 2a).

Table 6.1: Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	**0-17**	**0-23**

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

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Progression score	Probability of progression at 1 year		Probability of progression at 5 years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

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

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received 12 instillations over 5-6 months. No immediate postoperative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:

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

Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [123] (LE: 2a). The lower risks in the CUETO tables may be attributed to using BCG, which is a more effective instillation therapy. The CUETO risk calculator is available at: http://www.aeu.es/Cueto.html.

The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG and by long-term follow-up in an independent patient population [124, 125] (LE: 2a).

Further prognostic factors have been described in selected patient populations:

- In T1G3 tumours important prognostic factors were female sex and CIS in the prostatic urethra in patients treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG treated patients (62% with induction course only) [97, 126] (LE: 2b).
- Attention must be given to patients with T1G3 tumours in bladder (pseudo) diverticulum because of an absence of muscle layer in the diverticular wall [127] (LE: 3).
- In patients with high-risk disease, the tumour stage at the time of the 2nd TURB is an unfavourable prognostic factor [116, 120] (LE: 3)
- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [128] (LE: 2b).
- The prognostic value of pathological factors has been discussed elsewhere (see Section 4.6). More research is needed to determine the role of molecular markers in improving the predictive accuracy of currently existing risk tables [124, 129].

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [130] (LE: 3). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease. Publications are based on retrospective analyses of small series of patients and conclusions are not homogeneous. Some studies have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [131, 132], in extended CIS [133], and in CIS in the prostatic urethra [97] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [123-125, 128]. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [134, 135] (LE: 2a).

6.3 Patients´ stratification into risk groups

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

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, Ta, G1* (PUNLMP, LG), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk).
High-risk tumours	Any of the following: • T1 tumour • G3** (HG) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)*

Substratification of high-risk tumours for clinical purposes can be seen in Table 7.2.
**low grade is a mixture of G1 and G2*
*** high grade is a mixture of some G2 and all G3 (see Figure 4.1)*
CIS = carcinoma in situ; HG = high-grade; LG = low-grade.

6.3.1 *Recommendations for stratification of NMIBC*

	GR
Stratify patients into three risk groups according to Table 6.2.	B
Apply the EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B
In patients treated with BCG, use the CUETO risk tables for individual prediction of the risk of tumour recurrence and progression.	B

BCG = Bacillus Calmette-Guérin; CUETO = Club Urológico Español de Tratamiento Oncológico; GR = grade of recommendation; EORTC = European Organization for Research and Treatment of Cancer; TURB = transurethral resection of the bladder.

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [136, 137] LE: 3).

While it is still controversial whether smoking cessation in bladder cancer will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general risks connected with tobacco smoking [138-140, 141] (LE: 3).

7.2 Adjuvant treatment

7.2.1 *Intravesical chemotherapy*

Although TURB by itself can eradicate a Ta, T1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the 3-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [87]. It is therefore necessary to consider adjuvant therapy in all patients.

7.2.1.1 *A single, immediate, post-operative intravesical instillation of chemotherapy*

Immediate single instillation (SI) has been shown to act by the destruction of circulating tumour cells resulting from TURB, and by an ablative effect (chemoresection) on residual tumour cells at the resection site and on small overlooked tumours [142-145] (LE: 3).

Three large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that SI after TURB significantly reduced the recurrence rate by 11.7% to 13.0% compared to TURB alone [146-148] (LE: 1a). Although none of the three meta-analyses adequately answered the question concerning which patients benefitted the most, some underpowered data from two subgroup analyses [149, 150] suggest that SI is most effective in tumour types with the lowest tendency towards recurrence, i.e., in single primary or small tumours. Mitomycin C (MMC), epirubicin, and doxorubicin have all shown a beneficial effect; no efficacy comparisons have been made [146-148] (LE: 1a).

There is evidence from one subgroup- and one combined analysis that SI might have an impact on recurrence, even when further adjuvant instillations are given [151-153] (LE: 2a). In contrast, a sufficient number of delayed repeat chemotherapy instillations can also reduce recurrence stemming from tumour implantation [151-154]. Clearly, more studies comparing immediate and delayed-start regimens are needed.

The prevention of tumour cell implantation should be initiated within the first hours after cell seeding. Within a few hours, the cells are implanted firmly and are covered by extracellular matrix [142, 155-157] (LE: 3). In all SI studies, the instillation was administered within 24 hours. To maximize the efficacy of SI, one should devise flexible practices that allow the instillation to be given as early as possible, which is in the recovery room or even in the operating theatre.

As severe complications have been reported in patients with drug extravasation [158, 159], safety measures should be maintained (see Section 7.5).

7.2.1.2 *Additional adjuvant intravesical chemotherapy instillations*

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1, 6.2 and 6.3), a SI reduces the risk of recurrence and is considered to be the standard and sufficient treatment [146] (LE: 1a). For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1, 6.2 and 6.3). It was shown that further chemotherapy instillations can improve RFS in intermediate-risk tumours [154].

A large meta-analysis of 3,703 patients from 11 randomized trials showed a highly significant

44% reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [160]. This corresponds to an absolute difference of 13-14% in the number of patients with recurrence. Contrary to chemotherapy, two meta-analyses have demonstrated that BCG therapy may reduce the risk of tumour progression [161, 162] (LE: 1a) (see Section 8.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [163-165] (see Section 7.2.2) (LE: 1a). However, BCG causes significantly more side effects than does chemotherapy [165] (LE: 1a).

The length and frequency of chemotherapy instillations is still controversial. A systematic review of RCTs, comparing different schedules of intravesical chemotherapy instillations, concluded that the ideal duration and intensity of the schedule remains undefined because of conflicting data [153]. The available evidence does not support treatment longer than one year (LE: 3).

7.2.1.3 Options for improving efficacy of intravesical chemotherapy

Some promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia or electromotive drug administration (EMDA) in patients with high-risk tumours. The current evidence, however, is limited [166, 167] and both treatment modalities are considered to be experimental (LE: 2b).

One RCT using MMC has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduced the recurrence rate [168] (LE: 1b). Another trial reported that a 1-hour instillation of MMC was more effective than 30 minutes instillation, but no efficacy comparisons are available for 1- and 2-hour instillations [169] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [170] (LE: 1b). In view of these data, instructions are provided (see Section 7.5)

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

7.2.2.1 Efficacy of BCG

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing the recurrence of NMIBC [163, 171-174] (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin + interferon [175], MMC [176], or epirubicin alone [164] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long-lasting [164, 176] and was also observed in a separate analysis of patients with intermediate-risk tumours [164].

One meta-analysis [163] has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC versus BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance.

Two meta-analyses have demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [161, 162] (LE: 1a). A meta-analysis carried out by the EORTC-GUCG has evaluated data from 4,863 patients enrolled in 24 RCTs. Five different BCG strains were used, and in 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, in 260 out of 2,658 patients (9.8%) treated with BCG, tumours progressed compared to 304 out of 2,205 (13.8%) in the control groups (TURB alone, TURB + intravesical chemotherapy, or TURB + other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with Ta, T1 papillary tumours and in those with CIS [162]. A recent RCT with long-term observation has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [164] (LE: 1b). On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [163].

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

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [177]. In the most recent meta-analysis, however, BCG maintenance was more effective than MMC both in patients previously treated and not previously treated with chemotherapy [163] (LE: 1a).

It was demonstrated that BCG was less effective in patients > 70 years of age, but it was still more effective than epirubicin [178] (LE: 1a).

According to a published meta-analysis of 4 RCTs, the addition of chemotherapy to maintenance BCG does not improve the efficacy [179]. One smaller RCT demonstrated promising results of the addition of electromotive administered MMC to BCG, however, this requires further confirmation [167].

7.2.2.2 BCG strain

The EORTC meta-analysis suggested no large differences in efficacy between various BCG strains [162]. Recently published smaller studies without maintenance demonstrated some differences between strains. This clearly needs further evaluation in prospective trials [180, 181] (LE: 2a).

7.2.2.3 BCG toxicity

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy [162] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [182] (LE: 1b). It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [182]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [183].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.5).

The presence of leukocyturia, non-visible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [184, 185] (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (immunosuppression, human immunodeficiency virus [HIV] infection) [186], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients [187, 188] (LE: 3).

The management of side effects after BCG should reflect their type and grade according the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [189, 190] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [190-193]

Management options for local side effects (modified from the IBCG group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or NSAIDs.
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation; b. Perform a urine culture; c. Start empirical antibiotic treatment.
	If symptoms persist even with antibiotic treatment: d. With positive culture: antibiotic treatment according to sensitivity e. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [191].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis [192]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.

Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or anti-tuberculosis drugs [193].
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 > two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-TURB (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or Enterococcus.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

BCG = bacillus Calmette-Guérin; IBCG = International Bladder Cancer Group; NSAID = non-steroidal anti-inflammatory drug; TURBT = transurethral resection of bladder tumour.

7.2.2.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales in 1976 [194]. For optimal efficacy, BCG must be given in a maintenance schedule [161-163, 174] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks to 27 over 3 years [195]. The EORTC meta-analysis was unable to determine which BCG maintenance schedule was the most effective [162]. 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 [161] (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations remain unknown [196]. However, in a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, 3 years' maintenance reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or overall survival. In the 3-year arm, however, 36.1% of patients did not complete the 3-years schedule [197] (LE: 1b). The benefit of the two additional years of maintenance in the high-risk patients should be weighed against its added costs and inconvenience.

7.2.2.5 Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [198, 199] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [200] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one-third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year [183, 197] (LE: 1b). Moreover, the routine application is complicated by potential technical difficulties in preparing the reduced dose reliably.

7.2.2.6 Indications for BCG

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

*7.2.3 **Specific aspects of treatment of CIS***

7.2.3.1 Treatment strategy

The detection of concurrent CIS increases the risk of recurrence and progression of Ta,T1 tumours [122, 123], further treatment according to the criteria summarized in Sections 7.2.1, 7.2.2, 7.3 and 7.4 is mandatory.

CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but as many as 40-50% of patients might be over-treated [130] (LE: 3).

7.2.3.2 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 [130-133, 201] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [133, 195, 201, 202] (LE: 3).

7.2.3.3 Prospective randomized trials on intravesical BCG or chemotherapy

Unfortunately, there have been few randomized trials in patients with CIS alone. 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 [203] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression (a subgroup of 403 patients with CIS), BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different immunotherapy [162] (LE: 1b). The combination of BCG and MMC is not superior to BCG alone [204]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1a).

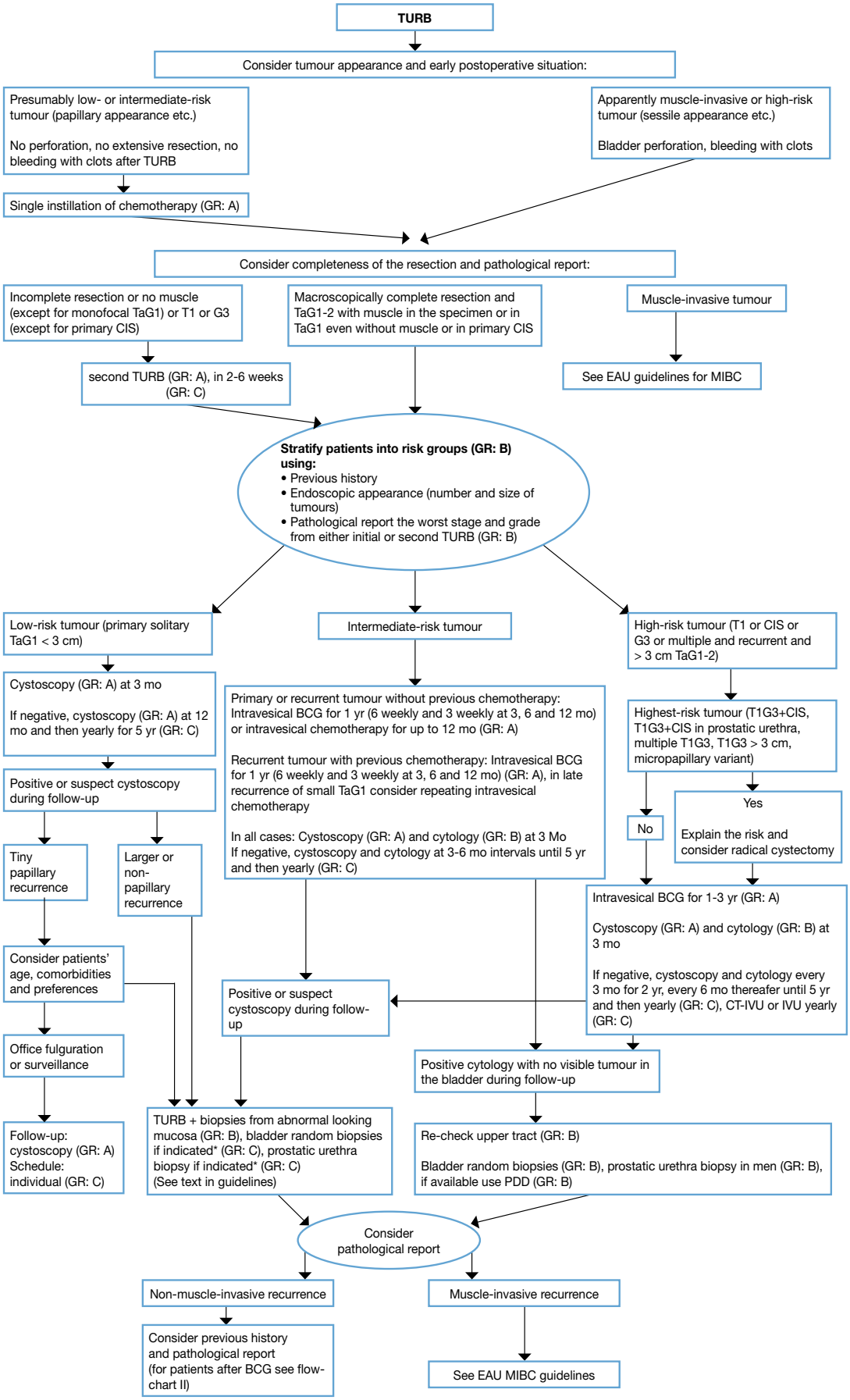
7.2.3.4 Treatment of extravesical CIS

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 [205]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [205] (LE: 3).

In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [29]. 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. TUR of the prostate can improve contact of BCG with the prostatic urethra [84, 206] (LE: 3).

In patients with prostatic duct involvement, there are promising results after BCG instillation, but only from small series, so the data are insufficient to provide clear treatment recommendations and radical surgery should be considered [206, 207] (LE: 3). Treatment of CIS that involves the UUT is discussed in the Guidelines on Urothelial Tumours of the Upper Urinary Tract (UTUCs).

Flowchart 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; GR = grade of recommendation; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.3 Treatment of failure of intravesical therapy

7.3.1 Failure of intravesical chemotherapy

Patients with non-muscle-invasive recurrence of BC after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation [163] (LE: 1a).

7.3.2 Recurrence and failure after intravesical BCG immunotherapy

Table 7.2: Categories of unsuccessful treatment with intravesical BCG

BCG failure
Whenever a MIBC is detected during follow-up.
BCG-refractory tumour: 1. If high-grade, non-muscle-invasive papillary tumour is present at 3 months [208]. Further conservative treatment with BCG is associated with increased risk of progression [134, 209] (LE: 3). 2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 months. In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [29] (LE: 3). 3. If high-grade tumour appears during BCG therapy*.
High-grade recurrence after BCG. Recurrence of high-grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response [210] (LE: 3)*.
BCG intolerance
Severe side effects that prevent further BCG instillation before completing induction [190].

** Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; LE = level of evidence.

7.3.3 Treatment of BCG failure and recurrences after BCG

Treatment recommendations are provided in Table 7.4. They reflect categories mentioned in Table 7.2 and tumour characteristics at the time of recurrence.

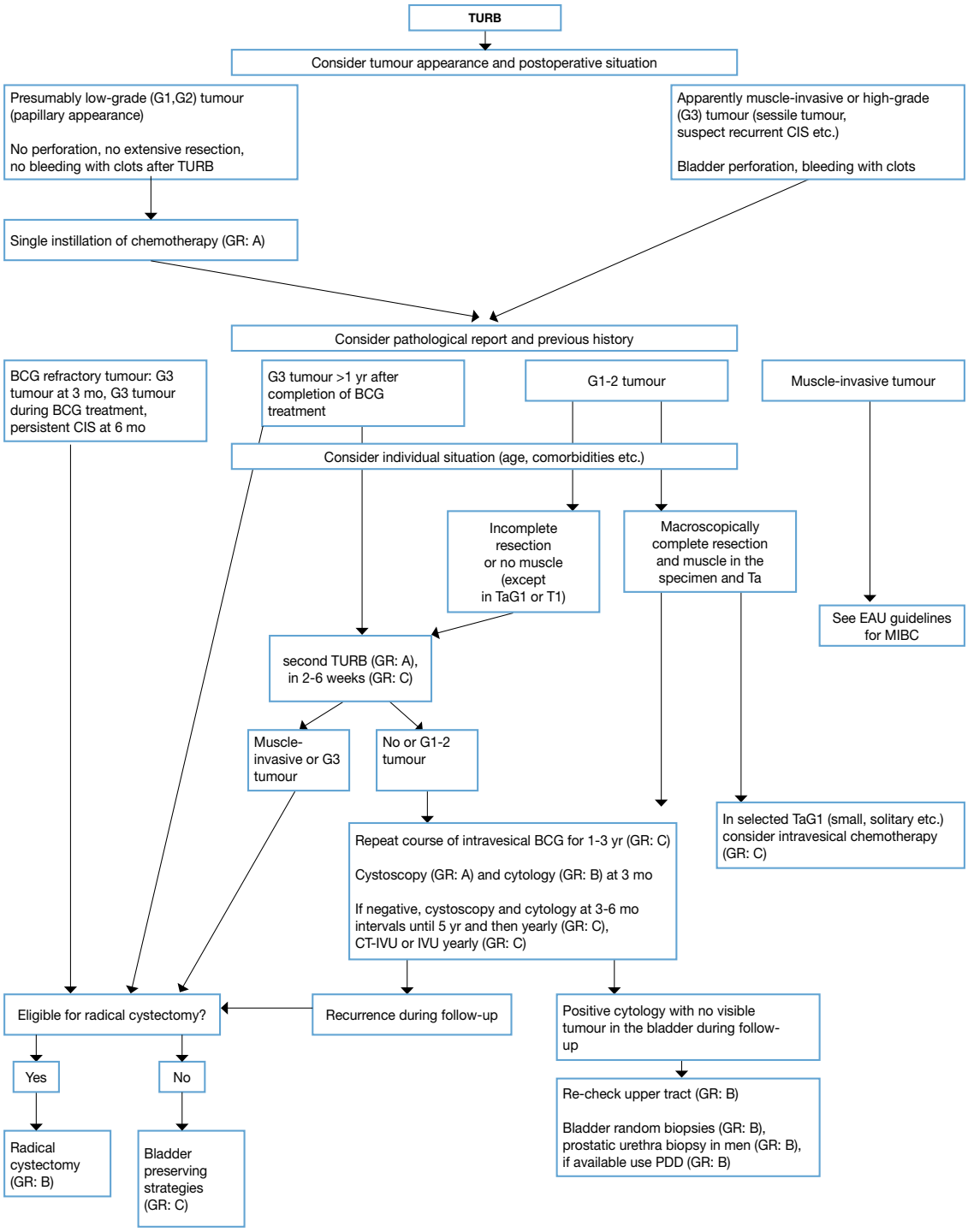
Patients with BCG failure are unlikely to respond to further BCG therapy; RC is therefore the preferred option. Various studies suggest that repeat BCG therapy is appropriate for non-high grade and even for some high-grade recurrent tumours [211, 212] (LE: 3). Additionally, there are now several bladder preservation strategies available that can be categorized as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [213]. Changing from BCG to these options can yield responses in selected cases with BCG treatment failure [211, 214-221] (LE: 3).

Treatments other than RC must be considered oncologically inferior in patients with BCG failure at the present time [134, 208, 209] (LE: 3).

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

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

Flowchart 7.2: Treatment strategy in recurrence during or after intravesical BCG*



**For details and explanations, see the text of the guidelines.*
BCG = bacillus Calmette-Guérin; GR = grade of recommendation; IVU = intravenous urography; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.4 Radical cystectomy for NMIBC

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

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 [99, 117, 222-227] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).

The potential benefit of RC must be weighed against the risk, morbidity, and impact on quality of life. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of progression (see Table 7.3) [44, 97, 122, 123] (LE: 3).

The benefits and risks of immediate and delayed RC should be discussed with patients. Individual additional prognostic factors in T1 G3 tumours mentioned in Section 6.1, as well as pathologic parameters (particularly LVI and unusual histologies) mentioned in Section 4.6, should be considered.

Early RC is strongly recommended in patients with BCG-refractory tumours, as mentioned above. A delay in RC might lead to decreased disease-specific survival [228] (LE: 3). In patients in whom RC is performed at the time of pathological NMIBC, the 5-year disease-free survival rate exceeds 80% [229-233] (LE: 3).

Table 7.3: Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, LG/G1,< 3 cm, no CIS	One immediate instillation of chemotherapy.
Intermediate-risk tumours	All cases between categories of low and high risk	One immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1-year full-dose BCG.
High-risk tumours	Any of the following: • T1 tumours; • HG/G3 tumours; • CIS; • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be present).	Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest-risk tumours).
Subgroup of highest-risk tumours	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, unusual histology of urothelial carcinoma, LVI (see Sections 4.6 and 6.2).	Radical cystectomy should be considered in those who refuse RC, intravesical full-dose BCG instillations for 1-3 years.
	BCG failures	Radical cystectomy is recommended.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; GR = grade of recommendation; HG = high-grade: LG = low-grade; LVI = lymphovascular invasion.

Table 7.4: Treatment recommendations for BCG failure and recurrences after BCG

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

BCG = bacillus Calmette-Guérin; GR = grade of recommendation; HG = high-grade.

7.5 Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS

	GR
Smokers with confirmed NMIBC should be counselled to stop smoking.	B
The type of further therapy after BCG should be based on the risk groups shown in Tables 6.3 and 7.3.	A
In patients with tumours presumed to be at low- or intermediate risk, one immediate chemotherapy instillation is recommended.	A
In patients with low-risk tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with intermediate-risk tumours, one immediate instillation of chemotherapy should be followed by 1-year full-dose BCG treatment, or by further instillation of chemotherapy for a maximum of 1 year. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconvenience.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG can be offered.	C
In patients at highest risk of tumour progression (Table 7.3), immediate radical cystectomy should be considered.	C
In patients with BCG failure, radical cystectomy is indicated.	B
Intravesical chemotherapy	
One immediate instillation of chemotherapy should be administered within 24 hours after TURB.	C
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extra-peritoneal perforation (after extensive TURB, or bleeding requiring bladder irrigation).	C
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined, but it should not exceed 1 year.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug by reducing fluid intake before and during instillation.	B
The length of an individual instillation should be 1-2 hours.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first 2 weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	C
The management of side effects after BCG intravesical instillation should reflect their type and grade (Table 7.1).	C

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; GR = grade of recommendation; MMC = mitomycin C; TUR = transurethral resection; TURB = transurethral resection of the bladder.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed up. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk. Using risk tables (see Tables 6.1 and 6.2), the short- and long-term risks of recurrence and progression in individual patients may be predicted and the follow-up schedule adapted accordingly [122, 123].

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

- The prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life-threatening.
- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [234-238] (LE: 2b). Fulguration of small papillary recurrences on

an outpatient basis could be a safe option that reduces the therapeutic burden [90] (LE: 3). Some authors have even defended temporary surveillance in selected cases [237-239] (LE: 3).

- The first cystoscopy after TURB at 3 months is a very important prognostic indicator for recurrence and progression [128, 134, 240-242] (LE: 1a). Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with Ta, T1 tumours and CIS.
- In tumours at low-risk, the risk of recurrence after 5 recurrence-free years is low [241] (LE: 3). Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [242].
- In tumours originally intermediate- or high-risk, recurrences after 10 years tumour-free are not unusual [243] (LE: 3). Therefore, life-long follow-up is recommended [242].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT)
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [55] (LE: 3).
- Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy [82] (LE: 1b). It supports the adjunctive role of urine tests during follow-up.

No non-invasive method has been proposed that can replace endoscopy and follow-up is therefore based on regular cystoscopy (see Section 5.7). There is a lack of randomized studies that have investigated the possibility of safely reducing the frequency of follow-up cystoscopy.

As CIS is often not visible, multiple biopsies may be necessary in selected cases to confirm the efficacy of intravesical treatment in patients treated for CIS [83].

The following recommendations are based mostly on retrospective data.

8.1 Guidelines for follow-up in patients after TURB of NMIBC

	GR
The follow-up of Ta, T1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	C
Patients with intermediate-risk Ta tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
Consider R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 months) in patients with CIS.	C
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

CIS = carcinoma in situ; CT-IVU = computed tomography intravenous urography; GR = grade of recommendation; IVU = intravenous urography; PDD = photodynamic diagnosis; R-biopsies = random biopsies.

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. 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.