

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

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1. BACKGROUND

1.1 Introduction

This overview represents the updated European Association of Urology (EAU) guidelines for Non-muscle-invasive Bladder Cancer (CIS, Ta, T1). The information presented is limited to urothelial carcinoma, if not specified otherwise. Aim is to provide practical guidance on the clinical management of non-muscle-invasive bladder cancer with a focus on clinical presentation and recommendations.

The EAU Guidelines Panel on Non-muscle-invasive Bladder Cancer consists of an international multidisciplinary group of clinicians, including a pathologist and a statistician.

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients - also taking personal values and preferences and individual circumstances of patients into account.

Separate EAU guidelines documents are available addressing upper urinary tract tumours (1), muscle-invasive bladder cancer (2), and primary urethral carcinomas (3).

1.2 Methodology

1.2.1 Data Identification

The systematic literature search for each section of the Non-muscle-invasive Bladder Cancer Guidelines was performed by the panel members. For identification of original and review articles, Medline, Web of Science, and Embase databases were used. For the current update, all articles published between 2010 and 2012 on non-muscle-invasive bladder cancer were considered. Focus of the searches was identification of all level 1 scientific papers (randomised controlled trials (RCTs), systematic reviews (SRs), and meta-analyses of RCTs) in accordance with the EAU guidelines methodology.

1.2.2 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (LE), and guideline recommendations have been graded follow the listings in Tables 1 and 2, based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (4). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

*Modified from Sackett et al. (4).

It should be noted that when recommendations are graded, the link between the LE and grade of recommendation (GR) is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level of evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as "upgraded based on panel consensus". The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences, and costs when a grade is assigned (5-7).

The EAU Guidelines Office does not perform structured cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever these data are available, the expert panel will include the information.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

*Modified from Sackett et al. (4).

1.3 Publication history

The first European Association of Urology (EAU) Guidelines on Bladder Cancer were published in 2000 (8). In 2004 it was decided to develop separate guidelines for muscle-invasive and infiltrative bladder cancer and a separate scientific publication on upper urinary tract tumours was presented (9), which was updated and has been included in the EAU Guidelines compilation print since 2011 (10). The complete updates of guidelines for non-muscle-invasive bladder cancer were prepared in 2006, 2008 and 2011 (11-14). Since 2011 the EAU Guidelines on TaT1 tumours and CIS were integrated in one guidelines document (14).

Several scientific summaries have been published in the EAU scientific journal, *European Urology* (9,15-19). A quick reference document (pocket guidelines) is available presenting the main findings of the Non-muscle-invasive Bladder Cancer Guidelines. This document follows the updating cycle of the underlying large texts.

All material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of translations and republications produced by national urological associations: <http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer-reviewed prior to publication.

1.3.1 Summary of changes

For all chapters the literature has been assessed.

Chapter 4 - Classification: a clear definition of non-muscle-invasive bladder cancer is presented. Since appropriate classification and grading directly influences treatment decisions, additional information on pathological parameters has been added.

Chapter 5 - Diagnosis: an illustration on bladder diagram to facilitate the description of cystoscopy finding has been added. The new data on endoscopic diagnosis and pathological evaluation of the tissue included in this section resulted in a number of changes in the recommendations.

Chapter 6 - Predicting disease recurrence and progression: the new stratification of patients into 3 risk groups facilitating treatment recommendation is presented

Chapter 7 - Adjuvant treatment: updated information on intravesical chemo- and immunotherapy is provided. The definition and stratification of BCG toxicity and side-effects is provided in an overview table. The definition of BCG failures has been specified.

Chapter 8: Radical cystectomy for NMIBC: the indication criteria were updated.

1.4 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guidelines/>.

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2. EPIDEMIOLOGY

Bladder Cancer (BC) is the most common malignancy of the urinary tract and the seventh most common cancer in men and the 17th in women. The worldwide age standardised incidence rate is 9 per 100,000 for men and 2 per 100,000 for women (2008 data) (1). In the European Union (EU) age standardised incidence rate is 27 per 100,000 for men and six per 100,000 for women (1).

Incidence varies between regions and countries; 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) (1). The variations can partly be attributed to different methodology and quality of data collection, thus warranting care in the interpretation of results (2,3).

The world global age standardised mortality rate is 3 for men versus 1 per 100,000 for women. In the EU, age standardised mortality rate is 8 for men and 3 per 100,000 for women, respectively (1). In 2008 BC was the eighth most common cause of cancer-specific mortality in Europe (1).

The incidence of BC has decreased in some registries possibly reflecting decreased impact of causative agents, mainly smoking and occupational exposure (4). The mortality of BC has also decreased, possibly reflecting increased standard of care (5).

Approximately 75% of patients with BC present with a disease that is confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). These categories are grouped as non-muscle-invasive bladder tumours. Non-muscle invasive BC (NMIBC) has a high prevalence due to low progression rates and long-term survival in many cases; patients with muscle-invasive BC (MIBC) are at higher risk of cancer-specific mortality (3). The prevalence of BC is among the highest of all urological malignancies (1).

3. RISK FACTORS

Increasing evidence suggests that genetic predisposition has a significant influence on bladder cancer incidence, especially via its impact on susceptibility to other risk factors (3,6). Tobacco smoking is the most important risk factor for BC, accounting for ~50% of cases (3,7) (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 in the modern era for ~10% of all cases. Such occupational exposure occurs mainly in industrial branches processing paint, dye, metal and petroleum products (3,8-10) (LE: 3).

Although the significance of the amount of fluid intake is uncertain, chlorination of drinking water and subsequent levels of trihalomethanes is potentially carcinogenic, and exposure to arsenic in drinking water increases BC risk (3,11) (LE: 3). The relation between personal hair dye use and BC risk remains uncertain; increased risk has been suggested in users of permanent hair dyes with NAT2 slow acetylation phenotype (12,13).

The exposure to ionizing radiation is connected with increased risk of BC (LE: 3). It is suggested that cyclophosphamide and pioglitazone are weakly associated with BC risk (3). Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is a cause of bladder cancer, particularly squamous cell carcinoma (3) (LE: 3).

4. CLASSIFICATION

4.1 Definition of non-muscle-invasive bladder cancer

A papillary tumour confined to the mucosa is classified as stage Ta according to the Tumour, Node, Metastasis (TNM) classification system. Tumours that have invaded the lamina propria are classified as stage T1. Ta and T1 tumours can be removed by transurethral resection (TUR), and therefore they are grouped under the heading of NMIBC for therapeutic purposes. Also included under this heading are flat, high-grade tumours that are confined to the mucosa, and classified as CIS (Tis). However, molecular biology techniques and clinical experience have demonstrated the highly malignant potential of CIS and T1 lesions. Therefore, the terms NMIBC and superficial BC are suboptimal descriptions. The latter term should no longer be used. Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.

4.2 Tumour, Node, Metastasis Classification (TNM)

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) has been widely accepted. This version was updated in 2009, but it has no changes for bladder tumours (Table 3) (14).

Table 3: 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 <i>in situ</i> : 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, 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 1998, a new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification) and published by the WHO in 2004 (15,16) (Table 4). Its major contribution is a detailed histological description of the various grades, which uses specific cytological and architectural criteria. 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: WHO grading in 1973 and in 2004 (15,16)

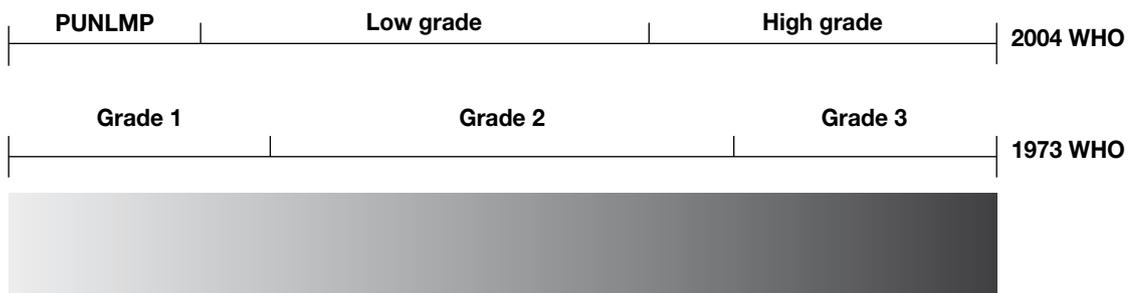
<p>1973 WHO grading Urothelial papilloma Grade 1: well differentiated Grade 2: moderately differentiated Grade 3: poorly differentiated</p> <p>2004 WHO grading Flat lesions Hyperplasia (flat lesion without atypia or papillary aspects) Reactive atypia (flat lesion with atypia) Atypia of unknown significance Urothelial dysplasia Urothelial CIS Papillary lesions Urothelial papilloma (completely benign lesion) Papillary urothelial neoplasm of low malignant potential Low-grade papillary urothelial carcinoma High-grade papillary urothelial carcinoma</p>
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The 2004 WHO classification of the flat lesions includes urothelial hyperplasia, reactive urothelial atypia, atypia of unknown significance, dysplasia, and CIS. Among non-invasive papillary urothelial lesions, the 2004 WHO grading differentiates between papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas.

Papillary urothelial neoplasms of low malignant potential (PUNLMPs) are defined as lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur. The intermediate grade (Grade 2), which was the subject of controversy in the 1973 WHO classification, has been eliminated (17-19) (Figure 1). The published comparisons, however, have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification (20,21).

The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. Attempts to demonstrate better prognostic value of one of the systems, however, have yielded controversial results (17-20,22-24). The majority of clinical trials published to date on TaT1 bladder tumours have been performed using the 1973 WHO classification, and therefore, the following guidelines are based on this version. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications should be used.

Figure 1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications (19)*



Histologic Spectrum of transitional cell carcinoma (urothelial carcinoma [UC] & spectrum)

**1973 WHO Grade 1 carcinomas have been reassigned to PUNLMP and Low-grade carcinomas in 2004 WHO classification, and Grade 2 carcinomas to Low-grade and High-grade carcinomas. All 1973 WHO Grade 3 carcinomas have been reassigned to High-grade carcinomas. Reproduced with permission from Elsevier.*

4.4 Inter- and intraobserver variability in staging and grading

Despite well-defined criteria for the diagnosis of urothelial carcinoma, there is significant variability among pathologists for diagnosis of CIS, for which agreement is achieved in only 70-78% of cases (25,26) (LE: 2a). There is interobserver variability in 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% (20,25-29) (LE: 2a).

In difficult cases, an additional review by an experienced genitourinary pathologist is recommended.

4.5 Further promising pathological parameters

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

In patients with 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 (30-33) (LE: 3). The presence of lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours (34) (LE: 3). It must be presented in pathological reports.

Detection of the micropapillary variant of urothelial carcinoma represents a poor prognostic factor even if it is non-muscle invasive at the time of diagnosis (35,36) (LE: 3). In micropapillary urothelial tumours with T1 invasion, some cases with distant metastases have been confirmed (35). Moreover, the risk of understaging in these tumours is substantial (37).

Rare cases of non-invasive squamous cell carcinoma in the bladder with poor prognosis have been described (38). Novel molecular markers, particularly FGFR3 mutation status, are promising but need further evaluation (17,33,39-41).

4.6 Specific character of CIS and its clinical classification

CIS is a flat, high-grade, non-invasive urothelial carcinoma. Macroscopically, CIS can be missed at cystoscopy or be considered as an inflammatory lesion if it is not biopsied. It is often multifocal and can occur not only in the bladder but also in the upper urinary tract, prostatic ducts, and prostatic urethra (42).

CIS is classified into one of four different clinical types (43):

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder;
- Recurrent: Repeat occurrence of isolated CIS after initial successful response to intravesical treatment.

5. DIAGNOSIS

5.1 Patient history

Patient history should be taken and recorded for all important information with possible connection to BC, including risk factors and history of suspect symptoms.

5.2 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 (LUTS). In patients who do complain of these symptoms, particularly in those with irritative LUTS refractory to symptomatic treatment, CIS might be suspected.

5.3 Physical examination

Physical examination does not reveal NMIBC.

5.4 Imaging

5.4.1 Intravenous urography and computed tomography

Intravenous urography (IVU) is used to detect filling defects in the calyces, renal pelvis and ureters, and hydronephrosis, which can indicate the presence of a ureteral tumour. Large exophytic tumours may be seen as filling defects in the bladder. The necessity to perform routine IVU once a bladder tumour has been detected is questioned because of the low incidence of significant findings obtained with this method (44-46) (LE: 2a). The incidence of upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone (45) (LE: 2b). The risk of tumour recurrence in the upper urinary tract during follow-up increases in multiple and high-risk tumours (47) (LE: 2b).

In most centres, computed tomography (CT) urography is used as an alternative to conventional IVU (48). Especially in muscle-invasive tumours of the bladder and upper urinary tract tumours, CT urography gives more information than IVU does (including status of lymph nodes and neighbouring organs). However, CT urography has the disadvantage of higher radiation exposure compared to IVU.

5.4.2 **Ultrasonography**

Ultrasonography (US) is often used as the initial tool to assess the urinary tract. This is not only because it avoids the use of contrast agents, but also because sensitive transducers have improved imaging of the upper urinary tract and bladder.

Transabdominal US permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder. It can be as accurate as IVU for diagnosis of upper urinary tract obstruction (44) (LE: 3). US is therefore a useful tool for detection of obstruction in patients with haematuria, however, it cannot exclude the presence of upper tract tumours.

CIS cannot be diagnosed with imaging methods (IVU, CT urography or US).

5.5 **Urinary cytology**

Examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in high-grade tumours but low sensitivity in low-grade tumours. As a result of loss of cell cohesion in the epithelial lining of the bladder in CIS, there is a larger number of floating cells in the urine, as well as a high degree of anaplasia. The sensitivity of cytology for CIS detection is 28-100% (49) (LE: 2b). Cytology is thus useful when a high-grade malignancy or CIS is present. However, urinary cytology often is negative in the presence of low-grade cancer. Positive voided urinary cytology can indicate a urothelial tumour anywhere in the urinary tract, from the calyx to the ureters, bladder, and proximal urethra. Negative cytology, however, does not exclude the presence of a tumour in the urinary tract.

Cytological interpretation is user-dependent (50). Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations. In experienced hands however, the specificity exceeds 90% (51) (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.

5.6 **Urinary molecular marker tests**

There are specified general requirements for good bladder cancer markers (51):

- The test must be as technically simple as possible (preferably a point-of-care test, with readily available results, easy to perform, with a short learning curve);
- Low cost;
- Good reliability and reproducibility;
- For individual patient populations and clinical situations, the test should have a high specificity to avoid unnecessary workup because of false-positive results, and high sensitivity to avoid the risk of missing a tumour;
- For clinical settings, it is of utmost importance to detect high-risk urothelial cancer before it escapes curative treatment.

Driven by the low sensitivity of urine cytology, extensive laboratory research has developed numerous urinary tests for BC detection (51-57). Considering the frequency of cystoscopy for follow-up, markers for recurrent urothelial cancer would be especially useful.

Numerous reviews of urinary markers have appeared in recent years (51-53,55-65). None of these markers have been accepted as standard diagnostic or follow-up procedures in routine urology or in guidelines. Some urine tests that have been evaluated in several laboratories/centres and in studies with sufficient numbers of patients are listed in Table 5. Sensitivity and specificity should be used to compare studies on urine tests because they remain constant, whereas positive and negative predictive values vary between populations with different numbers of positive and negative events (54,57).

The following conclusions can be drawn about the existing tests. Sensitivity is usually higher at the cost of lower specificity than urine cytology (51-65) (LE: 3). Benign conditions and BCG influence many urinary marker tests (51-65) (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), and follow-up (low/intermediate risk)) (54-57) (LE: 3). For example, sensitivity of a given urinary marker is higher for detection of a primary lesion than a recurrent lesion (54) (LE: 3). Patient selection explains the wide range in performance of the markers listed in Table 5.

Unlike other urine tests, some false-positive results of UroVysion and microsatellite analysis can be attributed to occult disease and thus identify those patients who are more likely to experience subsequent recurrence. It might also be useful to predict response to intravesical therapy (66-68) (LE: 3). Microsatellite analysis is the most promising of the methods listed in Table 5 (69-71).

Table 5: Summary of main urinary markers

Markers (or test specifications)	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumours (%)	Point-of-care test	Level of evidence (LE)
UroVysion	30-86	63-95	66-70	No	3
Microsatellite analysis	58 -92	73-100	90-92	No	1b
Immunocyt/uCyt +	52-100	63-75	62-92	No	3
Nuclear matrix protein 22	47-100	55-98	75-83	Yes	3
BTA stat	29-83	56-86	62-75	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.

5.7 Practical application of urinary cytology and markers

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

- 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 (72,73). The low incidence of BC in the general population and the short lead time impair feasibility and cost-effectiveness (57,72-74). Routine application of screening is not recommended.
- 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. Future studies should explore the feasibility of urine markers preceding/replacing cystoscopy in patients with microscopic haematuria.
- Facilitate surveillance of NMIBC (54,59,75,76).
 - a. 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. Specificity is more important than sensitivity in this subset of patients, because the urinary markers are used as an adjunct to cystoscopy. A urinary marker other than cytology is not recommended for high-risk NMIBC surveillance.
 - b. Follow-up 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/risk recurrences. Several urinary markers are better but still do not detect half of the low-grade tumours that are detected by cystoscopy (54,57) (LE: 3).

According to current knowledge, no urinary marker can replace cystoscopy during follow-up or help to lower cystoscopic frequency in routine fashion. One prospective randomised study confirmed that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy (77) (LE: 1b). It supports the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy. (77).

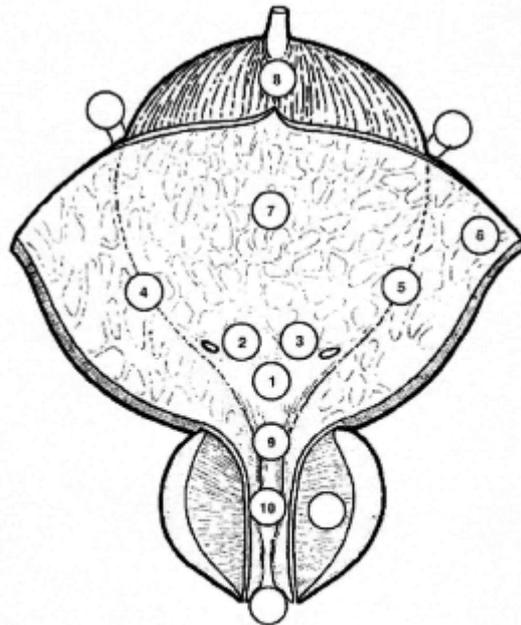
5.8 Cystoscopy

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 (78).

Cystoscopy is initially performed in the office. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance, especially in men (79). Careful inspection of the whole urothelial lining in the bladder should be performed to prevent missing the tumour.

If a bladder tumour has been visualised in earlier imaging studies, diagnostic cystoscopy can be omitted because the patient will undergo TUR (80).

A careful description of the findings is necessary. It should include the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended (Figure 2).



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 = Posterior urethra

Figure 2: Bladder diagram

5.9 Transurethral resection of Ta, T1 bladder tumours

The goal of the TURB in Ta, T1 BC is to make the correct diagnosis and remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of BC.

TUR of the bladder (TURB) should be performed systematically as follows:

- Procedure is initiated with careful bimanual palpation under general or spinal anaesthesia;
- Insertion of the resectoscope, in men under visual guidance, with inspection of the whole urethra;
- Inspection of the whole urothelial lining of the bladder;
- Biopsy from prostatic urethra (if indicated, see lower);
- Cold-cup bladder biopsies (if indicated, see lower);
- Resection of the tumour.

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm) can be resected *en bloc*, which includes the entire tumour and part of the underlying bladder wall. Larger tumours should be resected separately in fractions, including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. This approach provides good information about the vertical and horizontal extent of the tumour and helps to improve resection completeness (81) (LE: 3). Deep resection is not necessary in small, apparently low-grade lesions with a previous history of low-grade Ta (G1) tumour.

- In patients with palpable lesions before TURB, bimanual palpation should be repeated after resection
- The protocol is formulated, which must describe all previous steps of the procedure, as well as extent and completeness of resection
- An order form for pathological evaluation is prepared.

The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers and labelled separately, to enable him/her to make a correct diagnosis. Cauterisation should be avoided as much as possible during TURB to prevent tissue destruction.

Complete and correct TURB is essential to achieve a good prognosis (82). It has been confirmed that absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease

and early recurrence (83) (LE: 2b).

Training in the methods of TURB should be included in teaching programmes. It has been shown that surgical experience can improve TURB results (84).

5.10 Office-based fulguration

In patients with a history of small, low-grade (WHO 2004 classification)/G1 (1973 classification) Ta tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option (85) (LE: 3).

5.11 Bladder- and prostatic urethral biopsies

CIS can present as a velvet-like, reddish area that is indistinguishable from inflammation, or it might not be visible at all.

When abnormal areas of urothelium are seen, it is advised to take cold-cup biopsies or biopsies with a resection loop. Biopsies from normal-looking mucosa, so-called random (mapping) biopsies, should be performed in patients with positive urinary cytology and absence of visible bladder tumour, in addition to upper tract work-up/diagnostics. It is recommended to take biopsies from the trigone, bladder dome, and from the right, left, anterior and posterior bladder walls.

In patients with TaT1 tumours, mapping/random biopsies are not routinely recommended. The likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) (86) (LE: 2a). Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers as specified previously.

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.* (87) showed that in 128 men with T1G3 BC, the incidence of CIS in prostatic urethra was 11.7% (LE:2b). The risk of prostatic urethra or duct involvement seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours (88,89) (LE: 3). When bladder CIS is suspected, or cytology is positive with no evidence of bladder tumour, or abnormalities of prostatic urethra are visible, prostatic urethral biopsies are recommended (87). The biopsy is taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock positions) using a resection loop. In primary NMIBC when stromal invasion is not suspected, a cold-cup biopsy with forceps can be performed (90).

5.12 New TURB techniques

5.12.1 New resection techniques

Compared to monopolar resection, the bipolar electrocautery system may reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) (91) (LE: 3). This benefit however must be confirmed by a prospective trial.

5.12.2 New methods of tumour visualisation

As a standard procedure, cystoscopy and TUR 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.

5.12.2.1 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 (92,93) (LE: 2a). In the systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for both patient (92% versus 71%) and biopsy (93% versus 65%) level analyses (93).

PDD had lower specificity than white light endoscopy (63% versus 81%) (93). False-positivity can be induced by inflammation or recent TUR, and during the first 3 months after BCG instillation (94,95) (LE: 3).

Prospective randomised studies evaluating the impact of ALA fluorescence-guided TURB on disease recurrence rate have shown controversial results (93,96,97).

A large, multicentre, prospective randomised trial that compared HAL fluorescence-guided TURB with standard TURB reported an absolute reduction of no more than 9% in the recurrence rate within 9 months in the HAL arm. Median time to recurrence improved from 9.4 months in the white light arm to 16.4 months in the HAL arm after mean follow-up of 53 and 55 months, respectively (98,99) (LE: 1b).

The value of fluorescence cystoscopy for improvement of the outcome in relation to progression rate or survival remains to be demonstrated.

In summary, PDD improves tumour detection rate, particularly in CIS. HAL but not ALA fluorescence-guided TURB was shown to have a beneficial effect on disease recurrence rate.

Photodynamic diagnosis is recommended in patients who are suspected of harbouring a high-grade tumour, for example, for biopsy guidance in patients with positive cytology or with a history of high-grade tumour. The additional costs of the equipment and instillation for PDD should be taken into account.

5.12.2.2 *Narrow band imaging*

In narrow band imaging (NBI) the contrast between normal urothelium and hypervascular cancer tissue is enhanced by filtering white light into two bandwidths of 415 and 540 nm, which are absorbed by haemoglobin. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection (100) (LE: 3). These findings should be confirmed in large multi-institutional studies.

5.13 **Second resection**

The significant risk of residual tumour after initial TURB of Ta, T1 lesions has been demonstrated (82,101) (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-53% of patients (101-106).

Moreover, the tumour is often understaged by initial resection. The likelihood that a T1 tumour has been understaged and muscle-invasive disease detected by second resection ranges from 4 to 25%. This risk has increased up to 50% in some radical cystectomy series, although these studies have only enrolled selected patients (102,107-109) (LE: 2a). Treatment of a TaT1 high-grade tumour and a T2 tumour is completely different; therefore, correct staging is important.

It has been demonstrated that a second TURB can increase the recurrence-free survival (104,105) (LE: 2a).

A second TURB is recommended in the following situations:

- After incomplete initial TUR;
- If there was no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS;
- In all T1 tumours;
- In all G3 tumours, except primary CIS.

There is no consensus about the strategy and timing of second TURB. Most authors recommend resection at 2-6 weeks after initial TURB. The procedure should include resection of the primary tumour site.

5.14 **Pathological report**

Pathological investigation of the specimen obtained by TURB and biopsies is an essential step in the diagnosis and treatment decision making of bladder cancer.

High quality of resected and submitted tissue is essential for correct pathological assessment. The presence of sufficient muscle is necessary for correct assignment of pT category. Individual biopsies and portions of the tumour should be submitted in separate containers, and labelled individually. Pathologists should obtain from urologists order forms with sufficient clinical information regarding each sample, including the location of each sample.

The pathological report should specify (110):

- location of the evaluated sample (information obtained from the urologist order form);
- grade of each lesion;
- depth of tumour invasion (stage);
- presence of CIS;
- presence of detrusor muscle in the specimen;
- presence of lymphovascular invasion (LVI);
- presence of aberrant histology.

Close cooperation between urologists and pathologists is recommended.

5.15 Guidelines for primary assessment of non-muscle-invasive bladder cancers

Initial diagnosis	GR
Patient history should be taken and recorded regarding all important information with possible connection to bladder cancer, including risk factors and history of suspect symptoms.	A
Renal and bladder US may be used during initial work-up in patients with haematuria.	C
At the time of initial diagnosis of bladder cancer, CT urography or IVU should be performed only in selected cases (e.g., tumours located in the trigone).	B
Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or 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.	C
Voided urine cytology is advocated to predict high-grade tumour before TUR.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C
TURB	
TURB should be performed 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; bimanual palpation after resection; protocol formulation; formulation of order form for pathological evaluation.	C
Perform resection in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B
Perform resection in fractions (including muscle tissue) for tumours > 1 cm in diameter.	B
Biopsies should be taken from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended only when cytology is positive or when exophytic tumour has a non-papillary appearance.	C
Biopsy of the prostatic urethra is recommended for 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
Biopsy of the prostatic urethra should be taken from abnormal areas and from the precollicular area (between 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, fluorescence-guided (PDD) biopsy should be performed 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
The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers and labelled separately.	C
TURB protocol must describe all steps of the procedure, as well as extent and completeness of resection.	C
A second TURB is recommended in the following situations:	A
- after incomplete initial TURB; - if there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS; - in all T1 tumours; - in all G3 tumours, except primary CIS.	
A second TURB should be performed 2-6 weeks after initial resection.	C
Classification and pathological report	
Depth of tumour invasion is classified according to TNM system.	A
For histological classification, 1973 and 2004 WHO grading systems are used. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications should be used.	A
Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.	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 aberrant histology.	C

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 Ta,T1 tumours

The classic way to categorise patients with Ta, T1 tumours with or without concomitant CIS is to divide them into risk groups based on prognostic factors derived from multivariate analyses. Using such a technique, it has been proposed to divide patients into low-, intermediate- and high-risk groups (111). When using these risk groups, however, no distinction is usually drawn between the risk of disease recurrence and disease progression. Although prognostic factors may indicate a high risk of recurrence, the risk of progression might still be low, while other tumours might have a high risk of both recurrence and progression.

In order to predict separately the short-term 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 (GUCCG) has developed a scoring system and risk tables (112). The basis for these tables is the EORTC database, which provides individual patient data for 2,596 patients diagnosed with TaT1 tumours, who were randomised in seven EORTC-GUCCG 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 TUR or receive maintenance BCG. The scoring system is based on the six most significant clinical and pathological factors:

- number of tumours;
- tumour size;
- prior recurrence rate;
- T category;
- presence of concurrent CIS;
- tumour grade.

Table 6 illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 7 shows the total scores stratified, as in the original article (112), into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years.

Table 6: 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 cm	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 (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

Table 7: 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)

Note: Electronic calculators for Tables 6 and 7, 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 during 5-6 months. No immediate postoperative instillation or second TUR was performed in these patients. The scoring system is based on 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 (113). The lower risks in the CUETO tables may be attributed to using BCG, which is a more effective instillation therapy. Validations of the EORTC scoring system using the CUETO patients treated with BCG and in an independent patient population with long-term follow-up has confirmed its prognostic value (114,115) (LE: 2a).

Further prognostic factors have been described in selected patient populations. Female sex and CIS in the prostatic urethra are important prognostic factors in T1G3 patients treated with an induction course of BCG (87) (LE: 2b). Recurrence at 3 months was the most important predictor of progression in T1G2 tumours treated with TURB (116) (LE: 2b). The prognostic value of pathological factors, particularly T1 substaging, has been discussed elsewhere (see Chapter 4.4).

More work is required to determine the role of molecular markers in improving the predictive accuracy of the currently existing risk tables (114,117).

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease (118) (LE: 3). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease and specify the most dangerous cases. Publications are based on retrospective analyses of small series of patients, and their conclusions are not homogeneous. Some studies have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS (119,120), in extended CIS (121) and in CIS in the prostatic urethra (87) (LE: 3).

Various publications have shown that the response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by bladder cancer (113-116). Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders (122-124) (LE: 2a).

6.3 Recommendation for patients' stratification in risk groups

Based on available prognostic factors and particularly data from the EORTC risk tables, the Guidelines Panel recommends stratification of patients into three risk groups that will facilitate treatment recommendations. Their definition, which takes into account the EORTC risk tables probabilities of recurrence and especially progression, can be found in Table 8. The recommendation is similar but not identical to that provided by the International Bladder Cancer Group (125).

For individual prediction of the risk of tumour recurrence and progression at different intervals after TURB, application of EORTC risk tables and calculator is strongly recommended.

Table 8: Risk group stratification

Low-risk tumours	Primary, solitary, Ta, G1 (low grade), < 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: <ul style="list-style-type: none">• T1 tumour• G3 (high grade) tumour• CIS• Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

6.3.1 Recommendations for stratification of NMIBC

	GR
Stratify patients into three risk groups according to Table 8.	B
Application of EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B

7. ADJUVANT TREATMENT

7.1 Intravesical chemotherapy

Although state-of-the-art TUR 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 TUR is incomplete or provokes recurrences in a high percentage of patients (82). It is therefore necessary to consider adjuvant therapy in all patients.

7.1.1 One, immediate, postoperative intravesical instillation of chemotherapy

Early single instillation has been shown to function by the destruction of circulating tumour cells resulting from TUR, and by an ablative effect (chemoresection) on residual tumour cells at the resection site and on small overlooked tumours (126-129) (LE: 3).

In a meta-analysis of 1,476 patients, one immediate instillation of chemotherapy after TUR significantly reduced recurrence rate by 11.7% compared to TUR alone (130) (LE: 1a). The majority of patients (> 80%) in the meta-analysis had a single tumour. A similar efficacy was reported in two more recent studies (131,132), with subgroup analyses suggesting that immediate instillation is most effective in tumour types with the lowest tendency towards recurrence, that is, in single primary or small tumours. Mitomycin C, epirubicin, and doxorubicin have all shown a beneficial effect, with no efficacy comparisons made between the drugs (130) (LE: 1a).

There is evidence from one subgroup analysis and one combined analysis that immediate instillation might have an impact on recurrence even when further adjuvant instillations are given (133,134) (LE: 2a). In contrast, a sufficient number of delayed repeat chemotherapy instillations can also reduce recurrence stemming from tumour implantation (128,133,134). Nevertheless, it is likely that immediate instillation is more effective in preventing recurrence than any of the individual instillations that follow the immediate instillation (128,135) (LE: 3). Clearly, more studies comparing immediate and delayed start regimens are needed.

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 (127,136-138) (LE:

3). In all single instillation studies, the instillation was administered within 24 h. To maximise the efficacy of immediate instillation, one should devise flexible practices that allow the instillation to be given as early as possible, that is, in the recovery room or even in the operating theatre.

Immediate instillation of postoperative chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation, which is most likely to appear in extensive TUR procedures, and in situations with bleeding that requires bladder irrigation. Clear instructions should be given to the nursing staff to control the free flow of the bladder catheter at the end of the instillation. Severe complications have been reported in patients with drug extravasation (139).

7.1.2 **Additional adjuvant intravesical chemotherapy instillations**

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 7 and 8), a single immediate instillation reduces the risk of recurrence and is considered as the standard treatment (130) (LE: 1a). No further treatment should be given in these patients before subsequent recurrence. For other patients, however, a single immediate instillation remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 7 and 8).

A large meta-analysis of 3,703 patients from 11 randomised trials showed a highly significant 44% reduction in the odds of recurrence at 1 year in favour of chemotherapy over TUR alone (140). 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 tumour progression (141,142) (LE: 1a) (see section 7.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than regimens with mitomycin C (MMC) or epirubicin (143-145) (see section 7.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy does (145) (LE: 1a).

It is still controversial for how long and how frequently chemotherapy instillations should be given. From a systematic review of the literature of RCTs, which compared different schedules of intravesical chemotherapy instillations, one can only conclude that the ideal duration and intensity of the schedule remains undefined because of conflicting data (146). The available evidence does not support any treatment longer than 1 year (LE: 3).

7.1.3 **Options for improving efficacy of intravesical chemotherapy**

Some promising data have been presented about enhancing the efficacy of MMC using microwave-induced hyperthermia (Synergo) or electromotive drug administration (EMDA) in patients with high-risk tumours. The current evidence, however, is limited. The number of patients in the prospective series applying the microwave-induced hyperthermia was small and data on progression were inconclusive. In one study of 212 patients comparing BCG with sequential BCG and electromotive MMC, a significant benefit was found in favour of the electromotive arm regarding recurrence and progression (147,148) (LE: 2b). Still, both treatment modalities are considered to be experimental.

One RCT using MMC has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduces the recurrence rate (149) (LE: 1b). Another trial reported that a 1-h instillation of MMC is better than 30 min, but no efficacy comparisons are available for 1- and 2-h instillations (150) (LE: 3).

Another RCT using epirubicin has documented that concentration is more important than treatment duration (151) (LE: 1b). In view of these data, which need confirmation, it seems advisable to ask the patient not to drink on the morning before instillation, and to dissolve the drug in a buffered solution at optimal pH.

7.2 **Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy**

7.2.1 **Efficacy of BCG**

Five meta-analyses have confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy for prevention of recurrence of non-muscle-invasive tumours (143,152-155) (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have been conducted. BCG was compared with combination of epirubicin and interferon (156), MMC (157) or epirubicin alone (144). All of these studies have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). It has been shown that the effect was long lasting (144,157) and was also observed in a separate analysis of patients with intermediate-risk tumours (144).

One meta-analysis (143) 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, a 32% reduction in the risk of recurrence for BCG compared to MMC was found ($P < 0.0001$), whereas there was a 28% increase in the risk of recurrence ($P = 0.006$) 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 (141,142) (LE: 1a). A meta-analysis carried out by the EORTC-GUCG has evaluated data from 4,863 patients (81.6% with papillary tumours and 18.4% with primary or concurrent CIS) 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 (TUR alone, TUR plus intravesical chemotherapy, or TUR plus other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment ($P = 0.0001$). The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS (142). 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 (144) (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 (143).

The conflicting results in the outcomes of the studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. The majority of studies were however able to show 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 by the inclusion of patients who were previously treated with intravesical chemotherapy (158,159). In the most recent meta-analysis, however, BCG maintenance was more effective than MMC also in patients who were previously treated with chemotherapy (143) (LE: 1a).

7.2.2 **Optimal BCG schedule**

Induction BCG instillations are classically given according to the empirical 6-weekly schedule that was introduced by Morales in 1976 (160). For optimal efficacy, BCG must be given in a maintenance schedule (141-143,155) (LE: 1a). In the EORTC-GU group meta-analysis, only patients who received maintenance BCG benefited. Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks, to 27 over 3 years (161). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective (142). In their meta-analysis, Böhle et al. concluded that at least 1 year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression (141,155) (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations remain unknown (162). However, in an RCT of 1,355 patients, the EORTC has recently shown that when BCG is given at full dose, 3 years maintenance reduces the recurrence rate as compared to 1 year in high-risk but not in intermediate-risk patients. There were no differences in progression or overall survival (159) (LE: 1b). The benefit of the two additional years of maintenance in the high-risk patients should be weighed against its added costs and inconveniences.

7.2.3 **BCG toxicity**

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy (145) (LE: 1a). Serious side effects however are encountered in < 5% of patients and can be treated effectively in almost all cases (163) (LE: 1b). It has been shown that maintenance schedule is not associated with increased risk of side effects comparing to induction course (163).

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

BCG should not be administered (absolute contraindications):

- during the first 2 weeks after TUR;
- in patients with macroscopic haematuria;
- after traumatic catheterisation;
- in patients with symptomatic urinary tract infection.

The presence of leukocyturia or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases (164,165) (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (immunosuppression, human immunodeficiency virus (HIV) infection) (166), although some small studies have shown similar efficacy and no increase in complications comparing to non-immuno-compromised patients (167,168) (LE: 3).

The management of side effects after BCG should reflect their type and grade. Recommendations for individual situations have been provided by the International Bladder Cancer Group (IBCG) and by a Spanish group (169,170) (Table 9).

Table 9: Management options for side effects associated with intravesical BCG (169,171,172)

Management options for local side effects (modified from IBCG group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or NSAIDs
	If symptoms improve within a few days: continue instillations
	If symptoms persist or worsen: <ol style="list-style-type: none"> Postpone the instillations Perform a urine culture Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: <ol style="list-style-type: none"> With positive culture: antibiotic treatment according to sensitivity. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (to repeat cycle if necessary) (173).
	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 (172)	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 h, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs and if no/partial response proceed to corticosteroids, high-dose quinolones or antituberculous drugs (171).
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 ≥ 2 antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post TURBT (if no signs and symptoms of haematuria).
	Cessation of BCG
	For severe infection: <ul style="list-style-type: none"> - High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. - Early, high-dose corticosteroids as long as symptoms persist. Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or Enterococcus.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

7.2.4 **Optimal dose of BCG**

To reduce BCG toxicity, instillation of a reduced dose was proposed.

Comparing one-third dose to full-dose BCG in 500 patients, CUETO found no overall difference in efficacy. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours (174, 175) (LE: 1b). Although fewer patients have reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar in the standard- and reduced-dose groups. The same Spanish group has shown in a prospective RCT that 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 for prevention of recurrence with no decrease in toxicity (176) (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full dose BCG, however, the former was associated with a higher recurrence rate, especially when it was given only for 1 year (159) (LE: 1b).

7.2.5 **BCG strain**

There is no conclusive evidence that there may be a difference in clinical efficacy between various BCG strains.

7.2.6 **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 8):

- BCG does not alter the natural course of low-risk tumours (Table 8), and could be considered as overtreatment for this patient category.
- In patients with high-risk tumours, for whom radical cystectomy is not carried out, 1-3 years full-dose maintenance BCG is indicated. The additional beneficial effect of the second and third years of maintenance on recurrence in high-risk patients should be weighed against its added costs and inconveniences.
- In intermediate-risk patients, full-dose BCG with 1 year maintenance is more effective than chemotherapy for prevention of recurrence; however, it has more side effects than chemotherapy. For this reason both BCG with maintenance and intravesical chemotherapy remain an option. The final choice should reflect the individual patient's risk of recurrence and progression as well as efficacy and side effects of each treatment modality.

7.3 **Specific aspects of treatment of CIS**

7.3.1 **Treatment strategy**

If concurrent CIS is found in association with MIBC, therapy is determined according to the invasive tumour. The detection of CIS with TaT1 tumours increases the risk of recurrence and progression of TaT1 tumours (112,113) and further treatment is mandatory. The treatment strategy is generally based on the criteria that are summarised in Chapters 7.1, 7.2, 7.4 and 8.

CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy (LE: 4). No consensus exists about whether conservative therapy (intravesical BCG instillations) or aggressive therapy (radical cystectomy) should be done. There has been a lack of randomised trials of instillation therapy and early radical cystectomy as immediate primary treatment. Tumour-specific survival rates after early radical cystectomy for CIS are excellent, but as many as 40-50% of patients might be overtreated (177) (LE: 3).

7.3.2 **Cohort studies**

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG (118-121,178) (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence (121,161,178,179) (LE: 3).

7.3.3 **Prospective randomised trials**

Unfortunately, there have been few randomised trials in patients with CIS alone. Thus, the power to detect differences in treatment results has been low and the reliability of the conclusions is limited (177).

A meta-analysis of clinical trials that has compared intravesical BCG to intravesical chemotherapy (MMC, epirubicin, or adriamycin) 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 (OR = 0.41, $P = 0.0001$). In trials that have compared BCG with MMC, the long-term benefit of BCG was smaller, but BCG was superior to MMC in trials with BCG maintenance (OR = 0.57, $P = 0.04$) (180) (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different

immunotherapy (OR = 0.65, 95% CI = 0.36-1.16, $P = 0.10$) (142) (LE: 1b). There has been no single trial that has demonstrated superiority of combined BCG and MMC over BCG alone (181).

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).

7.3.4 Treatment of extravascular CIS

Patients with CIS are at high risk of extravascular involvement: in the upper urinary tract and in the prostatic urethra. Solsona et al. have found that 87 of 138 patients (63%) with CIS developed extravascular involvement initially or during follow-up (182). Patients with extravascular involvement had worse survival than those with bladder CIS alone (182) (LE: 3).

In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts (177). These situations should be distinguished from tumour invasion into the prostatic stroma, which is staged as T4a, 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 (78,177,183) (LE: 3).

In patients with prostatic duct involvement, there are promising results, but only from short series, so the data are insufficient to provide clear treatment recommendations (184). No conclusive results have been obtained with conservative therapy, therefore, radical surgery should be considered (183) (LE: 3).

Treatment of CIS that involves the upper urinary tract is discussed in the Guidelines on Urothelial Carcinomas of the Upper Urinary Tract.

7.4 Treatment of failure of intravesical therapy

7.4.1 Failure of intravesical chemotherapy

Patients with non-muscle-invasive recurrence of BC after chemotherapy regimen can profit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation (143) (LE: 1a).

7.4.2 Recurrence and failure after intravesical BCG immunotherapy

Table 10: Categories of unsuccessful treatment with intravesical BCG

BCG failure	
Whenever a muscle-invasive tumour is detected during follow-up.	
BCG-refractory tumour:	
	1. If high-grade, non-muscle-invasive papillary tumour is present at 3 months (185). Further conservative treatment with BCG is connected with increased risk of progression (122,186) (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 (42) 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 (187) (LE: 3).*	
BCG intolerance	
Severe side effects that prevent further BCG instillation before completing induction (170).	

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

7.4.3 Treatment of BCG failure and recurrences after BCG

Treatment recommendations are provided in Table 11. They reflect categories mentioned in the previous paragraph and tumour characteristics at the time of recurrence.

Patients with BCG failure are unlikely to respond to further BCG therapy; therefore, radical cystectomy is the preferred option. The results of various studies suggests that repeat BCG therapy is appropriate for non-high-grade and even for some high-grade recurrent tumours (188,189) LE: 3).

Additionally, there are now several bladder preservation strategies available that can be categorised as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy (190). Changing from BCG to these options can yield responses in selected cases with BCG treatment failure for NMIBC (188, 191-199) (LE: 3). However, experience is limited and treatments other than radical cystectomy must be considered oncologically inferior at the present time (122,185,186) (LE: 3).

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

	GR
The type of intravesical therapy should be based on the risk groups shown in Tables 8 and 11.	A
One immediate chemotherapy instillation is recommended in tumours presumed to be at low or intermediate risk.	
In patients with low-risk Ta tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with intermediate-risk Ta T1 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.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG is an option.	C
In patients at highest risk of tumour progression (Table 11), immediate radical cystectomy should be considered.	C
In BCG refractory tumours, radical cystectomy is indicated.	B
Intravesical chemotherapy.	
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation (after extensive TURB, or bleeding requiring bladder irrigation).	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined and 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 during instillation by reducing fluid intake.	B
The length of individual instillation should be 1-2 hours.	C
BCG intravesical immunotherapy.	
Absolute contraindications of BCG intravesical instillation are: during the first 2 weeks after TUR; in patients with macroscopic haematuria; after traumatic catheterization; and in patients with symptomatic urinary tract infection.	C
The management of side effects after BCG intravesical instillation should reflect their type and grade (Table 9).	C

8. RADICAL CYSTECTOMY FOR NON-MUSCLE-INVASIVE BLADDER CANCER

If cystectomy is indicated before pathologically confirmed progression into muscle-invasive tumour, immediate (immediately after NMIBC diagnosis) and early (after BCG failure) radical cystectomy can be distinguished.

There are several reasons to consider radical cystectomy 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 radical cystectomy (90,108,200-211) (LE: 3).
- Some patients with non-muscle invasive tumours experience disease progression in muscle-invasive disease (Table 7).
- It has been shown retrospectively that patients with high-risk NMIBC who undergo early rather than delayed cystectomy for tumour relapse after initial treatment with TURB and BCG have a better survival rate (212) (LE: 3).

Potential benefit of radical cystectomy must be weighed against the risk, morbidity, and impact on quality of life of radical cystectomy. It is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour who are at highest risk of progression. These are (35,87,112,113) (LE: 3):

- multiple and/ or large (> 3 cm) T1, high-grade (G3) tumours;
- T1, high-grade (G3) tumours with concurrent CIS;
- recurrent T1, high-grade (G3) tumours;
- T1G3 and CIS in prostatic urethra;
- micropapillary variant of urothelial carcinoma.

It is recommended to discuss immediate radical cystectomy and conservative treatment with BCG instillation. Patients should be informed about the benefits and risks of both approaches. Individual factors like gender and age of the patient should be considered because of worse prognosis between females and life-long risk of progression after BCG in high risk tumours.

Radical cystectomy is strongly recommended in patients with BCG refractory tumours, as mentioned above. Delay of radical cystectomy might lead to decreased disease-specific survival (213) (LE: 3). In patients in whom radical cystectomy is performed at the time of pathological non-muscle-invasive disease, the 5-year disease-free survival rate exceeds 80% (214-219) (LE: 3).

Table 11: Treatment recommendations in TaT1 tumours according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, 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: <ul style="list-style-type: none"> • T1 tumours • G3 tumours • CIS • Multiple <u>and</u> recurrent <u>and</u> large (> 3 cm) Ta G1G2 tumours (all these conditions must be presented) 	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, micropapillary variant of urothelial carcinoma	Cystectomy should be considered
	BCG refractory tumours	Cystectomy is recommended

Table 12: 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 not suitable for cystectomy	B
High-grade recurrence after BCG	1. Radical cystectomy 2. Repeat BCG course 3. Bladder-preserving strategies	C
Non-high-grade recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

9. FOLLOW-UP OF PATIENTS WITH NON-MUSCLE-INVASIVE BLADDER TUMOURS

As a result of the risk of recurrence and progression, patients with TaT1 bladder tumours and with CIS 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 and 7), we are able to predict the short- and long-term risks of recurrence and progression in individual patients, and can adapt the follow-up schedule accordingly (112). When planning the follow-up schedule and methods the following aspects should be considered:

- *The prompt detection of muscle-invasive and high-grade 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 low grade.*
Small, non-invasive (Ta), low-grade papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy (220-227) (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden (85) (LE: 3). Some authors have even defended temporary surveillance in selected cases (226-228) (LE: 3).
- *The first cystoscopy after TUR at 3 months is a very important prognostic indicator for recurrence and progression (112,116,122,229-231) (LE: 1a).* The first cystoscopy should thus always be performed 3 months after TUR in all patients with TaT1 BC.
- *In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low (230) (LE: 3).* Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered (231).
- *In tumours originally at intermediate or high risk, recurrences after 10 years tumour-free interval are not unusual (232) (LE: 3).* Therefore, lifelong follow-up is recommended (231).
- *The risk of upper urinary tract recurrence increases in patients with multiple and high-risk tumours (47) (LE: 3).*
- *Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy (77) (LE: 1b).* It supports the adjunctive role of urine tests during follow-up.

No non-invasive method has been proposed that can replace endoscopy, therefore, follow-up is based on regular cystoscopy (Section 5.8). There has been a lack of randomised studies that have investigated the possibility of safely reducing the frequency of follow-up cystoscopy. The following recommendations are therefore based mostly on retrospective experience.

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

	GR
The follow-up of TaT1 tumours 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 TaT1 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
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

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11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

5-ALA	5-aminolaevulinic acid
ASR	age standardised incidence rate
BCG	bacillus Calmette-Guérin
BTA	bladder tumour antigen
CIS	carcinoma <i>in situ</i>
CT	computed tomography
CUETO Club	Urológico Español de Tratamiento Oncológico (Spanish Oncology Group)
EAU	European Association of Urology
EORTC	European Organization for Research and Treatment of Cancer
EORTC-GUCG	EORTC Genito-Urinary Cancer Group
FISH	fluorescence in situ hybridisation
GR	grade of recommendation
HAL	hexaminolaevulinic acid
ISUP	International Society of Urological Pathology
IVU	intravenous urography
LE	level of evidence
MMC	mitomycin C
NMIBC	non-muscle-invasive bladder cancer
NVP	negative predictive value
PDD	photodynamic diagnosis
PUNLMP	papillary urothelial neoplasms of low malignant potential
RCT	randomised controlled trial
TCC	transitional cell carcinoma
TNM	tumour, node, metastasis
TUR	transurethral resection
UICC	Union International Contre le Cancer
US	ultrasonography
WHO	World Health Organization

Conflict of interest

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