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

M. Babjuk (chair), A. Böhle, M. Burger, E. Compérat, E. Kaasinen, J. Palou, B.W.G. van Rhijn, M. Rouprêt, S. Shariat, R. Sylvester, R. Zigeuner

European Association of Urology

TABLE OF CONTENTS PAGE

1. BACKGROUND

1.1 Introduction

This overview represents the updated European Association of Urology (EAU) guidelines for non-muscle-invasive bladder cancer (NMIBC): CIS and Ta, T1. 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.

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including a pathologist and a statistician.

It must be emphasized 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 expertize when making treatment decisions for individual patients, which involves taking into account personal values and preferences and the individual circumstances of patients.

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 NMIBC 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 in 2013 on NMIBC were considered. The literature searches focused on identification of all level 1 scientific papers (randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses of RCTs) in accordance with 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 according to the listings in Tables 1 and 2, which are 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 randomized trials.
1b	Evidence obtained from at least one randomized trial.
2a	Evidence obtained from one well-designed controlled study without randomization.
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 (4).*

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

Alternatively, the absence of a high LE does not necessarily preclude a grade A recommendation, provided there is overwhelming clinical experience and consensus. There may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons; in this situation, 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 this is 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 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 randomized trial.
B	Based on well-conducted clinical studies, but without randomized clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

**Modified from (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 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. The complete updated guidelines for NMIBC were prepared in 2006, 2008, 2009, 2011 and 2013 (9-13). Since 2011 the EAU Guidelines on Ta, T1 tumours and CIS have been integrated into one guidelines document (1).

Several scientific summaries have been published in the EAU scientific journal, European Urology (14-20). A quick reference document (pocket guidelines) is available presenting the main findings of the NMIBC Guidelines, including a separate document on the diagnosis and treatment of urothelial carcinoma in situ (16). 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/.

1.3.1 Summary of changes

For all chapters in these guidelines the literature has been assessed and has resulted in the inclusion of 23 new publications. Two new treatment algorithms have been provided: 'Management of patients with a primary or recurrent BC without previous BCG' and 'Management of patients with recurrence after intravesical BCG for NMIBC'.

A short new section on smoking cessation was added (see Section 7). Minor changes were performed in Chapters 3, 4.5, 5.5, 5.12.2, 5.13, 5.14, 5.15, 6.1, 8.1.1, 8.2.3, 8.4.3, 8.5 and 9.

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/.

1.5 References

1. Rouprêt M, Babjuk M, Compérat E, et al. EAU Guidelines on Urothelial Carcinomas of the Upper Urinary Tract. In: EAU Guidelines. Edition presented at the EAU Annual Congress Stockholm 2014. ISBN 978-90-79754-65-6.
2. Witjes JA, Compérat E, Cowan NC, et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. In: EAU Guidelines. Edition presented at the EAU Annual Congress Stockholm 2014. ISBN 978-90-79754-65-6.
3. Gakis G, Witjes JA, Compérat E, et al. Guidelines on Primary Urethral Carcinoma. Edition presented at the EAU Annual Congress Stockholm 2014. ISBN 978-90-79754-65-6.
4. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. http://www.cebm.net/index.aspx?o=1025 [Access date January 2014].
5. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004 Jun;328(7454):1490. http://www.ncbi.nlm.nih.gov/pubmed/15205295
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr;336(7650):924-6. http://www.ncbi.nlm.nih.gov/pubmed/18436948
7. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Going from evidence to recommendations. BMJ 2008 May;336(7652):1049-51. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376019/
8. Oosterlinck W, Jakse G, Malmström P-U, et al. EAU Guidelines on Bladder Cancer. In: EAU Guidelines. Edition presented at the EAU Annual Congress Brussels 2000.

9. Oosterlinck A, Van der Meijden A, Sylvester R et al. EAU Guidelines on Ta, T1 (non-muscle-invasive) Bladder Cancer. In: EAU Guidelines. Edition presented at the EAU Annual Congress Paris, 2006. ISBN 90-70244-37-3.
10. Babjuk M, Oosterlinck W, Sylvester R, et al. EAU Guidelines on Ta, T1 (Non-muscle-invasive) Bladder Cancer. In: EAU Guidelines. Edition presented at the EAU Annual Congress Milan 2008. ISBN 978-90-70244-91-0.
11. Babjuk M, Oosterlinck W, Sylvester R, et al. EAU Guidelines on Ta, T1 (non-muscle invasive) Bladder Cancer. In: EAU Guidelines. Edition presented at the EAU Annual Congress Stockholm 2009. ISBN 978-90-79754-09-0.
12. Babjuk M, Oosterlinck W, Sylvester R, et al. EAU Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1 and CIS). In: EAU Guidelines. Edition presented at the EAU Annual Congress Congress Vienna 2011. ISBN 978-90-79754-83-0.
13. Babjuk M, Oosterlinck W, Sylvester R, et al. EAU Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1 and CIS). In: EAU Guidelines. Edition presented at the EAU Annual Congress Congress Milan 2013. ISBN 978-90-79754-71-7.
14. Oosterlinck W, Lobel B, Jakse G, et al; European Association of Urology (EAU) Working Group on Oncological Urology. Guidelines on bladder cancer. Eur Urol 2002 Feb;41(2):105-12. http://www.ncbi.nlm.nih.gov/pubmed/12074395
15. Oosterlinck W, Solsona E, van der Meijden AP, et al; European Association of Urology. EAU guidelines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. Eur Urol 2004 Aug;46(2):147-54. http://www.ncbi.nlm.nih.gov/pubmed/15245806
16. Van der Meijden AP, Sylvester R, Oosterlinck W, et al; for the EAU Working Party on Non Muscle Invasive Bladder Cancer. EAU guidelines on the diagnosis and treatment of urothelial carcinoma in situ. Eur Urol 2005 Sep;48(3):363-71. http://www.ncbi.nlm.nih.gov/pubmed/15994003
17. Babjuk M, Oosterlinck W, Sylvester R, et al; European Association of Urology (EAU). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008 Aug;54(2):303-14. http://www.ncbi.nlm.nih.gov/pubmed/18468779
18. Rouprêt M, Zigeuner R, Palou J, et al. European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. Eur Urol 2011 Apr;59(4):584-94. http://www.ncbi.nlm.nih.gov/pubmed/21269756
19. Babjuk M, Oosterlinck W, Sylvester R, et al; European Association of Urology (EAU). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. Eur Urol 2011 Jun;59(6):997-1008. http://www.ncbi.nlm.nih.gov/pubmed/21458150
20. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013 Oct;64(4):639-53. http://www.ncbi.nlm.nih.gov/pubmed/23827737

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-standardized incidence rate is 9 per 100,000 for men and 2 per 100,000 for women (2008 data) (1). In the European Union (EU), the age-standardized incidence rate is 27 per 100,000 for men and six per 100,000 for women (1).

The incidence of BC varies between regions and countries; in Europe, the highest age-standardized 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 are partly caused by the different methodology and quality of data collection, so care should be taken in interpreting the results (2,3).

Worldwide age-standardized mortality rate is 3 for men versus 1 per 100,000 for women. In the EU, the age-standardized 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 the decreased impact of causative agents, mainly smoking and occupational exposure (4). Mortality from BC has also decreased, possibly reflecting an increased standard of care (5).

Approximately 75% of patients with BC present with a disease 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).

3. RISK FACTORS

Increasing evidence suggests that genetic predisposition has a significant influence on the incidence of BC, especially via its impact on susceptibility to other risk factors (3,6). Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases (3,7) (LE: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted. Tobacco smoking was a pronounced risk factor in recent prediction models of BC (8,9).

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 (3,10-12) (LE: 3). In developed industrial settings, these risks have been reduced by the work safety guidelines so that chemical workers no longer have a higher incidence of BC compared to the general population (13).

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 (3,14) (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 (15,16).

Exposure to ionizing radiation is connected with increased risk (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 BC (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 of the bladder (TURB), and are therefore 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. The terms NMIBC and superficial BC are therefore suboptimal descriptions. Superficial BC should no longer be used. Whenever 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 (7th version), but it has no changes for bladder tumours (Table 3) (17).

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 *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 classification of non-invasive urothelial tumours (18,19) (Table 4). Its major contribution is a detailed histological description of individual 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.

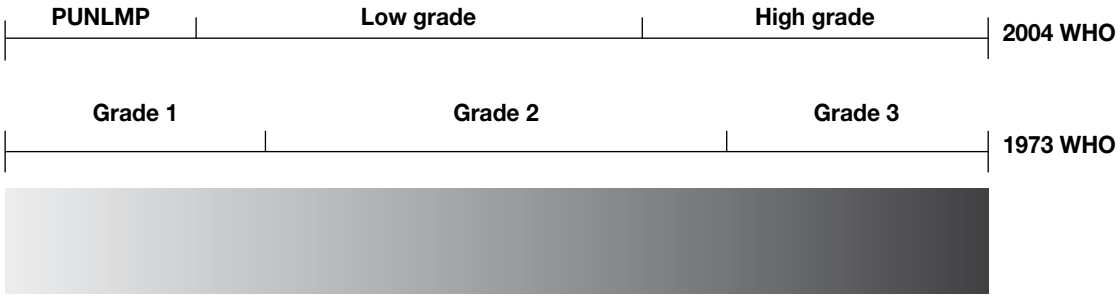
Table 4: WHO grading in 1973 and in 2004 (18,19)

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
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 is always high-grade (HG)
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

Table 4 provides details of the 1973 and 2004 WHO grading systems. 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, some of which might have been classified as G1 in the 1973 WHO. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur. The category of PUNLMP is reserved for Ta tumours only. The intermediate grade (Grade 2) of the 1973 WHO classification, which was the subject of controversy, has been eliminated from the 2004 WHO classification (20-22) (Figure 1). The published comparisons, however, have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification (23,24).

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 (20-23,25-27) (LE: 2a). 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. Until the WHO 2004 system is validated by more prospective trials and incorporated into prognostic models, both classifications should be used.

Figure 1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications (22)*



**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.

4.4 Inter- and intra-observer 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 (28,29) (LE: 2a). There is 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% (23,28-33) (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 (34-37) (LE: 3); nevertheless it is not recommended in the WHO classification. The presence of lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours (38) (LE: 3). It must be presented in pathological reports.

Detection of several variants of urothelial carcinoma (such as the micropapillary variant, the nested variant, the plasmocytoid, sarcomatoid or squamous variants of urothelial carcinoma) represents a poor prognostic factor even if it is non-muscle invasive at the time of diagnosis (39,40,42-44) (LE: 3). In the presence of these variants, distant metastases even in T1 tumours have been reported (39) (LE: 3). Moreover, the risk of understaging in these tumours is substantial (41) (LE: 3).

Novel molecular markers, particularly FGFR3 mutation status, are promising but need further evaluation (20,37,45-47).

4.6 Specific character of CIS and its clinical classification

Carcinoma *in situ* (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 (48).

Classification of CIS into clinical type (49):

- 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

The patient history should be taken, including all information possibly associated with BC, including risk factors and a history of suspicious 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). Carcinoma *in situ* might be suspected in patients who do complain of these symptoms, particularly in those with irritative LUTS refractory to symptomatic treatment.

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 (50-52) (LE: 2a). The incidence of upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone (51) (LE: 2b). The risk of tumour recurrence in the upper urinary tract during follow-up increases in multiple and high-risk tumours (53) (LE: 2b).

Computed tomography (CT) urography is the preferred method of urinary tract imaging. IVU can be an alternative if CT is not available (54) (LE: 3). Particularly 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 **Ultrasound***

Ultrasound (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 characterization of renal masses, detection of hydronephrosis, and visualization of intraluminal masses in the bladder. It can be as accurate as IVU for diagnosis of upper urinary tract obstruction (50) (LE: 3). Ultrasound is therefore a useful tool for detection of obstruction in patients with haematuria. However, it cannot exclude the presence of upper tract tumours.

The diagnosis of CIS cannot be made with imaging methods (IVU, CT urography 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 high-grade tumours but low sensitivity in low-grade tumours. It is considered useful for detection of CIS, where its sensitivity is 28-100%. (55) (LE: 2b). Cytology is useful, particularly as an adjunct to cystoscopy, when a high-grade malignancy or CIS is present. However, urinary cytology is often negative in the presence of low-grade cancer. Positive voided urinary cytology can indicate an urothelial tumour anywhere in the urinary tract,

from the calyx to the ureters, bladder, and proximal urethra. However, negative cytology does not exclude the presence of a tumour in the urinary tract.

Cytological interpretation is user-dependent (56). Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, but in experienced hands, specificity exceeds 90% (57) (LE: 2b).

Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis. One cytospin slide from the sample is usually sufficient (58). In patients with suspect cytology it is reasonable to repeat the investigation (59) (LE: 3). In patients with positive cytology, but negative cystoscopy, it is necessary to exclude a tumour in the upper tract (CT-urography), CIS in the bladder (random biopsies or photodynamic diagnosis (PDD) targeted biopsies) and tumour in prostatic urethra (prostatic urethra biopsy).

5.6 Urinary molecular marker tests

There are specified general requirements for good bladder cancer markers (57):

- 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 high specificity to avoid unnecessary work-up 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 (57,60-65). 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 (57,60,61,63-73). 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 (62,65).

The following conclusions can be drawn about the existing tests. Sensitivity is usually higher and at the cost of lower specificity compared to urine cytology (57,60-73) (LE: 3). Benign conditions and BCG influence many urinary marker tests (57,60-73) (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)) (62-65) (LE: 3). For example, the sensitivity of a given urinary marker is higher for detection of a primary lesion than a recurrent lesion (62) (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 likely to experience subsequent recurrence. It might also be useful in predicting a response to intravesical therapy (74-76) (LE: 3). Microsatellite analysis is the most promising of the methods listed in Table 5 (77-79).

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.

*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 (80,81). The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness (65,80-82). 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. Future studies should explore the feasibility of urine markers preceding/replacing cystoscopy in patients with microscopic haematuria.

*5.7.3 **Surveillance of NMIBC***

Research has been carried out into the usefulness of urinary cytology versus markers in follow-up of NMIBC (62,67,83,84).

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. 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.

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 detected 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 routine fashion. One prospective randomized study confirmed that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy (85) (LE: 1b). It supports the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy (85).

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

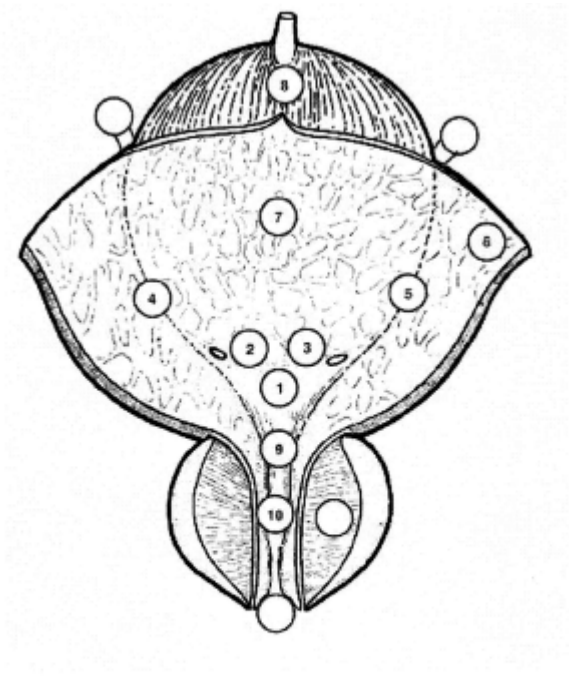
histological evaluation of multiple bladder biopsies (86).

Cystoscopy is initially performed in the office. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance, especially in men (87). Careful inspection of the whole urothelial lining in the bladder should be performed to prevent missing the tumour.

If a bladder tumour has been visualized in earlier imaging studies, diagnostic cystoscopy can be omitted because the patient will undergo TURB (88).

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).

Figure 2: Bladder diagram



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

5.9 Transurethral resection of Ta, T1 bladder tumours

Knowledge of cytology at the time of TURB can be beneficial for patient management. The goal of 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.

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 below);
- Cold-cup bladder biopsies (if indicated, see below);
- Resection of the tumour.

*5.9.1 **Resection of 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 (89) (LE: 3);

- Deep resection is not necessary in small, apparently LG (G1) lesions with a previous history of LG (G1) Ta 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 the 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;
- Cauterization should be avoided as much as possible during TURB to prevent tissue destruction.

Complete and correct TURB is essential to achieve a good prognosis (90). It has been confirmed that the absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and early recurrence (91) (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 (92).

5.10 Office-based fulguration

In patients with a history of small, LG/G1 Ta tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option (93) (LE: 3).

5.11 Bladder and prostatic urethral biopsies

Carcinoma *in situ* can present as a velvet-like, reddish area indistinguishable from inflammation. However, CIS may 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 the 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. If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy in these patients (see 5.12.2.1).

In patients with Ta, T1 tumours, mapping/random biopsies are not routinely recommended. The likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) (94) (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. (95) 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 (96,97) (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 (95). 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 (98).

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) (99) (LE: 3). This benefit, however, has yet to be confirmed by a prospective trial.

5.12.2 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.

5.12.2.1 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 (100,101) (LE: 2a). In the 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 TUR and during the first 3 months after BCG instillation (102,103) (LE: 3). Prospective randomized studies evaluating the impact of ALA fluorescence-guided TURB on disease recurrence rate have given controversial results (101,104,105).
A large, multicentre, prospective, randomized trial that compared HAL fluorescence-guided TURB with standard TURB reported an absolute reduction of ≤ 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 a mean follow-up of 53 and 55 months, respectively (106,107) (LE: 1b).

A raw-data based meta-analysis of controlled trials comparing HAL fluorescence-guided TURB with standard TURB reported an increase in detection of tumour lesions across all risk groups, but an absolute reduction of ≤ 10% in recurrence rates within 12 months in the HAL arms (108) (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 (109).
The value of fluorescence cystoscopy for improvement of outcome in relation to progression rate, survival and clinical management remains to be demonstrated.

Photodynamic diagnosis is recommended in patients who are suspected of harbouring a high-grade tumour, e.g., 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 (110) (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 (90,111) (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-53% of patients, after resection of TaG3 tumour in 41.4% (111-117).

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 4-25%. This risk has increased up to 50% in some radical cystectomy series, although these studies have only enrolled selected patients (112,118-120) (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 (114,115) (LE: 2a).
A second TURB is recommended in the following situations:

- after incomplete initial TURB;
- if there was no muscle in the specimen after initial resection, with exception of TaG1 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 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 process for BC.

A high quality of resected and submitted tissue is essential for correct pathological assessment. The presence of sufficient muscle is necessary for correct assignment of T 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 (121):

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

Close co-operation between urologists and pathologists is recommended.

5.15 Guidelines for primary assessment of NMIBC

Initial diagnosis	GR
Patient history should be taken and recorded regarding all important information with a possible association with BC, including risk factors and suspicious symptoms.	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 BC, 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 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.	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
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 the extent and completeness of resection.	C
A second TURB is recommended in the following situations: • after incomplete initial TURB; • if there is no muscle in the specimen after initial resection, with exception of TaG1 tumours and primary CIS; • in all T1 tumours; • in all G3 tumours, except primary CIS.	A
When done, a second TURB should be performed within 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, both the 1973 and 2004 WHO grading systems should be used. Until the WHO 2004 is validated by more prospective trials and incorporated into prognostic models, 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 unusual histology.	C

CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; US = ultrasound; TURB = transurethral resection of the bladder.

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 Ta, T1 tumours

The classic way to categorize 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 (122). 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- 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 (123). The basis for these tables is the EORTC database, which provides individual patient data for 2596 patients diagnosed with Ta, T1 tumours, who were randomized into seven EORTC-GUCG trials. Patients with CIS alone were not included. Seventy-eight per cent 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 (123), into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years (LE: 2a).

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)

NB: 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 1062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received 12 instillations over 5-6 months. No immediate post-operative instillation or second TUR 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 (124) (LE: 2a). The lower risks in the CUETO tables may be attributed to using BCG, which is a more effective instillation therapy. 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 (125,126) (LE: 2a). The CUETO risk calculator is available at: http://www.aeu.es/Cueto.html.

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 (95) (LE: 2b). Recurrence at 3 months was the most important predictor of progression in T1G2 tumours treated with TURB (127) (LE: 2b). The prognostic value of pathological factors, particularly T1 substaging and unusual pathologies, has been discussed elsewhere (see Chapter 4.5). More work is required to determine the role of molecular markers in improving the predictive accuracy of currently existing risk tables (125,128).

Special attention must be offered to patients with T1G3 tumours in bladder (pseudo)diverticulum because of an absence of muscle layer in diverticular wall (129) (LE: 3).

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 and specify the most dangerous cases. Publications are based on retrospective analyses of a 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 (95) (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 BC (124-127). Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders (134-136) (LE: 2a).

6.3 Recommendation to stratify 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 that will facilitate treatment recommendations. Table 8 provides a definition of these risk groups, which takes into account the EORTC risk tables' probabilities of recurrence and especially progression. The recommendation is similar but not identical to that provided by the International Bladder Cancer Group (137).

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

Table 8: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, Ta, G1 (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 11.*
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 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. COUNSELLING OF SMOKING CESSATION

It has been confirmed that smoking increases the risk of tumour recurrence and progression. Moreover, in BC patients who previously smoked, improved outcomes have been reported following smoking cessation (138-142) (LE: 2-3). All smokers with confirmed NMIBC should be advised to stop smoking.

8. ADJUVANT TREATMENT

8.1 Intravesical chemotherapy

Although state-of-the-art 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 TURB is incomplete or provokes recurrences in a high percentage of patients (90). It is therefore necessary to consider adjuvant therapy in all patients.

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

Early single instillation 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 (143-146) (LE: 3).

Three large meta-analyses comprising 1476 to 3103 patients have consistently shown that one immediate instillation of chemotherapy after TURB significantly reduced the recurrence rate by 11.7% to 13.0% compared to TURB alone (147-149) (LE: 1a). Although none of the three meta-analyses adequately answered the question concerning which patients benefitted the most from an immediate instillation, some underpowered data from two subgroup analyses (150,151) suggest that immediate instillation is most effective in tumour types with the lowest tendency towards recurrence, i.e., in single primary or small tumours. Mitomycin C, epirubicin, and doxorubicin have all shown a beneficial effect; no efficacy comparisons have been made (147-149) (LE: 1a).

There is evidence from one subgroup and one combined analysis that immediate instillation might have an impact on recurrence, even when further adjuvant instillations are given (152,153) (LE: 2a). In contrast, a sufficient number of delayed repeat chemotherapy instillations can also reduce recurrence stemming from tumour implantation (145,152,153). Nevertheless, it is likely that immediate instillation is more effective in preventing recurrence than any of the individual instillations that follow the immediate instillation (145,154) (LE: 3). 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 (144,155-157) (LE: 3). In all single-instillation studies, the instillation was administered within 24 hours. To maximize the efficacy of immediate instillation, 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.

Immediate instillation of post-operative chemotherapy should be omitted in any case of overt or suspected intra- or extra-peritoneal perforation, which is most likely to appear in extensive TURB procedures, and in situations with bleeding that require 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 (158).

8.1.2 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 to be the standard treatment (147) (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 3703 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 (159). 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 (160,161) (LE: 1a) (see Section 8.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than regimens with mitomycin C (MMC) or epirubicin (162-164) (see Section 8.2.1) (LE: 1a). However, BCG causes significantly more side effects than does chemotherapy (164) (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 (165). The available evidence does not support any treatment longer than one year (LE: 3).

8.1.3 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 using microwave-

induced hyperthermia was small with inconclusive data on progression. 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 (166,167) (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 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, 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.

8.2 Intravesical bacillus Calmette-Guérin (BCG) immunotherapy

*8.2.1 **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 non-muscle-invasive tumours (162,171-174) (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have been conducted. BCG was compared with epirubicin + interferon (175), MMC (176), or epirubicin alone (163). All of these studies have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting (163,176) and was also observed in a separate analysis of patients with intermediate-risk tumours (163).

One meta-analysis (162) has evaluated the individual data from 2820 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 ($p < 0.0001$) compared to 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 (160,161) (LE: 1a). A meta-analysis carried out by the EORTC-GUCG has evaluated data from 4863 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 2658 patients (9.8%) treated with BCG, tumours progressed compared to 304 out of 2205 (13.8%) in the control groups (TURB alone, TURB + intravesical chemotherapy, or TUR + 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 Ta, T1 papillary tumours and in those with CIS (161). 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 (163) (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 (162).

The conflicting results in the outcomes of the 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 (177,178). In the most recent meta-analysis, however, BCG maintenance was more effective than MMC in patients previously treated with chemotherapy (162) (LE: 1a).

*8.2.2 **Optimal BCG schedule***

Induction BCG instillations are classically given according to the empirical 6-weekly schedule introduced by Morales in 1976 (179). For optimal efficacy, BCG must be given in a maintenance schedule (160-162,174) (LE: 1a). In the EORTC-GU group meta-analysis, only patients who received maintenance BCG benefitted. Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks to 27 over 3 years (180). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective (161). 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 (160,174) (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations remain unknown (181). However, in an RCT of 1355 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 (178) (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.

8.2.3 ***BCG toxicity***

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy (164) (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 maintenance schedule is not associated with an increased risk of side effects comparing 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. BCG should not be administered (absolute contraindications):

- during the first 2 weeks after TURB;
- in patients with macroscopic haematuria;
- after traumatic catheterization;
- in patients with a symptomatic urinary tract infection.

The presence of leukocyturia, microscopic haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases (184-186) (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (immunosuppression, human immunodeficiency virus (HIV) infection) (187), although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients (188,189) (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 (190,191) (Table 9).

Table 9: Management options for side effects associated with intravesical BCG (190,192,193)

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: a. Postpone the instillations 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) (194).
		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 (193)		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 (192).
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; NSAID = non-steroidal anti-inflammatory drug; TURBT = transurethral resection of bladder tumour.

*8.2.4 **Optimal dose of BCG***

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

When the CUETO study compared one-third dose to full-dose BCG in 500 patients, there was no overall difference in efficacy. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours (195,196) (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 (197) (LE: 1b).

However, the EORTC did not find any difference in toxicity between one-third and full-dose BCG, as one-third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year (178) (LE: 1b).

*8.2.5 **BCG strain***

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

*8.2.6 **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 to 3 years of 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 the efficacy and side effects of each treatment modality.

8.3 Specific aspects of treatment of CIS

*8.3.1 **Treatment strategy***

If concurrent CIS is found in association with MIBC, therapy is determined according to the invasive tumour. The detection of CIS with Ta,T1 tumours increases the risk of recurrence and progression of Ta,T1 tumours (123,124) and further treatment is mandatory. The treatment strategy is generally based on the criteria summarized in Chapters 8.1, 8.2, 8.4 and 9.

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). There is no consensus on whether to carry out conservative (intravesical BCG instillations) or aggressive (radical cystectomy) therapy. There has been a lack of randomized 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 over-treated (198) (LE: 3).

*8.3.2 **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 (130-133,199) (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence (133,180,199,200) (LE: 3).

*8.3.3 **Prospective randomized trials***

Unfortunately, there have been few randomized 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 (198).

A meta-analysis of clinical trials comparing 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) (201) (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 (OR = 0.65; 95% CI = 0.36-1.16; p = 0.10) (161) (LE: 1b). There has been no single trial that has demonstrated superiority of combined BCG and MMC over BCG alone (202).

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).

*8.3.4 **Treatment of extravesical CIS***

Patients with CIS are at high risk of extravesical involvement in the upper urinary tract and in the prostatic urethra. Solsona et al. found that 87 of 138 patients (63%) with CIS developed extravesical involvement initially or during follow-up (203). Patients with extravesical involvement had worse survival than those with bladder CIS alone (203) (LE: 3).

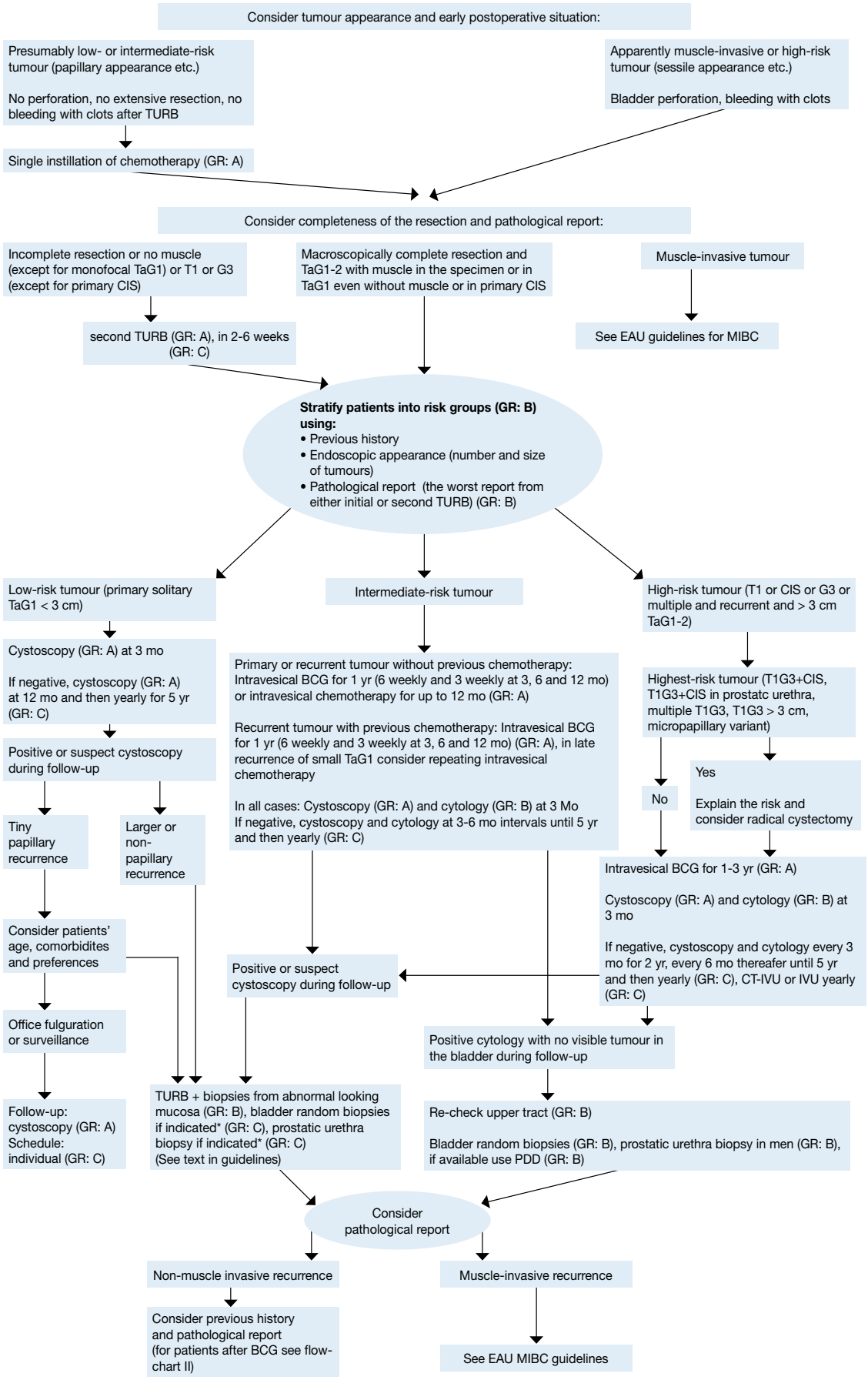
In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts (198). These situations should be distinguished from tumour invasion into the prostatic stroma, which is staged as T4a, and for which immediate radical cystoprostatectomy is mandatory.

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 (87,198,204) (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 (205). No conclusive results have been obtained with conservative therapy, and radical surgery should be considered (204) (LE: 3).

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

Flowchart I: TURB in patients with a 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.

8.4 Treatment of failure of intravesical therapy

*8.4.1 **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 (162) (LE: 1a).

*8.4.2 **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 (206). Further conservative treatment with BCG is associated with increased risk of progression (134,207) (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 (48) (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 (208) (LE: 3).*
BCG intolerance
Severe side effects that prevent further BCG instillation before completing induction (191).

** 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.

*8.4.3 **Treatment of BCG failure and recurrences after BCG***

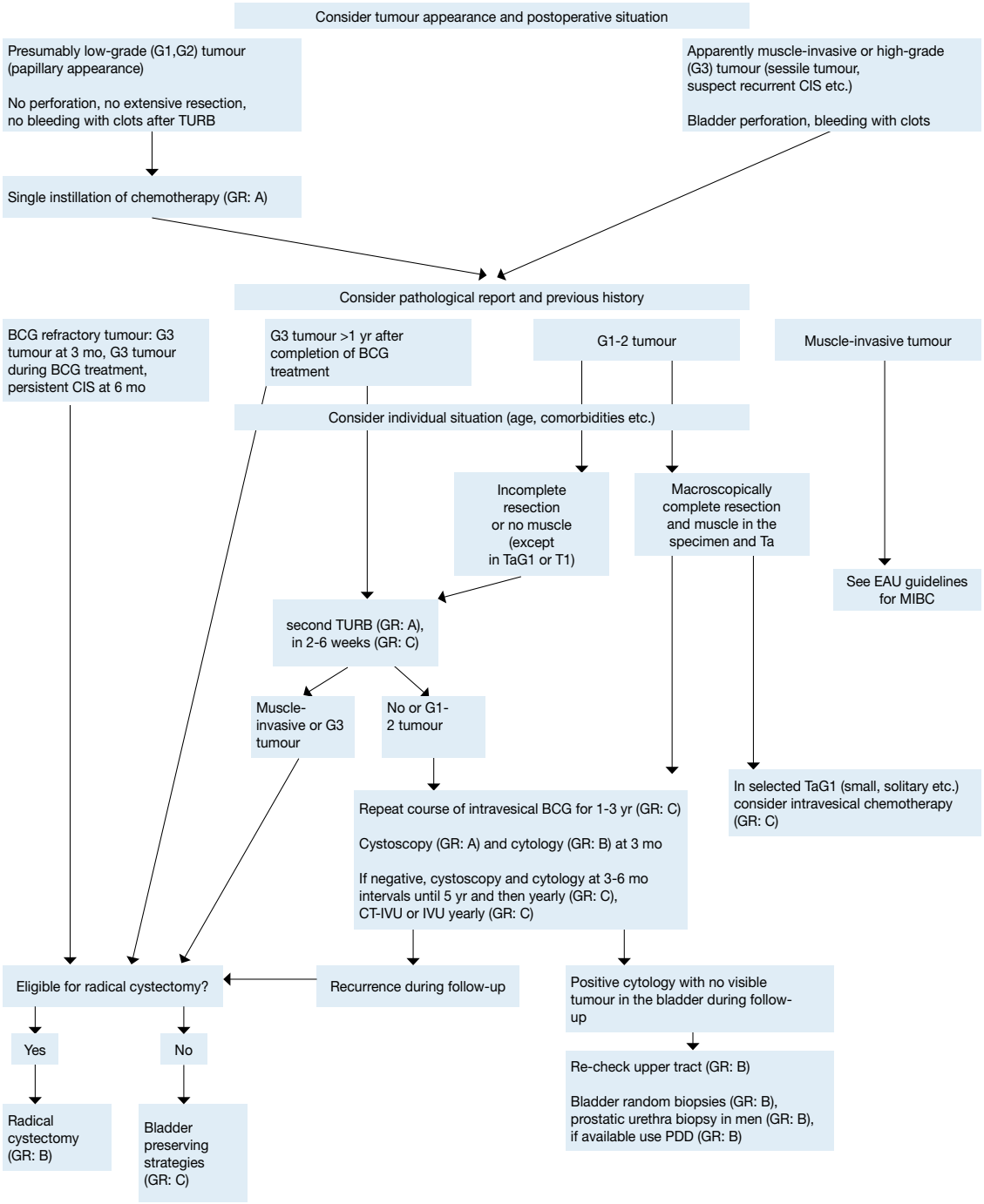
Treatment recommendations are provided in Table 11. They reflect categories mentioned in Table 10 and tumour characteristics at the time of recurrence.

Patients with BCG failure are unlikely to respond to further BCG therapy; radical cystectomy 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 (209,210) (LE: 3). Additionally, there are now several bladder preservation strategies available that can be categorized as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy (211). Changing from BCG to these options can yield responses in selected cases with BCG treatment failure for NMIBC (209,212-221) (LE: 3).

There is limited evidence on which option is most beneficial. One study showed that gemcitabine is superior to MMC in patients with previous BCG immunotherapy (LE: 2) (222). However, treatments other than radical cystectomy must be considered oncologically inferior in patients with BCG failure at the present time (134,206,207) (LE: 3).

There is little known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance. Instillations of gemcitabine or MMC in combination with hyperthermia appear to be good options in these patients (166,222) (LE: 3).

Flowchart II: TURB of a recurrence during or after intravesical BCG*



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

8.5 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 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.	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 Ta 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 can be offered.	C
In patients at highest risk of tumour progression (Table 11), immediate radical cystectomy should be considered.	C
In patients with BCG failure, radical cystectomy is indicated.	B
In patients with BCG failure ineligible for radical cystectomy, gemcitabine or MMC in combination with hyperthermia are options.	C
Intravesical chemotherapy	
One immediate instillation 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
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 TURB; • in patients with macroscopic haematuria; • after traumatic catheterization; • 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

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

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

If cystectomy is indicated before progression to muscle-invasive tumour has been pathologically confirmed, then the choice of timing for radical cystectomy is either immediate (immediately after NMIBC diagnosis) or early (after BCG failure).

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 (98,119,223-234) (LE: 3).
- Some patients with non-muscle invasive tumours experience disease progression to muscle-invasive disease (Table 7).
- It has been shown retrospectively that patients with high-risk NMIBC who undergo early rather than delayed radical cystectomy for tumour relapse after initial treatment with TURB and BCG have a better survival rate (235) (LE: 3).

The potential benefit of radical cystectomy must be weighed against the risk, morbidity, and impact on quality of life. It is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour as they are at highest risk of progression (39,95,123,124) (LE: 3), including:

- multiple and/ or large (> 3 cm) T1, HG (G3) tumours;
- T1, HG (G3) tumours with concurrent CIS;
- early recurrent T1, HG (G3) tumours;
- T1G3 and CIS in prostatic urethra;
- presence of unusual histology of urothelial carcinoma (see Chapter 4.5);
- LVI;
- Non-functioning bladder.

The benefits and risks of immediate and delayed cystectomy should be discussed with patients. Patients should be informed about the benefits and risks of both approaches. Individual factors like gender, age or tumour location in (pseudo)diverticulum should be considered because of the worse prognosis in females, life-long risk of progression after BCG in high-risk tumours and the potential risk of tumours in diverticulum (129).

Radical cystectomy is strongly recommended in patients with BCG-refractory tumours, as mentioned above. A delay in radical cystectomy might lead to decreased disease-specific survival (236) (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% (237-242) (LE: 3).

Table 11: Treatment recommendations in Ta, T1 tumours 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 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, unusual histology of urothelial carcinoma, LVI	Radical cystectomy should be considered
	BCG failures	Radical cystectomy is recommended

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

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 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; HG = high-grade.

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

As a result of the risk of recurrence and progression, patients with Ta, T1 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 (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, non-invasive (Ta), LG/G1 papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy (243-250) (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden (93) (LE: 3). Some authors have even defended temporary surveillance in selected cases (249-251) (LE: 3).
- *The first cystoscopy after TURB at 3 months is a very important prognostic indicator for recurrence and progression* (123,127,134,252-254) (LE: 1a). The first cystoscopy should thus 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* (253) (LE: 3). Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered (254).
- *In tumours originally intermediate- or high-risk, recurrences after 10 years tumour-free are not unusual* (255) (LE: 3). Therefore, life-long follow-up is recommended (254).
- *The risk of upper urinary tract recurrence increases in patients with multiple and high-risk tumours* (53) (LE: 3).
- *Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy* (85) (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 5.8). There has been a lack of randomized 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.

10.1 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
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; IVU = intravenous urography; PDD = photodynamic diagnosis.

11. REFERENCES

1. Ferlay J, Bray F, Forman D, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 2010, International Agency for Research on Cancer: Lyon, France. http://www.iarc.fr/en/publications/eresources/cancerbases/index.php
2. Ploeg M, Aben KKH, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol 2009 Jun;27(3):289-93. http://www.ncbi.nlm.nih.gov/pubmed/19219610
3. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013 Feb;63(2):234-41. http://www.ncbi.nlm.nih.gov/pubmed/22877502
4. Bosetti C, Bertuccio P, Chatenoud L, et al. Trends in mortality from urologic cancers in Europe, 1970-2008. Eur Urol 2011 Jul;60(1):1-15. http://www.ncbi.nlm.nih.gov/pubmed/21497988
5. Ferlay J, Randi G, Bosetti C, et al. Declining mortality from bladder cancer in Europe. BJU Int 2008 Jan;101(1):11-9. http://www.ncbi.nlm.nih.gov/pubmed/17971176
6. Rafnar T, Vermeulen SH, Sulem P, et al. European genome-wide association study identifies SLC14A1 as a new urinary bladder cancer susceptibility gene. Hum Mol Genet 2011 Nov;20(21):4268-81. http://www.ncbi.nlm.nih.gov/pubmed/21750109
7. Freedman ND, Silverman DT, Hollenbeck AR, et al. Association between smoking and risk of bladder cancer among men and women. JAMA 2011 Aug;306(7):737-45. http://www.ncbi.nlm.nih.gov/pubmed/21846855
8. Martini T, Mayr R, Lodde M, et al. Validation of RiskCheck Bladder Cancer©, version 5.0 for risk-adapted screening of bladder cancer. Urol Int 2013;91(2):175-81. http://www.ncbi.nlm.nih.gov/pubmed/23860006
9. Mir MC, Stephenson AJ, Grubb RL 3rd, et al. Predicting risk of bladder cancer using clinical and demographic information from prostate, lung, colorectal, and ovarian cancer screening trial participants. Cancer Epidemiol Biomarkers Prev 2013 Dec;22(12):2241-9. http://www.ncbi.nlm.nih.gov/pubmed/24089460
10. Rushton L, Bagga S, Bevan R, et al. Occupation and cancer in Britain. Br J Cancer 2010 Apr;102(9):1428-37. http://www.ncbi.nlm.nih.gov/pubmed/20424618
11. Rushton L, Hucthings SJ, Fortunato L, et al. Occupational cancer burden in Great Britain. Br J Cancer 2012 Jun;107 Suppl 1:S3-S7. http://www.ncbi.nlm.nih.gov/pubmed/22710676
12. Samanic CM, Kogevinas M, Silverman DT, et al. Occupation and bladder cancer in a hospital-based case-control study in Spain. Occup Environ Med 2008 May;65(5):347-53. http://www.ncbi.nlm.nih.gov/pubmed/17951336
13. Pesch B, Taeger D, Johnen G, et al. Screening for bladder cancer with urinary tumor markers in chemical workers with exposure to aromatic amines. Int Arch Occup Environ Health 2013 Oct 16. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/24129706
14. Ros MM, Bas Bueno-de-Mesquita HB, Büchner FL, et al. Fluid intake and the risk of urothelial cell carcinomas in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 2011 Jun;128(11):2695-708. http://www.ncbi.nlm.nih.gov/pubmed/20715171
15. Koutros S, Silverman DT, Baris D, et al. Hair dye use and risk of bladder cancer in the New England bladder cancer study. Int J Cancer 2011 Dec;129(12):2894-904. http://www.ncbi.nlm.nih.gov/pubmed/21678399
16. Ros MM, Gago-Dominguez M, Aben KK, et al. Personal hair dye use and the risk of bladder cancer: a case-control study from The Netherlands. Cancer Causes Control 2012 Jul;23(7):1139-48. http://www.ncbi.nlm.nih.gov/pubmed/22581032
17. Sobin LH, Gospodariwicz M, Wittekind C, eds. TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edn. Wiley-Blackwell, 2009 Dec; pp. 262-265. http://www.uicc.org/tnm/
18. Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol 1998 Dec;22(12):1435-48. http://www.ncbi.nlm.nih.gov/pubmed/9850170

19. Sauter G, Algaba F, Amin M, et al. Tumours of the urinary system: non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. WHO classification of classification of tumours of the urinary system and male genital organs. Lyon: IARCC Press, 2004, pp. 29-34. http://www.iarc.fr/en/publications/pdfs-online/pat-gen/index.php
20. Pan CC, Chang YH, Chen KK, et al. Prognostic significance of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality of non-muscle-invasive urothelial tumors of the urinary bladder: a clinicopathologic study of 1,515 cases. Am J Clin Pathol 2010 May;133(5):788-95. http://www.ncbi.nlm.nih.gov/pubmed/20395527
21. Burger M, Van der AA MN, Van Oers JM, et al. Prediction of Progression of Non-Muscle-Invasive Bladder Cancer by WHO 1973 and 2004 Grading and by FGFR3 Mutation Status: A Prospective Study. Eur Urol 2008 Oct;54(4):835-43. http://www.ncbi.nlm.nih.gov/pubmed/18166262
22. MacLennan GT, Kirkali Z, Cheng L. Histologic grading of noninvasive papillary urothelial neoplasms. Eur Urol 2007 Apr;51(4):889-98. http://www.ncbi.nlm.nih.gov/pubmed/17095142
23. May M, Brookman-Amissah S, Roigas J, et al. Prognostic accuracy of individual uropathologists in Non-invasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation Classifications. Eur Urol 2010 May;57(5):850-8. http://www.ncbi.nlm.nih.gov/pubmed/19346063
24. van Rhijn BW, van Leenders GJ, Ooms BC, et al. The pathologist's mean grade is constant and individualizes the prognostic value of bladder cancer grading. Eur Urol 2010 Jun;57(6):1052-7. http://www.ncbi.nlm.nih.gov/pubmed/19765886
25. Otto W, Denzinger S, Fritsche HM, et al. The WHO classification of 1973 is more suitable than the WHO classification of 2004 for predicting survival in pT1 urothelial bladder cancer. BJU Int 2011 Feb;107(3):404-8. http://www.ncbi.nlm.nih.gov/pubmed/20707791
26. Pellucchi F, Freschi M, Ibrahim B, et al. Clinical reliability of the 2004 WHO histological classification system compared with the 1973 WHO system for Ta primary bladder tumors. J Urol 2011 Dec;186(6):2194-9. http://www.ncbi.nlm.nih.gov/pubmed/22019037
27. Cao D, Vollmer RT, Luly J, et al. Comparison of 2004 and 1973 World Health Organization grading systems and their relationship to pathologic staging for predicting long-term prognosis in patients with urothelial carcinoma. Urology 2010 Sep;76(3):593-9. http://www.ncbi.nlm.nih.gov/pubmed/20381131
28. Murphy WM, Takezawa K, Maruniak NA. Interobserver discrepancy using the 1998 WHO/ISUP classification of urothelial neoplasms: practical choices for patient care. J Urol 2002 Sep;168(3): 968-72. http://www.ncbi.nlm.nih.gov/pubmed/12187201
29. Witjes JA, Moonen PMJ, van der Heijden AG. Review pathology in a diagnostic bladder cancer trial. Urology 2006 Apr;67(4):751-5. http://www.ncbi.nlm.nih.gov/pubmed/16566990
30. Bol MG, Baak J, Buhr-Wildhagen S, et al. Reproducibility and prognostic variability of grade and lamina propria invasion in stages Ta, T1 urothelial carcinoma of the bladder. J Urol 2003 Apr;169(4):1291-4. http://www.ncbi.nlm.nih.gov/pubmed/12629345
31. Van der Meijden A, Sylvester R, Collette L, et al. The role and impact of pathology review on stage and grade assessment on stages Ta and T1 bladder tumors: a combined analysis of 5 European Organization for Research and Treatment of Cancer trials. J Urol 2000 Nov;164(5):1533-7. http://www.ncbi.nlm.nih.gov/pubmed/11025698
32. Van Rhijn BWG, van der Kwast TH, Kakiashvili DM, et al. Pathological stage review is indicated in primary pT1 bladder cancer. BJU Int 2010 Jul;106(2):206-11. http://www.ncbi.nlm.nih.gov/pubmed/20002439
33. Compérat E, Egevad L, Lopez-Beltran A, et al. An interobserver reproducibility study on invasiveness of bladder cancer using virtual microscopy and heatmaps. Histopathology 2013 Dec;63(6):756-66. http://www.ncbi.nlm.nih.gov/pubmed/24102813
34. Orsola A, Trias I, Raventós CX, et al. Initial high-grade T1 urothelial cell carcinoma: feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. Eur Urol 2005 Aug;48(2):231-8, discussion 238. http://www.ncbi.nlm.nih.gov/pubmed/15963635

35. Andius P, Johansson SL, Holmäng S. Prognostic factors in stage T1 bladder cancer: tumor pattern (solid or papillary) and vascular invasion more important than depth of invasion. Urology 2007 Oct;70(4):758-62.
http://www.ncbi.nlm.nih.gov/pubmed/17991551
36. van Rhijn BW, van der Kwast TH, Alkhateeb SS, et al. A new and highly prognostic system to discern T1 bladder cancer substage. Eur Urol 2012 Feb;61(2):378-84.
http://www.ncbi.nlm.nih.gov/pubmed/22036775
37. van Rhijn BW, Liu L, Vis AN, et al. Prognostic value of molecular markers, sub-stage and European Organisation for the Research and Treatment of Cancer risk scores in primary T1 bladder cancer. BJU Int 2012 Oct;110(8):1169-76.
http://www.ncbi.nlm.nih.gov/pubmed/22448597
38. Cho KS, Seo HK, Joung JY et al. Lymphovascular invasion in transurethral resection specimens as predictor of progression and metastasis in patients with newly diagnosed t1 bladder urothelial cancer. J Urol 2009 Dec;182(6):2625-31.
http://www.ncbi.nlm.nih.gov/pubmed/19836779
39. Kamat AM. The case for early cystectomy in the treatment of non-muscle invasive micropapillary bladder carcinoma. J Urol 2006 Mar;175(3 Pt 1):881-5.
http://www.ncbi.nlm.nih.gov/pubmed/16469571
40. Amin A, Epstein JI. Noninvasive micropapillary urothelial carcinoma: a clinicopathologic study of 18 cases. Hum Pathol 2012 Dec;43(12):2124-8.
http://www.ncbi.nlm.nih.gov/pubmed/22939957
41. Comperat E, Roupret M, Yaxley J, et al. Micropapillary urothelial carcinoma of the urinary bladder: a clinicopathological analysis of 72 cases. Pathology 2010 Dec;42(7):650-4.
http://www.ncbi.nlm.nih.gov/pubmed/21080874
42. Blochin EB, Park KJ, Tickoo SK, et al. Urothelial carcinoma with prominent squamous differentiation in the setting of neurogenic bladder: role of human papillomavirus infection. Mod Pathol 2012 Nov;25(11):1534-42.
http://www.ncbi.nlm.nih.gov/pubmed/22766788
43. Wasco MJ, Daignault S, Zhang Y, et al. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. Urology 2007 Jul;70(1):69-74.
http://www.ncbi.nlm.nih.gov/pubmed/17656211
44. Hansel DE, Amin MB, Compérat E, et al. A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. Eur Urol 2013 Feb;63(2):321-32.
http://www.ncbi.nlm.nih.gov/pubmed/23088996
45. Fristrup N, Ulhøi BP, Birkenkamp-Demtröder K, et al. Cathepsin E, maspin, Plk1, and survivin are promising prognostic protein markers for progression in non-muscle invasive bladder cancer. Am J Pathol 2012 May;180(5):1824-34.
http://www.ncbi.nlm.nih.gov/pubmed/22449953
46. Palou J, Algaba F, Vera I, et al. Protein expression patterns of ezrin are predictors of progression in T1G3 bladder tumours treated with nonmaintenance bacillus Calmette-Guérin. Eur Urol 2009 Nov;56(5):829-36.
http://www.ncbi.nlm.nih.gov/pubmed/18926620
47. van Rhijn BW, van der Kwast TH, Liu L, et al. The FGFR3 mutation is related to favorable pT1 bladder cancer. J Urol 2012 Jan;187(1):310-4.
http://www.ncbi.nlm.nih.gov/pubmed/22099989
48. Sylvester R, van der Meijden A, Witjes JA, et al. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. Urology 2005 Dec;66(6 Suppl 1):90-107.
http://www.ncbi.nlm.nih.gov/pubmed/16399418
49. Lamm DL, Herr HW, Jakse G, et al. Updated concepts and treatment of carcinoma in situ. Urol Oncol 1998 Jul-Oct;4(4-5):130-8.
http://www.ncbi.nlm.nih.gov/pubmed/21227218
50. Goessl C, Knispel HH, Millar K, et al. Is routine excretory urography necessary at first diagnosis of bladder cancer? J Urol 1997 Feb;157(2):480-1.
http://www.ncbi.nlm.nih.gov/pubmed/8996338
51. Palou J, Rodriguez-Rubio F, Huguet J, et al. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumours. J Urol 2005 Sep;174(3):859-61.
http://www.ncbi.nlm.nih.gov/pubmed/16093970

52. Holmang S, Hedelin H, Anderstrom C, et al. Long-term follow-up of a bladder carcinoma cohort: routine followup urography is not necessary. J Urol 1998 Jul;160(1):45-8.
http://www.ncbi.nlm.nih.gov/pubmed/9628602
53. Millán-Rodríguez F, Chéchile-Toniolo G, Salvador-Bayarri J, et al. Upper urinary tract tumours after primary superficial bladder tumours: prognostic factors and risk groups. J Urol 2000 Oct;164(4): 1183-7.
http://www.ncbi.nlm.nih.gov/pubmed/10992362
54. Nolte-Ernsting C, Cowan N. Understanding multislice CT urography techniques: many roads lead to Rome. Eur Radiol 2006 Dec;16(12):2670-86.
http://www.ncbi.nlm.nih.gov/pubmed/16953373
55. Têtu B. Diagnosis of urothelial carcinoma from urine. Mod Pathol 2009 Jun;22 Suppl 2:S53-9.
http://www.ncbi.nlm.nih.gov/pubmed/19494853
56. Raitanen M-P, Aine R, Rintala E, et al; FinnBladder Group. Differences between local and review urinary cytology and diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol 2002 Mar;41(3):284-9.
http://www.ncbi.nlm.nih.gov/pubmed/12180229
57. Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumour markers beyond cytology: international consensus panel on bladder tumour markers. Urology 2005 Dec;66(6 Suppl 1):35-63.
http://www.ncbi.nlm.nih.gov/pubmed/16399415
58. Burton JL, Goepel JR, Lee JA. Demand management in urine cytology: a single cytospin slide is sufficient. J Clin Pathol 2000 Sep;53(9):718-9.
http://www.ncbi.nlm.nih.gov/pubmed/11041065
59. Nabi G, Greene D, O'Donnell MO. Suspicious urinary cytology with negative evaluation for malignancy in the diagnostic investigation of haematuria: how to follow up? J Clin Pathol 2004 Apr;57(4):365-8.
http://www.ncbi.nlm.nih.gov/pubmed/15047737
60. Glas AS, Roos D, Deutekom M, et al. Tumour markers in the diagnosis of primary bladder cancer. A systematic review. J Urol 2003 Jun;169(6):1975-82.
http://www.ncbi.nlm.nih.gov/pubmed/12771702
61. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumour markers versus cytology: results of a comprehensive literature review and meta-analysis. Urology 2003 Jan;61(1):109-18.
http://www.ncbi.nlm.nih.gov/pubmed/12559279
62. Van Rhijn BW, van der Poel HG, van der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. Eur Urol 2005 Jun;47(6):736-48.
http://www.ncbi.nlm.nih.gov/pubmed/15925067
63. Vrooman OPJ, Witjes JA. Urinary markers in bladder cancer. Eur Urol 2008 May;53(5):909-16.
http://www.ncbi.nlm.nih.gov/pubmed/18162285
64. Lotan Y, Shariat SF, Schmitz-Drager BJ, et al. Considerations on implementing diagnostic markers into clinical decision making in bladder cancer. Urol Oncol 2010 Jul-Aug;28(4):441-8.
http://www.ncbi.nlm.nih.gov/pubmed/20610281
65. Van Rhijn BWG, van der Poel HG, van der Kwast HG. Cytology and urinary markers for the diagnosis of bladder cancer. Eur Urol Suppl 2009;8:536-41.
http://www.sciencedirect.com/science/article/pii/S1569905609000554
66. Catto JWF. Old and new urinary markers: Which one is the PSA for bladder cancer? Eur Urol Suppl 2008 Feb;7:422-5.
http://www.journals.elsevierhealth.com/periodicals/eursup/article/S1569-9056(07)00237-0/abstract
67. Yutkin V, Nisman B, Pode D. Can urinary biomarkers replace cystoscopic examination in bladder cancer surveillance? Expert Rev Anticanc 2010 Jun;10(6):787-90.
http://www.ncbi.nlm.nih.gov/pubmed/20553203
68. Zwarthoff EC. Detection of tumours of the urinary tract in voided urine. Scand J Urol Nephrol 2008 Sep;218:147-53.
http://www.ncbi.nlm.nih.gov/pubmed/18815929
69. Shirodkar SP, Lokeshwar VB. Bladder tumor markers: from hematuria to molecular diagnostics-where do we stand? Expert Rev Anticanc 2008 Jul;8(7):1111-23.
http://www.ncbi.nlm.nih.gov/pubmed/18588456
70. Shariat SF, Karam JA, Lerner SP. Molecular markers in bladder cancer. Curr Opin Urol 2008 Jan;18(1):1-8.
http://www.ncbi.nlm.nih.gov/pubmed/18090481

71. Kim WJ, Bae SC. Molecular biomarkers in urothelial bladder cancer. Cancer Sci 2008 Apr;99(4): 646-52.
http://www.ncbi.nlm.nih.gov/pubmed/18377416
72. Agarwal PK, Black PC, Kamat AM. Considerations on the use of diagnostic markers in management of patients with bladder cancer. World J Urol 2008 Feb;26(1):39-44.
http://www.ncbi.nlm.nih.gov/pubmed/18092171
73. Kausch I, Böhle A. Bladder cancer II. Molecular aspects and diagnosis. Eur Urol 2001 May;39(5): 498-506.
http://www.ncbi.nlm.nih.gov/pubmed/11464029
74. Hajdinjak T. UroVysion FISH test for detecting urothelial cancers: Meta-analysis of diagnostic accuracy and comparison with urinary cytology testing. Urol Oncol 2008 Nov-Dec;26(6):645-51.
http://www.ncbi.nlm.nih.gov/pubmed/18367109
75. Schlomer BJ, Ho R, Sagalowsky A, et al. Prospective validation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. J Urol 2010 Jan;183(1):62-7.
http://www.ncbi.nlm.nih.gov/pubmed/19913822
76. Bergman J, Reznichek RC, Rajfer J. Surveillance of patients with bladder carcinoma using fluorescent in-situ hybridization on bladder washings. BJU Int 2008 Jan;101(1):26-9.
http://www.ncbi.nlm.nih.gov/pubmed/17850364
77. Van der Aa MN, Zwarthoff EC, Steyerberg EW, et al. Microsatellite analysis of voided-urine samples for surveillance of low-grade non-muscle-invasive urothelial carcinoma: feasibility and clinical utility in a prospective multicenter study (Cost-Effectiveness of Follow-Up of Urinary Bladder Cancer Trial (CEFUB)). Eur Urol 2009 Mar;55(3):659-67.
http://www.ncbi.nlm.nih.gov/pubmed/18501499
78. De Bekker-Grob EW, van der Aa MN, Zwarthoff EC, et al. Non-muscle-invasive bladder cancer surveillance for which cystoscopy is partly replaced by microsatellite analysis of urine: a cost-effective alternative? BJU Int 2009 Jul;104(1):41-7.
http://www.ncbi.nlm.nih.gov/pubmed/19500328
79. Rouprêt M, Hupertan V, Yates DR, et al. A comparison of the performance of microsatellite and methylation urine analysis for predicting the recurrence of urothelial cell carcinoma, and definition of a set of markers by Bayesian network analysis. BJU Int 2008 Jun;101(11):1448-53.
http://www.ncbi.nlm.nih.gov/pubmed/18325051
80. Grossman HB, Messing E, Soloway M, et al. Detection of bladder cancer using a point-of-care proteomic assay. JAMA 2005 Feb;293(7):810-6.
http://www.ncbi.nlm.nih.gov/pubmed/15713770
81. Lotan Y, Svatek RS, Malats N. Screening for bladder cancer: a perspective. World J Urol 2008 Feb;26(1):13-8.
http://www.ncbi.nlm.nih.gov/pubmed/18030473
82. Roobol MJ, Bangma CH, el Bouazzaoui S, et al. Feasibility study of screening for bladder cancer with urinary molecular markers (the BLU-P project). Urol Oncol 2010 Nov-Dec;28(6):686-90.
http://www.ncbi.nlm.nih.gov/pubmed/21062653
83. Grossman HB, Soloway M, Messing E, et al. Surveillance for recurrent bladder cancer using a point-of-care proreomic assay. JAMA 2006 Jan;295(3):299-305.
http://www.ncbi.nlm.nih.gov/pubmed/16418465
84. Babjuk M, Soukup, V, Pesl, M. et al. Urinary cytology and quantitative BTA and UBC tests in surveillance of patients with pTapT1 bladder urothelial carcinoma. Urology 2008 Apr;71(4):718-22.
http://www.ncbi.nlm.nih.gov/pubmed/18387400
85. van der Aa MN, Steyerberg EW, Bangma C, et al. Cystoscopy revisited as the gold standard for detecting bladder cancer recurrence: diagnostic review bias in the randomized, prospective CEFUB trial. J Urol 2010 Jan;183(1):76-80.
http://www.ncbi.nlm.nih.gov/pubmed/19913254
86. Kurth KH, Schellhammer PF, Okajima E, et al. Current methods of assessing and treating carcinoma in situ of the bladder with or without involvement of the prostatic urethra. Int J Urol 1995 Jun;2 (Suppl 2):8-22.
http://www.ncbi.nlm.nih.gov/pubmed/7553309
87. Aaronson DS, Walsh TJ, Smith JF, et al. Meta-analysis: does lidocaine gel before flexible cystoscopy provide pain relief? BJU Int 2009 Aug;104(4):506-9;discussion 509-10.
http://www.ncbi.nlm.nih.gov/pubmed/19239453

88. Blick CG, Nazir SA, Mallett S, et al. Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: results for 778 patients from a hospital haematuria clinic. BJU Int 2012 Jul;110(1):84-94. http://www.ncbi.nlm.nih.gov/pubmed/22122739
89. Richterstetter M, Wullich B, Amann K, et al. The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. BJU Int 2012 Jul;110(2 Pt 2):E76-9. http://www.ncbi.nlm.nih.gov/pubmed/22313727
90. Brausi M, Collette L, Kurth K, et al; EORTC Genito-Urinary Tract Cancer Collaborative Group. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol 2002 May;41(5): 523-31. http://www.ncbi.nlm.nih.gov/pubmed/12074794
91. Mariappan P, Zachou A, Grigor KM. Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. Eur Urol 2010 May;57(5):843-9. http://www.ncbi.nlm.nih.gov/pubmed/19524354
92. Mariappan P, Finney SM, Head E, et al. Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU Int 2012 Jun;109(11):1666-73. http://www.ncbi.nlm.nih.gov/pubmed/22044434
93. Herr HW, Donat SM, Reuter VE. Management of low grade papillary bladder tumors. J Urol 2007 Oct;178(4 Pt 1):1201-5. http://www.ncbi.nlm.nih.gov/pubmed/17698090
94. Van der Meijden A, Oosterlinck W, Brausi M, et al. Significance of bladder biopsies in Ta, T1 bladder tumours: a report of the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. Eur Urol 1999 Apr;35(4):267-71. http://www.ncbi.nlm.nih.gov/pubmed/10419345
95. Palou J, Sylvester RJ, Faba OR, et al. Female gender and carcinoma in situ in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guérin. Eur Urol 2012 Jul;62(1):118-25. http://www.ncbi.nlm.nih.gov/pubmed/22101115
96. Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. J Urol 1991 Nov;146(5):1207-12. http://www.ncbi.nlm.nih.gov/pubmed/1942262
97. Mungan MU, Canda AE, Tuzel E, et al. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. Eur Urol 2005 Nov;48(5):760-3. http://www.ncbi.nlm.nih.gov/pubmed/16005563
98. Huguet J, Crego M, Sabaté S, et al. Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. Eur Urol 2005 Jul;48(1):53-9;discussion 59. http://www.ncbi.nlm.nih.gov/pubmed/15967252
99. Gupta NP, Nayyar R, Hemal AK, et al. Outcome analysis of robotic pyeloplasty: a large single-centre experience. BJU Int 2010 Apr;105(7):980-3. http://www.ncbi.nlm.nih.gov/pubmed/19874304
100. Kausch I, Sommerauer M, Montorsi F, et al. Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies. Eur Urol 2010 Apr;57(4):595-606. http://www.ncbi.nlm.nih.gov/pubmed/20004052
101. Mowatt G, N'Dow J, Vale L, et al; Aberdeen Technology Assessment Review (TAR) Group. Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: Systematic review and meta-analysis. Int J Technol Assess Health Care 2011 Jan;27(1):3-10. http://www.ncbi.nlm.nih.gov/pubmed/21262078
102. Draga RO, Grimbergen MC, Kok ET, et al. Photodynamic diagnosis (5 aminolevulinic acid) of transitional cell carcinoma after bacillus Calmette-Guérin immunotherapy and mitomycin C intravesical therapy. Eur Urol 2010 Apr;57(4):655-60. http://www.ncbi.nlm.nih.gov/pubmed/19819064
103. Ray ER, Chatterton K, Khan MS, et al. Hexylaminolaevulinate fluorescence cystoscopy in patients previously treated with intravesical bacille Calmette-Guérin. BJU Int 2010 Mar;105(6):789-94. http://www.ncbi.nlm.nih.gov/pubmed/19832725

104. Schumacher MC, Holmäng S, Davidsson T, et al. Transurethral resection of non-muscle-invasive bladder transitional cell cancers with or without 5-aminolevulinic acid under visible and fluorescent light: results of a prospective, randomised, multicentre study. Eur Urol 2010 Feb;57(2):293-9. http://www.ncbi.nlm.nih.gov/pubmed/19913351
105. Stenzl A, Penkoff H, Dajc-Sommerer E, et al. Detection and clinical outcome of urinary bladder cancer with 5-aminolevulinic acid-induced fluorescence cystoscopy: a multicenter, randomized, double-blind, placebo-controlled trial. Cancer 2011 Mar;117(5):938-47. http://www.ncbi.nlm.nih.gov/pubmed/21351082
106. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol 2010 Nov;184(5):1907-13. http://www.ncbi.nlm.nih.gov/pubmed/20850152
107. Grossman HB, Stenzl A, Fradet Y, et al. Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. J Urol 2012 Jul;188(1):58-62. http://www.ncbi.nlm.nih.gov/pubmed/22583635
108. Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. Eur Urol 2013 Nov;64(5):846-54. http://www.ncbi.nlm.nih.gov/pubmed/23602406
109. O'Brien T, Ray E, Chatterton K, et al. Prospective randomized trial of hexylaminolevulinate photodynamic-assisted transurethral resection of bladder tumour (TURBT) plus single-shot intravesical mitomycin C vs conventional white-light TURBT plus mitomycin C in newly presenting non-muscle-invasive bladder cancer. BJU Int 2013 Dec;112(8):1096-104. http://www.ncbi.nlm.nih.gov/pubmed/24053153
110. Cauberg EC, Kloen S, Visser M, et al. Narrow band imaging cystoscopy improves the detection of non-muscle-invasive bladder cancer. Urology 2010 Sep;76(3):658-63. http://www.ncbi.nlm.nih.gov/pubmed/20223505
111. Miladi M, Peyromaure M, Zerbib M, et al. The value of a second transurethral resection in evaluating patients with bladder tumours. Eur Urol 2003 Mar;43(3):241-5. http://www.ncbi.nlm.nih.gov/pubmed/12600426
112. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? J Urol 2001 Mar;165(3):808-10. http://www.ncbi.nlm.nih.gov/pubmed/11176474
113. Schips L, Augustin H, Zigeuner RE, et al. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? Urology 2002 Feb;59(2):220-3. http://www.ncbi.nlm.nih.gov/pubmed/11834389
114. Grimm M-O, Steinhoff Ch, Simon X, et al. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol 2003 Aug;170(2 Pt 1):433-7. http://www.ncbi.nlm.nih.gov/pubmed/12853793
115. Divrik RT, Yildirim Ü, Zorlu F, et al. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumours of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. J Urol 2006 May;175(5):1641-4. http://www.ncbi.nlm.nih.gov/pubmed/16600720
116. Jahnson S, Wiklund F, Duchek M, et al. Results of second-look resection after primary resection of T1 tumour of the urinary bladder. Scand J Urol Nephrol 2005;39(3):206-10. http://www.ncbi.nlm.nih.gov/pubmed/16127800
117. Lazica DA, Roth S, Brandt AS, et al. Second transurethral resection after Ta high-grade bladder tumor: a 4.5-year period at a single university center. Urol Int 2013 Aug 23. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/23988813
118. Dalbagni G, Vora K, Kaag M, et al. Clinical outcome in a contemporary series of restaged patients with clinical T1 bladder cancer. Eur Urol 2009 Dec;56(6):903-10. http://www.ncbi.nlm.nih.gov/pubmed/19632765
119. Fritsche HM, Burger M, Svatek RS, et al. Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. Eur Urol 2010 Feb;57(2):300-9. http://www.ncbi.nlm.nih.gov/pubmed/19766384
120. Kulkarni GS, Hakenberg OW, Gschwend JE, et al. An updated critical analysis of the treatment strategy for newly diagnosed high-grade T1 (previously T1G3) bladder cancer. Eur Urol 2010 Jan;57(1):60-70. http://www.ncbi.nlm.nih.gov/pubmed/19740595

121. Lopez-Beltran A, Bassi P, Pavone-Macaluso M, et al. Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. Eur Urol 2004 Mar;45(3):257-66. http://www.ncbi.nlm.nih.gov/pubmed/15036668
122. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, et al. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol 2000 Sep;164(3 Pt 1):680-4. http://www.ncbi.nlm.nih.gov/pubmed/10954628
123. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta, T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006 Mar;49(3):466-5. http://www.ncbi.nlm.nih.gov/pubmed/16442208
124. Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol 2009 Nov;182(5):2195-203. http://www.ncbi.nlm.nih.gov/pubmed/19758621
125. Van Rhijn BW, Zuiverloon TC, Vis AN, et al. Molecular grade (FGFR3/MIB-1) and EORTC risk scores are predictive in primary non-muscle-invasive bladder cancer. Eur Urol 2010 Sep;58(3):433-41. http://www.ncbi.nlm.nih.gov/pubmed/20646825
126. Fernandez-Gomez J, Madero R, Solsona E, et al; Club Urológico Español de Tratamiento Oncológico. The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin: external validation of the EORTC risk tables. Eur Urol 2011 Sep;60(3):423-30. http://www.ncbi.nlm.nih.gov/pubmed/21621906
127. Palou J, Rodríguez-Rubio F, Millán F, et al. Recurrence at three months and high-grade recurrence as prognostic factor of progression in multivariate analysis of T1G2 bladder tumors. Urology 2009 Jun;73(6):1313-7. http://www.ncbi.nlm.nih.gov/pubmed/19362341
128. Alkhateeb SS, Neill M, Bar-Moshe S, et al. Long-term prognostic value of the combination of EORTC risk group calculator and molecular markers in non-muscle-invasive bladder cancer patients treated with intravesical Bacille Calmette-Guérin. Urol Ann 2011 Sep;3(3):119-26. http://www.ncbi.nlm.nih.gov/pubmed/21976923
129. Golijanin D, Yossepowitch O, Beck SD, et al. Carcinoma in a bladder diverticulum: presentation and treatment outcome. J Urol 2003 Nov;170(5):1761-4. http://www.ncbi.nlm.nih.gov/pubmed/14532771
130. Lamm DL. Carcinoma in situ. Urol Clin North Am 1992 Aug;19(3):499-508. http://www.ncbi.nlm.nih.gov/pubmed/1636234
131. Losa A, Hurle R, Lembo A. Low dose bacillus Calmette-Guerin for carcinoma in situ of the bladder: long-term results. J Urol 2000 Jan;163(1):68-72. http://www.ncbi.nlm.nih.gov/pubmed/10604316
132. Griffiths TRL, Charlton M, Neal DE, et al. Treatment of carcinoma in situ with intravesical bacillus Calmette-Guerin without maintenance. J Urol 2002 Jun;167(6):2408-12. http://www.ncbi.nlm.nih.gov/pubmed/11992047
133. Takenaka A, Yamada Y, Miyake H, et al. Clinical outcomes of bacillus Calmette-Guérin instillation therapy for carcinoma in situ of urinary bladder. Int J Urol 2008 Apr;15(4):309-13. http://www.ncbi.nlm.nih.gov/pubmed/18380817
134. Solsona E, Iborra I, Dumont R, et al. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 2000 Sep;164(3 Pt 1):685-9. http://www.ncbi.nlm.nih.gov/pubmed/10953125
135. Van Gils-Gielen RJ, Witjes WP, Caris CT, et al. Risk factors in carcinoma in situ of the urinary bladder. Urology 1995 Apr;45(4):581-6. http://www.ncbi.nlm.nih.gov/pubmed/7716838
136. Hudson MA, Herr HW. Carcinoma in situ of the bladder. J Urol 1995 Mar;153(3 Pt 1):564-72. http://www.ncbi.nlm.nih.gov/pubmed/7861485
137. Brausi M, Witjes JA, Lamm D, et al. A review of current guidelines and best practice recommendations for the management of nonmuscle invasive bladder cancer by the International Bladder Cancer Group. J Urol 2011 Dec;186(6):2158-67. http://www.ncbi.nlm.nih.gov/pubmed/22014799
138. Lammers RJ, Witjes WP, Hendricksen K, et al. Smoking status is a risk factor for recurrence after transurethral resection of non-muscle-invasive bladder cancer. Eur Urol 2011 Oct;60(4):713-20. http://www.ncbi.nlm.nih.gov/pubmed/21794974

139. Rink M, Furberg H, Zabor EC, et al.Impact of smoking and smoking cessation on oncologic outcomes in primary non-muscle-invasive bladder cancer. Eur Urol 2013 Apr;63(4):724-32. http://www.ncbi.nlm.nih.gov/pubmed/22925575
140. Rink M, Xylinas E, Babjuk M, et al. Impact of smoking on outcomes of patients with a history of recurrent non-muscle invasive bladder cancer. J Urol 2012 Dec;188(6):2120-7. http://www.ncbi.nlm.nih.gov/pubmed/23083868
141. Serretta V, Altieri V, Morgia G, et al. Cigarette smoking status at diagnosis and recurrence in intermediate-risk non-muscle-invasive bladder carcinoma. Urology 2013 Feb;81(2):277-81. http://www.ncbi.nlm.nih.gov/pubmed/23374781
142. Crivelli JJ, Xylinas E, Kluth LA, et al. Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. Eur Urol 2013 Jun 19. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/23810104
143. Soloway MS, Masters S. Urothelial susceptibility to tumor cell implantation: influence of cauterization. Cancer 1980 Sep;46(5):1158-63. http://www.ncbi.nlm.nih.gov/pubmed/7214299
144. Pan JS, Slocum HK, Rustum YM, et al. Inhibition of implantation of murine bladder tumor by thiotepa in cauterized bladder. J Urol 1989 Dec;142(6):1589-93. http://www.ncbi.nlm.nih.gov/pubmed/2511340
145. Brocks CP, Büttner H, Böhle A. Inhibition of tumor implantation by intravesical gemcitabine in a murine model of superficial bladder cancer. J Urol 2005 Sep;174(3):1115-8. http://www.ncbi.nlm.nih.gov/pubmed/16094076
146. Oosterlinck W, Kurth KH, Schröder F, et al. A prospective European Organization for Research and Treatment of Cancer Genitourinary Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. J Urol 1993 Apr;149(4):749-52. http://www.ncbi.nlm.nih.gov/pubmed/8455236
147. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a metaanalysis of published results of randomized clinical trials. J Urol 2004 Jun;171(6 Pt 1):2186-90. http://www.ncbi.nlm.nih.gov/pubmed/15126782
148. Abern MR, Owusu RA, Anderson MR, et al. Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. J Natl Compr Canc Netw 2013 Apr;11(4):477-84. http://www.ncbi.nlm.nih.gov/pubmed/23584348
149. Perlis N, Zlotta AR, Beyene J, et al. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. Eur Urol 2013 Sep;64(3):421-30. http://www.ncbi.nlm.nih.gov/pubmed/23830475
150. Berrum-Svennung I, Granfors T, Jahnson S, et al. A single instillation of epirubicin after transurethral resection of bladder tumors prevents only small recurrences. J Urol 2008 Jan;179(1):101-5. http://www.ncbi.nlm.nih.gov/pubmed/17997459
151. Gudjonsson S, Adell L, Merdasa F, et al. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomised multicentre study. Eur Urol 2009 Apr;55(4):773-80. http://www.ncbi.nlm.nih.gov/pubmed/19153001
152. Bouffioux C, Kurth KH, Bono A, et al. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol 1995 Mar;153(3 Pt 2):934-41. http://www.ncbi.nlm.nih.gov/pubmed/7853578
153. Kaasinen E, Rintala E, Hellstrom P, et al; FinnBladder Group. Factors explaining recurrence in patients undergoing chemo-immunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol 2002 Aug;42(2):167-74. http://www.ncbi.nlm.nih.gov/pubmed/12160589
154. Tolley DA, Parmar MK, Grigor KM, et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. J Urol 1996 Apr;155(4):1233-8. http://www.ncbi.nlm.nih.gov/pubmed/8632538

155. Pode D, Alon Y, Horowitz AT, et al. The mechanism of human bladder tumor implantation in an in vitro model. J Urol 1986 Aug;136(2):482-6.
http://www.ncbi.nlm.nih.gov/pubmed/3525861
156. Günther JH, Jurczok A, Wulf T, et al. Optimizing syngeneic orthotopic murine bladder cancer (MB49). Cancer Res 1999 Jun;59(12):2834-7.
http://www.ncbi.nlm.nih.gov/pubmed/10383142
157. Böhle A, Jurczok A, Ardelt PU, et al. Inhibition of bladder carcinoma cell adhesion by oligopeptide combinations in vitro and in vivo. J Urol 2002 Jan;167(1):357-63.
http://www.ncbi.nlm.nih.gov/pubmed/11743356
158. Oddens JR, van der Meijden AP, Sylvester R. One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? Eur Urol 2004 Sep;46(3):336-8.
http://www.ncbi.nlm.nih.gov/pubmed/15306104
159. Huncharek M, McGarry R, Kupelnick B. Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res 2001 Jan-Feb;21(1B):765-9.
http://www.ncbi.nlm.nih.gov/pubmed/11299841
160. Böhle A, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumour progression. Urology 2004 Apr;63(4):682-6. Discussion 686-7.
http://www.ncbi.nlm.nih.gov/pubmed/15072879
161. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002 Nov;168(5):1964-70.
http://www.ncbi.nlm.nih.gov/pubmed/12394686
162. Malmström P-U, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the longterm outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol 2009 Aug;56(2):247-56.
http://www.ncbi.nlm.nih.gov/pubmed/19409692
163. Sylvester RJ, Brausi MA, Kirkels WJ, et al; EORTC Genito-Urinary Tract Cancer Group. Longterm efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010 May;57(5):766-73
http://www.ncbi.nlm.nih.gov/pubmed/20034729
164. Shang PF, Kwong J, Wang ZP, et al. Intravesical Bacillus Calmette-Guérin versus epirubicin for Ta and T1 bladder cancer. Cochrane Database Syst Rev 2011 May 11;(5):CD006885.
http://www.ncbi.nlm.nih.gov/pubmed/21563157
165. Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non muscle invasive bladder cancer: a systematic review of the published results of randomized clinical trials. Eur Urol 2008 Apr;53(4):709-19.
http://www.ncbi.nlm.nih.gov/pubmed/18207317
166. Lammers RJ, Witjes JA, Inman BA, et al. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review. Eur Urol 2011 Jul;60(1):81-93.
http://www.ncbi.nlm.nih.gov/pubmed/21531502
167. Di Stasi SM, Giannantoni A, Giurioli A, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. Lancet Oncol 2006 Jan;7(1):43-51.
http://www.ncbi.nlm.nih.gov/pubmed/16389183
168. Au JL, Baladament RA, Wientjes MG, et al; International Mitomycin C Consortium. International Mitomycin C Consortium. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst 2001 Apr;93(8):597-604.
http://www.ncbi.nlm.nih.gov/pubmed/11309436
169. Giesbers AA, Van Helsdingen PJ, Kramer AE. Recurrence of superficial bladder carcinoma after intravesical instillation of mitomycin-C. Comparison of exposure times. Br J Urol 1989 Feb;63(2): 176-9.
http://www.ncbi.nlm.nih.gov/pubmed/2495144

170. Kuroda M, Niijima T, Kotake T, et al; 6th Trial of the Japanese Urological Cancer Research Group. Effect of prophylactic treatment with intravesical epirubicin on recurrence of superficial bladder cancer -The 6th Trial of the Japanese Urological Cancer Research Group (JUCRG): a randomized trial of intravesical epirubicin at dose of 20mg/40ml, 30 mg/40 ml, 40 mg/40 ml. Eur Urol 2004 May;45(5): 600-5.
http://www.ncbi.nlm.nih.gov/pubmed/15082202
171. Shelley MD, Kynaston H, Court J, et al. A systematic review of intravesical bacillus Calmette-Guérin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int 2001 Aug;88(3):209-16.
http://www.ncbi.nlm.nih.gov/pubmed/11488731
172. Han RF, Pan JG. Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urology 2006 Jun;67(6):1216-23.
http://www.ncbi.nlm.nih.gov/pubmed/16765182
173. Shelley MD, Wilt TJ, Court J, et al. Intravesical bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a metaanalysis of randomized trials. BJU Int 2004 Mar;93(4):485-90.
http://www.ncbi.nlm.nih.gov/pubmed/15008714
174. Böhle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003 Jan;169(1):90-5.
http://www.ncbi.nlm.nih.gov/pubmed/12478111
175. Duchek M, Johansson R, Jahnson S, et al. Bacillus Calmette-Guérin Is superior to a combination of epirubicin and interferon-a2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. Eur Urol 2010 Jan;57(1):25-31.
http://www.ncbi.nlm.nih.gov/pubmed/19819617
176. Järvinen R, Kaasinen E, Sankila A, et al. Long-term efficacy of maintenance bacillus Calmette-Guérin versus maintenance mitomycin C instillation therapy in frequently recurrent Ta, T1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. Eur Urol 2009 Aug;56(2):260-5.
http://www.ncbi.nlm.nih.gov/pubmed/19395154
177. Huncharek M, Kupelnick B. The influence of intravesical therapy on progression of superficial transitional cell carcinoma of the bladder: a metaanalytic comparison of chemotherapy versus bacilli Calmette-Guerin immunotherapy. Am J Clin Oncol 2004 Oct;27(5):522-8.
http://www.ncbi.nlm.nih.gov/pubmed/15596924
178. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU Cancers Group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013 Mar;63(3):462-72.
http://www.ncbi.nlm.nih.gov/pubmed/23141049
179. Morales, A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 1976 Aug;116(2):180-3.
http://www.ncbi.nlm.nih.gov/pubmed/820877
180. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000 Apr;163(4):1124-9.
http://www.ncbi.nlm.nih.gov/pubmed/10737480
181. Zlotta AR, van Vooren JP, Huygen K, et al. What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? Eur Urol 2000 Apr;37(4):470-7.
http://www.ncbi.nlm.nih.gov/pubmed/10765079
182. Van der Meijden AP, Sylvester RJ, Oosterlinck W, et al; EORTC Genito-Urinary Tract Cancer Group. Maintenance bacillus Calmette-Guerin for Ta, T1 bladder tumours is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. Eur Urol 2003 Oct;44(4):429-34.
http://www.ncbi.nlm.nih.gov/pubmed/14499676
183. Brausi M, Oddens J, Sylvester R, et al. Side effects of bacillus Calmette-Guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC Genito-Urinary Cancers Group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol 2014 Jan;65(1):69-76.
http://www.ncbi.nlm.nih.gov/pubmed/23910233

184. Herr HW. Intravesical bacillus Calmette-Guérin outcomes in patients with bladder cancer and asymptomatic bacteriuria. J Urol 2012 Feb;187(2):435-7.
http://www.ncbi.nlm.nih.gov/pubmed/22177154
185. Herr HW. Outpatient urological procedures in antibiotic-naive patients with bladder cancer with asymptomatic bacteriuria. BJU Int 2012 Dec;110(11 Pt B):E658-60.
http://www.ncbi.nlm.nih.gov/pubmed/22883017
186. Zhao LC, Meeks JJ, Helfand BT, et al. Screening urine analysis before bacille Calmette-Guérin instillation does not reduce the rate of infectious complications. BJU Int 2012 Jun;109(12):1819-21.
http://www.ncbi.nlm.nih.gov/pubmed/22077819
187. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 1992 Mar;147(3):596-600.
http://www.ncbi.nlm.nih.gov/pubmed/1538436
188. Palou J, Angerri O, Segarra J, et al. Intravesical bacillus Calmette-Guèrin for the treatment of superficial bladder cancer in renal transplant patients. Transplantation 2003 Nov;76(10):1514-6.
http://www.ncbi.nlm.nih.gov/pubmed/14657696
189. Yossepowitch O, Eggener SE, Bochner BH, et al. Safety and efficacy of intravesical bacillus Calmette-Guerin instillations in steroid treated and immunocompromised patients. J Urol 2006 Aug;176(2):482-5.
http://www.ncbi.nlm.nih.gov/pubmed/16813873
190. Rodríguez F, Palou J, Martínez R, et al. [Practical guideline for the management of adverse events associated with BCG installations.] Arch Esp Urol 2008 Jun;61(5):591-6. [Article in Spanish]
http://www.ncbi.nlm.nih.gov/pubmed/18709813
191. Witjes JA, Palou J, Soloway M, et al. Clinical practice recommendations for the prevention and management of intravesical therapy-associated adverse events. Eur Urol Suppl 2008 Oct;7(10):667-74.
http://www.europeanurology.com/article/S1569-9056(08)00110-3/abstract
192. Tinazzi E, Ficarra V, Simeoni S, et al. Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. Rheumatol Int 2006 Apr;26(6):481-8.
http://www.ncbi.nlm.nih.gov/pubmed/16220289
193. Falkensammer C, Gozzi C, Hager M, et al. Late occurrence of bilateral tuberculous-like epididymoorchitis after intravesical bacille Calmette-Guerin therapy for superficial bladder carcinoma. Urology 2005 Jan;65(1):175.
http://www.ncbi.nlm.nih.gov/pubmed/15667898
194. Palou J, Rodríguez-Villamil L, Andreu-Crespo A, et al. Intravesical treatment of severe bacillus Calmette-Guerin cystitis. Int Urol Nephrol 2001;33(3):485-9.
http://www.ncbi.nlm.nih.gov/pubmed/12230277
195. Martinez-Pineiro JA, Flores N, Isorna S, et al. Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guerin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int 2002 May;89(7):671-80.
http://www.ncbi.nlm.nih.gov/pubmed/11966623
196. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsona E, et al. Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005 Oct;174(4 Pt 1):1242-7.
http://www.ncbi.nlm.nih.gov/pubmed/16145378
197. Ojea A, Nogueira JL, Solsona E, et al; CUETO Group (Club Urológico Español De Tratamiento Oncológico). A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27mg) versus very low-dose bacillus Calmette-Guerin (13.5mg) versus mitomycin C. Eur Urol 2007 Nov;52(5):1398-406.
http://www.ncbi.nlm.nih.gov/pubmed/17485161
198. Van der Meijden APM, Sylvester R, Oosterlinck W, et al; for the EAU Working Party on Non Muscle Invasive Bladder Cancer. EAU guidelines on the diagnosis and treatment of urothelial carcinoma in situ. Eur Urol 2005 Sep;48(3):363-71.
http://www.ncbi.nlm.nih.gov/pubmed/15994003
199. Jakse G, Hall R, Bono A, et al and members of the EORTC GU Group. Intravesical BCG in patients with carcinoma in situ of the urinary bladder: long-term results of EORTC GU Group phase II protocol 30861. Eur Urol 2001 Aug;40(2):144-50.
http://www.ncbi.nlm.nih.gov/pubmed/11528191

200. Gofrit ON, Pode D, Pizov G, et al. The natural history of bladder carcinoma in situ after initial response to bacillus Calmette-Gúerin immunotherapy. Urol Oncol 2009 May-Jun;27(3):258-62. http://www.ncbi.nlm.nih.gov/pubmed/18440839
201. Sylvester RJ, van der Meijden APM, Witjes JA, et al. Bacillus Calmette-Guerin versus chemotherapy in the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. J Urol 2005 Jul;174(1):86-92. http://www.ncbi.nlm.nih.gov/pubmed/15947584
202. Kaasinen E, Wijkstrom H, Malmstrom PU, et al. Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma in situ of the urinary bladder: a Nordic study. Eur Urol 2003 Jun;43(6):637-45. http://www.ncbi.nlm.nih.gov/pubmed/12767365
203. Solsona E, Iborra I, Ricos JV, et al. Extravesical involvement in patients with bladder carcinoma in situ: biological and therapy implications. J Urol 1996 Mar;155(3):895-9. http://www.ncbi.nlm.nih.gov/pubmed/8583601
204. Palou J, Baniel J, Klotz L, et al. Urothelial carcinoma of the prostate. Urology 2007 Jan;69(1 Suppl): 50-61. http://www.ncbi.nlm.nih.gov/pubmed/17280908
205. Palou Redorta J, Schatteman P, Huguet Pérez J, et al. Intravesical instillations with bacillus calmette guérin for the treatment of carcinoma in situ involving prostatic ducts. Eur Urol 2006 May;49(5):834-8; discussion 838. http://www.ncbi.nlm.nih.gov/pubmed/16426729
206. Herr HW, Dalbagni G. Defining bacillus Calmette-Guerin refractory superficial bladder tumours. J Urol 2003 May;169(5):1706-8. http://www.ncbi.nlm.nih.gov/pubmed/12686813
207. Lerner SP, Tangen CM, Sucharew H, et al. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non muscle invasive bladder cancer. Urol Oncol 2009 Mar-Apr;27(2):155-9. http://www.ncbi.nlm.nih.gov/pubmed/18367117
208. van den Bosch S, Alfred Witjes J. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. Eur Urol 2011 Sep;60(3):493-500. http://www.ncbi.nlm.nih.gov/pubmed/21664041
209. Gallagher BL, Joudi FN, Maymi JL, et al. Impact of previous bacille Calmette-Guérin failure pattern on subsequent response to bacille Calmette-Guérin plus interferon intravesical therapy. Urology 2008 Feb;71(2):297-301. http://www.ncbi.nlm.nih.gov/pubmed/18308107
210. Rosevear HM, Lightfoot AJ, Birusingh KK, et al. Factors affecting response to bacillus Calmette-Guérin plus interferon for urothelial carcinoma in situ. J Urol 2011 Sep;186(3):817-23. http://www.ncbi.nlm.nih.gov/pubmed/21788050
211. Yates DR, Brausi MA, Catto JW, et al. Treatment options available for bacillus Calmette-Guérin failure in non-muscle-invasive bladder cancer. Eur Urol 2012 Dec;62(6):1088-96. http://www.ncbi.nlm.nih.gov/pubmed/22959049
212. Dalbagni G, Russo P, Bochner B, et al. Phase II trial of intravesical gemcitabine in bacille Calmette-Guerin-refractory transitional cell carcinoma of the bladder. J Clin Oncol 2006 Jun;24(18):2729-34. http://www.ncbi.nlm.nih.gov/pubmed/16782913
213. Mohanty NK, Nayak RL, Vasudeva P, et al. Intravesicle gemcitabine in management of BCG refractory superficial TCC of urinary bladder-our experience. Urol Oncol 2008 Nov-Dec;26(6):616-9. http://www.ncbi.nlm.nih.gov/pubmed/18367121
214. Barlow L, McKiernan J, Sawczuk I, et al. A single-institution experience with induction and maintenance intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to bacilli Calmette-Guerin therapy. BJU Int 2009 Oct;104(8):1098-102. http://www.ncbi.nlm.nih.gov/pubmed/19389012
215. Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. J Urol 2000 Mar;163(3):761-7. http://www.ncbi.nlm.nih.gov/pubmed/10687972
216. Nativ O, Witjes JA, Hendricksen K, et al. Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guerin. J Urol 2009 Oct; 182(4):1313-7. http://www.ncbi.nlm.nih.gov/pubmed/19683278

217. Joudi FN, Smith BJ, O'Donnell MA. Final results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. Urol Oncol 2006 Jul-Aug;24(4):344-8. http://www.ncbi.nlm.nih.gov/pubmed/16818189
218. Di Lorenzo G, Perdonà S, Damiano R, et al. Gemcitabine versus bacille Calmette-Guérin after initial bacille Calmette-Guérin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. Cancer 2010 Apr;116(8):1893-900. http://www.ncbi.nlm.nih.gov/pubmed/20162706
219. Yates DR, Rouprêt M. Failure of bacille Calmette-Guérin in patients with high risk non-muscle-invasive bladder cancer unsuitable for radical cystectomy: an update of available treatment options. BJU International 2010 Jul;106(2):162-7. http://www.ncbi.nlm.nih.gov/pubmed/20201829
220. Zlotta AR, Fleshner NE, Jewett MA. The management of BCG failure in non-muscle-invasive bladder cancer: an update. Can Urol Assoc J 2009 Dec;3(6 Suppl 4):S199-205. http://www.ncbi.nlm.nih.gov/pubmed/20019985
221. Jones G, Cleves A, Wilt TJ, et al. Intravesical gemcitabine for non-muscle invasive bladder cancer. Cochrane Database Syst Rev 2012 Jan;1:CD009294. http://www.ncbi.nlm.nih.gov/pubmed/22259002
222. Addeo R, Caraglia M, Bellini S, et al. Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. J Clin Oncol 2010 Feb;28(4):543-8. http://www.ncbi.nlm.nih.gov/pubmed/19841330
223. Turker P, Bostrom PJ, Wroclawski ML, et al. Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome. BJU Int 2012 Sep;110(6):804-11. http://www.ncbi.nlm.nih.gov/pubmed/22321341
224. Chalasani V, Kassouf W, Chin JL, et al. Radical cystectomy for the treatment of T1 bladder cancer: the Canadian Bladder Cancer Network experience. Can Urol Assoc J 2011 Apr;5(2):83-7. http://www.ncbi.nlm.nih.gov/pubmed/21470529
225. May M, Bastian PJ, Brookman-May S, et al. Pathological upstaging detected in radical cystectomy procedures is associated with a significantly worse tumour-specific survival rate for patients with clinical T1 urothelial carcinoma of the urinary bladder. Scand J Urol Nephrol 2011 Sep;45(4):251-7. http://www.ncbi.nlm.nih.gov/pubmed/21388337
226. Svatek RS, Shariat SF, Novara G, et al. Discrepancy between clinical and pathological stage: external validation of the impact on prognosis in an international radical cystectomy cohort. BJU Int 2011 Mar;107(6):898-904. http://www.ncbi.nlm.nih.gov/pubmed/21244604
227. Gupta A, Lotan Y, Bastian PJ, et al. Outcomes of patients with clinical T1 grade 3 urothelial cell bladder carcinoma treated with radical cystectomy. Urology 2008 Feb;71(2):302-7. http://www.ncbi.nlm.nih.gov/pubmed/18308108
228. Denzinger S, Fritsche HM, Otto W, et al. Early versus deferred cystectomy for initial high-risk pT1G3 urothelial carcinoma of the bladder: do risk factors define feasibility of bladder-sparing approach? Eur Urol 2008 Jan;53(1):146-52. http://www.ncbi.nlm.nih.gov/pubmed/17624657
229. Lambert EH, Pierorazio PM, Olsson CA, et al. The increasing use of intravesical therapies for stage T1 bladder cancer coincides with decreasing survival after cystectomy. BJU Int 2007 Jul;100(1):33-6. http://www.ncbi.nlm.nih.gov/pubmed/17552951
230. Shariat SF, Palapattu GS, Karakiewicz PI, et al. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. Eur Urol 2007 Jan;51(1):137-49;discussion 149-51. http://www.ncbi.nlm.nih.gov/pubmed/16793197
231. Thalmann GN, Markwalder R, Shahin O, et al. Primary T1G3 bladder cancer: organ preserving approach or immediate cystectomy? J Urol 2004 Jul;172(1):70-5. http://www.ncbi.nlm.nih.gov/pubmed/15201740
232. Amling CL, Thrasher JB, Frazier HA, et al. Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol 1994 Jan;151(1):31-5;discussion 35-6. http://www.ncbi.nlm.nih.gov/pubmed/8254828
233. Freeman JA, Esrig D, Stein JP, et al. Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. Cancer 1995 Sep;76(5):833-9. http://www.ncbi.nlm.nih.gov/pubmed/8625187

234. Bianco FJ Jr, Justa D, Grignon DJ, et al. Management of clinical T1 bladder transitional cell carcinoma by radical cystectomy. Urol Oncol 2004 Jul-Aug;22(4):290-4.
http://www.ncbi.nlm.nih.gov/pubmed/15283885
235. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol 2001 Oct;166(4):1296-9.
http://www.ncbi.nlm.nih.gov/pubmed/11547061
236. Raj GV, Herr H, Serio AM, et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. J Urol 2007 Apr;177(4):1283-6.
http://www.ncbi.nlm.nih.gov/pubmed/17382713
237. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001 Feb;19(3):666-75.
http://www.ncbi.nlm.nih.gov/pubmed/11157016
238. Hautmann RE, Gschwend JE, de Petriconi RC, et al. Cystectomy for transitional cell carcinoma of the bladder: results of surgery only series in the neobladder era. J Urol 2006 Aug;176(2):486-92.
http://www.ncbi.nlm.nih.gov/pubmed/16813874
239. Ghoneim MA, Abdel-Latif M, El-Mekresh M, et al. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 year later. J Urol 2008 Jul;180(1):121-7.
http://www.ncbi.nlm.nih.gov/pubmed/18485392
240. Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today-a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003 Feb;21(4):690-6.
http://www.ncbi.nlm.nih.gov/pubmed/12586807
241. Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the bladder cancer research consortium. J Urol 2006 Dec;176(6 Pt 1):2414-22.
http://www.ncbi.nlm.nih.gov/pubmed/17085118
242. Shariat SF, Palapattu GS, Amiel GE, et al. Characteristics and outcomes of patients with carcinoma in situ only at radical cystectomy. Urology 2006 Sep;68(3):538-42.
http://www.ncbi.nlm.nih.gov/pubmed/16979748
243. Oge O, Erdem E, Atsu N, et al. Proposal for changes in cystoscopic follow-up of patients with low grade pTa bladder tumour. Eur Urol 2000 Mar;37(3):271-4.
http://www.ncbi.nlm.nih.gov/pubmed/10720851
244. Holmäng S, Andius P, Hedelin H, et al. Stage progression in Ta papillary urothelial tumours: relationship to grade, immunohistochemical expression of tumour markers, mitotic frequency and DNA ploidy. J Urol 2001 Apr;165(4);1124-8.
http://www.ncbi.nlm.nih.gov/pubmed/11257652
245. Fujii Y, Kawakami S, Koga F, et al. Long-term outcome of bladder papillary urothelial neoplasms of low malignant potential. BJU Int 2003 Oct;92(6):559-62.
http://www.ncbi.nlm.nih.gov/pubmed/14511033
246. Leblanc B, Duclos AJ, Bénard F, et al. Long-term follow-up of initial Ta grade 1 transitional cell carcinoma of the bladder. J Urol 1999 Dec;162(6):1946-50.
http://www.ncbi.nlm.nih.gov/pubmed/10569544
247. Zieger K, Wolf H, Olsen PR, et al. Long-term follow-up of non-invasive bladder tumours (stage Ta): recurrence and progression. BJU Int 2000 May;85(7):824-8.
http://www.ncbi.nlm.nih.gov/pubmed/10792160
248. Borhan A, Reeder JE, O'Connell MJ, et al. Grade progression and regression in recurrent urothelial cancer. J Urol 2003 Jun;169(6):2106-9.
http://www.ncbi.nlm.nih.gov/pubmed/12771728
249. Soloway M, Bruck DS, Kim SS. Expectant management of small recurrent, non-invasive papillary bladder tumours. J Urol 2003 Aug;170(2 Pt 1):438-41.
http://www.ncbi.nlm.nih.gov/pubmed/12853794
250. Gofrit ON, Pode D, Lazar A, et al. Watchful waiting policy in recurrent Ta G1 bladder tumours. Eur Urol 2006 Feb;49(2):303-6.
http://www.ncbi.nlm.nih.gov/pubmed/16413659
251. Pruthi RS, Baldwin N, Bhalani V, et al. Conservative management of low risk superficial bladder tumors. J Urol 2008 Jan;179(1):87-90.
http://www.ncbi.nlm.nih.gov/pubmed/17997444
252. Holmang S, Johansson SL. Stage Ta-T1 bladder cancer: the relationship between findings at first follow-up cystoscopy and subsequent recurrence and progression. J Urol 2002 Apr;167(4):1634-7.
http://www.ncbi.nlm.nih.gov/pubmed/11912378

253. Mariappan P, Smith G. A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on a 25-year prospective database. J Urol 2005 Apr;173(4):1008-11.
http://www.ncbi.nlm.nih.gov/pubmed/15758711
254. Soukup V, Babjuk M, Bellmunt J, et al. Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. Eur Urol 2012 Aug;62(2):290-302.
http://www.ncbi.nlm.nih.gov/pubmed/22609313
255. Holmäng S, Ströck V. Should follow-up cystoscopy in bacillus Calmette-Guérin-treated patients continue after five tumour-free years? Eur Urol 2012 Mar;61(3):503-7.
http://www.ncbi.nlm.nih.gov/pubmed/22119022

12. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

5-ALA	5-aminolaevulinic acid
ASR	age-standardized incidence rate
BCG	bacillus Calmette-Guérin
BTA	bladder tumour antigen
CIS	carcinoma *in situ*
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* hybridization
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	randomized controlled trial
TCC	transitional cell carcinoma
TNM	tumour, node, metastasis
TUR	transurethral resection
UICC	Union International Contre le Cancer
US	ultrasound
WHO	World Health Organization

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. 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.