Guidelines on TaT1 (Non-muscle invasive)

Bladder Cancer

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1. BACKGROUND

The first European Association of Urology (EAU) Guidelines on Bladder Cancer were published in 2002 (1). It was later decided to develop separate guidelines for different categories of bladder tumours:

- TaT1 papillary tumours (non-muscle invasive bladder cancer)
- Upper urinary tract tumours
- Carcinoma in situ (CIS)
- Muscle invasive bladder tumours.

Separate guidelines have been published in European Urology for CIS and upper urinary tract tumours (2-3). This overview represents the updated EAU guidelines on TaT1 (non-muscle invasive) bladder cancer.

2. EPIDEMIOLOGY

Bladder carcinoma is the most common malignancy of the urinary tract. In Europe, the highest incidence (given as ASR = age-standardized rate) is reported from its Western (23.6 in males and 5.4 in females) and Southern parts (27.1 in males and 4.1 in females), followed by Northern Europe (16.9 in males and 4.9 in females). The lowest incidence can be observed in Eastern European countries (14.7 in males and 2.2 in females, respectively) (4).

Approximately 75-85% of patients with bladder cancer present with disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1).

3. CLASSIFICATION

3.1 Tumour, Nodes, Metastases Classification (TNM)

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) has been widely accepted (Table 1) (5). It differs from the previous versions in the definition of stage T2 and T3 tumours.

Table 1: 2002 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 2 cm or less in greatest dimension	
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension	
N3	Metastasis in a lymph node more than 5 cm in greatest dimension	

M - Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

3.2 Histological grading of non-muscle invasive bladder tumours

In 1998, the new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification) and published by the WHO in 2004 (6,7) (Table 2). Its major contribution is a detailed histological description of the various grades, employing specific cytological and architectural criteria. A website (www.pathology.jhu.edu/bladder) illustrating examples of various grades was developed to improve accuracy further in using the system.

Table 2: WHO grading in 1973 and in 2004 (6,7)

1973 WHO grading	
Urothelial papilloma	
Grade 1:	well differentiated
Grade 2:	moderately differentiated
Grade 3:	poorly differentiated

2004 WHO grading
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

3.2.1 WHO/ISUP grading

The 2004 WHO grading differentiates between papillary urothelial neoplasms of low malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas.

PUNLMP are defined as lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur. The intermediate grade (grade 2), which was the subject of controversy in the 1973 WHO classification, has been eliminated.

The use of the 2004 WHO classification is advocated, as this should result in a uniform diagnosis of tumours, which is better classified according to risk potential. However, until the 2004 WHO classification has been validated by more clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications (8).

The majority of clinical trials published so far on TaT1 bladder tumours have been performed using the 1973 WHO classification, and therefore the following guidelines are based on the 1973 WHO grade classification.

3.3 Controversial definition of non-muscle invasive (superficial) tumours

A papillary tumour confined to the mucosa is classified as stage Ta according to the TNM system. Tumours that have invaded the lamina propria are classified as stage T1. As Ta and T1 tumours can be removed by transurethral resection (TUR), they are grouped under the heading of non-muscle invasive (superficial) bladder cancer for therapeutic purposes. Also included under this heading are flat, high-grade tumours confined to the mucosa, classified as carcinoma in situ (CIS). However, molecular biology techniques and clinical experience have demonstrated the highly malignant, invasive potential of CIS and T1 lesions. Therefore, the terms non-muscle invasive and superficial bladder cancer are a suboptimal description.

3.4 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 defining dysplasia and CIS. There is also important interobserver variability in classifying stage T1 versus Ta tumours and grading tumours (9,10). As a consequence, this working party strongly recommends that the urologist reviews histological findings with the pathologist.

4. RISK FACTORS

Many of the aetiological factors for the development of bladder tumours are known and the urologist should be aware of the types of occupational exposures that may be related to urothelial carcinogens (11). Aromatic amines were the first to be recognized. At-risk groups include workers in the following industries: printing, iron and aluminium processing, industrial painting, gas and tar manufacturing (level of evidence: 3).

Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer (12,13) (level of evidence: 3a). Smoking leads to higher mortality from bladder cancer during long-term follow-up, even though in a multivariate analysis the prognostic effect of smoking was weaker than that of other factors, such as stage, grade, size and multifocality of the tumour (14).

5. DIAGNOSIS

5.1 Symptoms of TaT1 bladder tumours

Haematuria is the most common finding in TaT1 bladder tumours. TaT1 tumours do not cause bladder pain and rarely present with bladder irritation, dysuria or urgency. In patients who do complain of these symptoms, CIS may be suspected.

5.2 Physical examination

Physical examination will not reveal TaT1 bladder tumours.

5.3 Imaging

5.3.1 Intravenous urography and CT scan

Large tumours may be seen as filling defects in the bladder. Intravenous urography (IVU) is also used to detect filling defects in the calyces, renal pelvis and ureters, and hydronephrosis, which may indicate the presence of a ureteral tumour. The necessity to perform routine IVP once a bladder tumour has been detected is now questioned because of the low incidence of significant findings obtained with this method (15-17) (level of evidence: 3). The incidence of upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone (16). The risk of tumour recurrence in the upper urinary tract during follow-up increases in multiple and high-risk tumours (18).

In many centres, computed tomography (CT) urography is used as an alternative to conventional IVU (19). Especially in invasive tumours of the upper tract, CT urography gives more information than IVU (level of evidence: 4). However, CT urography has the disadvantage of a much higher radiation exposure than IVU.

5.3.2 Ultrasonography (US)

Ultrasonography (US) has been used with increasing frequency 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 filling defects in the bladder. Combined with plain abdominal film, it can be as accurate as IVU in the diagnosis of the cause of haematuria (15,16) (level of evidence: 3).

5.4 Urinary cytology

Examination of a voided urine or bladder-washing specimen for exfoliated cancer cells has high sensitivity in high-grade tumours but low sensitivity in low-grade tumours (level of evidence: 3). It is thus useful when a high-grade malignancy or CIS is present; however, a negative result cannot exclude the presence of a low-grade cancer.

Positive urinary cytology may indicate urothelial tumour anywhere in the urinary tract, from the calyx, through the ureters, into the bladder and proximal urethra. Cytological interpretation is user-dependent (20). The evaluation can be hampered by low cellular yield, urinary tract infections, stones or intravesical instillations. In experienced hands however the specificity exceeds 90% (21) (level of evidence: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable as cytolysis may be often present.

5.5 Urine molecular tests

Many studies have focused on evaluating urinary molecular markers. Several tests based on detection of soluble markers or cell-associated markers are available (21). Most of these tests have a better sensitivity

for detecting bladder cancer than urinary cytology, but specificity is lower (level of evidence: 2b). It remains unclear whether these tests offer additional information that is useful for decision-making, follow-up, treatment and prognosis of non-muscle invasive bladder tumours (21-24). Moreover, the additional costs of some of these tests should be considered.

5.6 Cystoscopy

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. In general, cystoscopy is initially performed in the office, using flexible instruments. If a bladder tumour has been visualized in earlier imaging studies, a diagnostic cystoscopy can be omitted since the patient will undergo TUR.

A careful description of the finding 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.

5.7 Transurethral resection of TaT1 bladder tumours

The goal of the TUR in TaT1 bladder tumours is to make the correct diagnosis and remove all visible lesions.

The strategy of resection depends on the size of the lesion. Small tumours (less than 1 cm) can be resected en bloc, where the specimen contains the complete tumour plus a part of the underlying bladder wall. Some experts believe that a deep resection is not necessary in small apparently low grade lesions with a previous history of TaG1 tumour. Larger tumours should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and the edges of the resection area. The specimens from different fractions must be referred to the pathologist in separate containers to enable him to make a correct diagnosis. Cauterization has to be avoided as much as possible during the resection to prevent tissue destruction.

A complete and correct TUR is essential for the prognosis of the patient (25).

5.8 Bladder and prostatic urethra biopsies

Bladder tumours are often multifocal. Moreover TaT1 tumours can be accompanied by CIS or dysplasia. These lesions may present themselves as velvet-like, reddish areas indistinguishable from inflammation or may be not visible at all.

The biopsies from normal-looking mucosa in patients with TaT1 tumours, so called random biopsies (R-biopsies) or selected site mucosal biopsies, are not routinely recommended. The likelihood of detecting CIS, especially in low-risk tumours, is extremely low (less than 2%) and the choice of adjuvant intravesical therapy is not influenced by the biopsy result (26) (level of evidence: 2a). Cold cup biopsies from normal-looking mucosa should be performed when cytology is positive or when exophytic tumour is of non-papillary appearance. When abnormal areas of urothelium are seen, it is advised to take ‘cold cup’ biopsies or biopsies with a resection loop. Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers.

The involvement of the prostatic urethra and ducts in male patients with TaT1 bladder tumours has been reported. Although the exact risk is not known, it seems to be higher if tumour is located on the trigone or bladder neck, in the presence of bladder CIS and in multiple tumours (27,28) (level of evidence: 3). In these cases and when cytology is positive, with no evidence of tumour in the bladder, or when abnormalities of prostatic urethra are visible, biopsies of the prostatic urethra are recommended. The biopsy is taken using resection loop from the precolicular area.

5.9 Fluorescence cystoscopy

As a standard procedure, cystoscopy and TUR are performed using white light. However, the use of white light may lead to missing lesions that are present but not visible.

Fluorescence cystoscopy is performed using violet light after intravesical instillation of a photosensitizer, usually 5-aminolaevulinic acid (5-ALA) or hexaminolaevulinate (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumour, particularly CIS (29-31) (level of evidence: 2a). However, false-positivity can be induced by inflammation and recent TUR or intravesical instillation.

The benefit of fluorescence-guided TUR for recurrence-free survival was shown in several, small, randomized clinical trials (32-34), but its value remains to be proven in improving the outcome of patients for progression rates or survival. The additional costs of the equipment should be considered.

5.10 Second resection

The significant risk of residual tumour after the initial TUR of TaT1 lesions has been demonstrated (25,35) (level of evidence: 1). Persistent disease after resection of T1 tumours was observed in 33-53% of patients (35-41).

Moreover, the tumour may be understaged by the initial resection. The likelihood that a TaT1, high-grade tumour has been understaged and is therefore muscle invasive is 10% (36,37). As the treatment of a TaT1, high-grade tumour and a T2 tumour is completely different, correct staging is important.

A second TUR should be considered when the initial resection was incomplete, e.g. when multiple and/or large tumours are present, or when the pathologist has reported that the specimen contained no muscle tissue. Furthermore, a second TUR should be performed when a high-grade, non-muscle invasive tumour or a T1 tumour has been detected at the initial TUR.

It has been demonstrated that a second TUR can increase recurrence-free survival (39,40) (level of evidence: 2a). There is no consensus about the strategy and timing of a second TUR. Most authors recommend resection at 2-6 weeks after the initial TUR. The procedure should include a resection of the primary tumour site.

5.11 Pathological report

Pathological investigation of the specimen obtained by TUR and biopsies is an essential step in the diagnosis of bladder cancer. The pathological report should specify the grade of the lesion and the depth of tumour invasion into the bladder wall and should give information about whether the lamina propria and muscle are present in the specimen (42).

Close cooperation between urologist and pathologist is recommended.

5.12 Recommendations for primary assessment of TaT1 bladder tumours

- Renal and bladder ultrasonography, IVU or CT in selected cases (tumours located in the trigone). (Grade of recommendation: B)
- Cystoscopy with description of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended. (Grade of recommendation: C)
- Urine analysis
- Urine cytology
- TUR in one piece for small tumours (less than 1 cm), including a part from the underlying bladder wall. (Grade of recommendation: B)
- TUR in fractions (including muscle tissue) for larger tumours. (Grade of recommendation: B)
- Biopsies of abnormal-looking urothelium, biopsies from normal-looking mucosa when cytology is positive or when exophytic tumour is of non-papillary appearance. (Grade of recommendation: C)
- Biopsy of the prostatic urethra in the case of bladder neck tumour, when bladder CIS is present or suspected, in the case of positive cytology without evidence of tumour in the bladder or when abnormalities of prostatic urethra are visible. If it was not performed during the initial procedure it can be completed at the time of the second resection. The biopsy is taken using resection loop from the precolicular area (Grade of recommendation: C)
- If equipment is available, fluorescence-guided biopsy when bladder CIS is suspected (e.g. positive cytology, recurrent tumour with previous history of a high grade lesion) (Grade of recommendation: C)
- A second TUR at 2-6 weeks after the initial resection when it was incomplete or when a high-grade or T1 tumour was detected. (Grade of recommendation: B)
- The pathological report should specify the grade, the depth of tumour invasion and whether the lamina propria and muscle are present in the specimen. (Grade of recommendation: C)

6. PREDICTING RECURRENCE AND PROGRESSION IN TaT1 TUMOURS

The classic way to categorize patients with TaT1 tumours is to divide them into risk groups based on prognostic factors derived from multivariate analyses. Using such a technique, it was proposed to divide patients into low-risk, intermediate-risk and high-risk groups (43). When using these risk groups, however, no difference is usually made between the risk of recurrence and progression. Although prognostic factors may indicate a high risk for recurrence, the risk of progression may still be low and other tumours may have a high risk of both recurrence and progression.

In order to separately predict the short-term and long-term risks of both recurrence and progression in individual patients, the European Organization for Research and Treatment of Cancer (EORTC) developed a scoring system and risk tables (44). The basis for these tables is the EORTC database, which provided

individual patient data for 2,596 patients diagnosed with TaT1 tumours who were randomized in seven EORTC trials. Patients with CIS only were not included. Seventy eight percent received intravesical treatment, mostly chemotherapy. They did not however have 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 concomitant CIS
- tumour grade.

Table 3 illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 4 shows the total scores stratified, as in the original article (44), into four categories reflecting various probabilities of recurrence and progression at 1 and 5 years. With combining two of the four categories distinctly in recurrence and progression, the EAU working group suggests to use, as shown in the rightmost column in table 4, a 3-tier system defining low, intermediate and high risk groups for recurrence and progression.

Table 3: Weighting used to calculate 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
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

CIS = carcinoma in *situ*

Table 4: Probability of recurrence and progression according to total score

Recurrence score	Probability of recurrence at 1 year %	(95% CI)	Probability of recurrence at 5 years %	(95% CI)	Recurrence risk group
0	15	(10-19)	31	(24-37)	Low risk
1-4	24	(21-26)	46	(42-49)	Intermediate risk
5-9	38	(35-41)	62	(58-65)	
10-17	61	(55-67)	78	(73-84)	High risk
Progression score	**Probability of progression at 1 year %**	**(95% CI)**	**Probability of progression at 5 years %**	**(95% CI)**	**Progression risk group**
0	0.2	(0-0.7)	0.8	(0-1.7)	Low risk
2-6	1	(0.4-1.6)	6	(5-8)	Intermediate risk
7-13	5	(4-7%)	17	(14-20)	High risk
14-23	17	(10-24)	45	(35-55)	

Note: Electronic calculators for Tables 3 and 4 are available at http://www.eortc.be/tools/bladdercalculator/

7. ADJUVANT TREATMENT

7.1 Intravesical chemotherapy

7.1.1 One, immediate, post-operative intravesical instillation of chemotherapy

Although a state-of-the-art TUR by itself could eradicate a TaT1 tumour completely, these tumours will recur in a high percentage of cases and progress to muscle invasive bladder cancer in a limited number of cases. The high variability in the 3-month recurrence rate indicates that TUR is incomplete or provokes recurrences in a considerable percentage of patients (25). It is therefore necessary to consider adjuvant therapy in all patients.

In a meta-analysis of seven randomized trials (1,476 patients with a median follow-up of 3.4 years), one immediate instillation of chemotherapy after TUR decreased the percentage of patients with recurrence by 12% (from 48.4% to 36.7%) and the odds of recurrence by 39%. The benefit was confirmed in both single and multiple tumours (45) (level of evidence: 1a).

The difference of 12% means that in every 100 patients, 12 TURs may be avoided with one post-operative instillation, i.e. that 8.5 patients must be treated to prevent one recurrence. Since the costs of a TUR, anaesthesia and hospitalization in most countries exceed the cost of 8.5 times one instillation, this procedure is considered to be cost-effective. The effect can be explained by the destruction of circulating tumour cells, immediately after TUR, or as an ablative effect (chemoresection) of residual tumour cells at the resection site.

The timing of the instillation is crucial. In all studies, the instillation was administered within 24 hours. One study reported that if the first instillation was not given the same day as TUR, there was a twofold increase in the relative risk of recurrence (46) (level of evidence: 2a).

There is no single drug that is superior with regards to efficacy. Mitomycin C, epirubicin and doxorubicin have all shown a beneficial effect (45) (level of evidence: 1b).

One immediate post-operative instillation of chemotherapy should be given in all patients after TUR of presumably non-muscle invasive bladder cancer. Severe complications have been reported in patients in whom extravasation of the drug occurred (47). Thus, an immediate instillation should be omitted in case of overt or suspected intra- or extra-peritoneal perforation, which is most likely to appear in extensive TUR procedures.

Clear instructions should be given to the nursing staff for controlling the free flow of the bladder catheter at the end of the instillation.

7.1.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on the patient's prognosis. In patients with a low risk of tumour recurrence (see Table 4), a single immediate instillation reduces the risk of recurrence and may be considered to be the standard treatment in these patients (45) (level of evidence: 1a). No further treatment should be given in these patients prior to a subsequent recurrence. For other patients, however, it remains an incomplete treatment as the likelihood of recurrence and/or progression is considerable.

The effect of the immediate instillation of chemotherapy occurs during the first and second year (48,49) (level of evidence: 1b). It has been calculated from the data of five randomized trials (49) that the

reduction of recurrence lasts for a period of approximately 500 days.

The choice between further chemotherapy or immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. A meta-analysis of EORTC and Medical Research Council data, comparing intravesical chemotherapy to TUR alone, demonstrated that chemotherapy prevents recurrence but not progression (50) (level of evidence: 1a). The efficacy of intravesical chemotherapy in reducing the risk of tumour recurrence was confirmed by two other meta-analyses in primary (51) and recurrent tumours (52).

It is still controversial how long and how frequently instillations of intravesical chemotherapy have to be given. From a systematic review of the literature of randomized clinical trials, which compared different schedules of intravesical chemotherapy instillations, one could only conclude that the ideal duration and intensity of the schedule remains undefined because of conflicting data (53).

7.1.3 Optimizing intravesical chemotherapy

One randomized trial has demonstrated that adapting the urinary pH, decreasing the urinary excretion and buffering the intravesical solution reduced the recurrence rate (54) (level of evidence: 1b).

Another randomized trial documented that concentration was more important than the duration of the treatment (55) (level of evidence: 1b). In view of these data, which need confirmation, it seems advisable to ask the patient not to drink the morning before instillation and to dissolve the drug in a buffered solution at optimal pH.

7.2 Intravesical BCG immunotherapy

7.2.1 Efficacy of Bacillus Calmette-Guérin (BCG)

Several meta-analyses have addressed important questions concerning the efficacy of BCG in TaT1 bladder tumours. None of them however are based on individual patient data.

Four meta-analyses confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy in preventing recurrences of TaT1 tumours (56-59) (level of evidence: 1a).

Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression (60,61) (level of evidence: 1a). A meta-analysis carried out by the EORTC evaluated data from 4,863 patients enrolled in 24 randomized trials. A total of 3,967 (81.6%) patients had only papillary tumours and 896 (18.4%) had primary or concomitant CIS. Five different BCG strains were used, and in 20 out of the 24 trials some form of BCG maintenance was used. In four trials only, a 6-week induction course was used. Based on a median follow-up of 2.5 years and a maximum of 15 years, 260 out of 2,658 patients (9.8%) on BCG progressed compared to 304 out of 2,205 (13.8%) in the control groups (TUR alone, TUR plus intravesical chemotherapy, or TUR plus another immunotherapy). This result is a reduction of 27% in the odds of progression with BCG treatment ($p = 0.0001$). The size of the reduction is similar in patients with TaT1 papillary tumours and in those with CIS (61).

However, another two meta-analyses suggested a possible bias in favour of BCG by the inclusion of patients previously treated with intravesical chemotherapy in the studies (62,63).

7.2.2 The optimal BCG schedule

For optimal efficacy, BCG must be given in a maintenance schedule (59-61) (level of evidence: 1a). In the EORTC meta-analysis, only patients receiving maintenance BCG benefited. In the four trials where no maintenance was given, no reduction in progression was observed. In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the odds of progression was observed ($p = 0.00004$). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective (61). In their meta-analyses, Böhle et al. concluded that at least 1 year of maintenance BCG was required to show the superiority of BCG over mitomycin C in preventing recurrence or progression (59,60).

Although some modifications have been tried, induction BCG instillations are classically given according to the empirical 6-weekly induction schedule introduced by Morales 30 years ago. However, many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks, to 30 instillations given over 3 years (64). The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown. Based on the extent of intravesical immune response, it is suggested that three, consecutive, weekly instillations give a maximum response (65).

7.2.3 The optimal dose of BCG

To reduce BCG toxicity, a number of authors have proposed one-third and one-quarter dose instillations of BCG. Comparing one-third dose to full-dose BCG in 500 patients, the Spanish Oncology Group (CUETO) found no overall difference in efficacy. However, there was a suggestion that a full dose of BCG may be more effective in multifocal disease (66,67) (level of evidence: 1b). Although fewer patients 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 showed in a prospective randomized trial that one-third of the standard dose of BCG

may be the minimum effective dose in intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy for preventing recurrence with no decrease in toxicity (68).

7.2.4 BCG toxicity

Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. Due to the more pronounced side-effects of BCG compared to intravesical chemotherapy, reluctance still exists about BCG use. Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis have compromised the use of BCG. However, with increased experience in applying BCG, the side-effects now appear to be less prominent. Serious side-effects are encountered in less than 5% of patients and can be effectively treated in virtually all cases (69) (level of evidence: 1b).

Major complications can appear after systemic absorption of the drug. Thus, BCG should not be administered during the first 2 weeks after TUR, in patients with haematuria and after traumatic catheterization.

7.2.5 Indications for BCG

Although BCG is a very effective treatment, consensus exists that not all patients with non-muscle invasive bladder cancer should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment will depend upon the patient's risk of recurrence and progression.

The use of BCG will not alter the natural course of the disease in tumours at low risk of recurrence and progression (see Table 4) and may be considered to be over-treatment for this category. In patients with tumours at high risk of progression, for whom a cystectomy is not carried out, after an immediate instillation of chemotherapy, BCG including a maintenance schedule is indicated.

Although patients at intermediate-risk of progression were included in the meta-analyses (59,60), a separate confirmation of the superiority of BCG in these patients is not available.

BCG can be offered in this group if chemotherapy is badly tolerated or if the patient continues to have recurrences in spite of repeated chemotherapy instillations. BCG should then be given for at least 1 year.

7.3 Treatment of failures of intravesical therapy

7.3.1 Failure of intravesical chemotherapy

Patients with non-muscle invasive recurrences after intravesical chemotherapy can profit from BCG instillations (62).

7.3.2 Failure of intravesical BCG immunotherapy

Treatment with BCG is considered to have failed in following situations:

a. Whenever muscle invasive tumour is detected during follow-up.
b. If high-grade, non-muscle invasive tumour is present at both 3 and 6 months (70). In patients with tumour present at 3 months, an additional BCG course provokes complete response in more than 50% of cases, both in patients with papillary tumours and CIS (70,71).
c. Any worsening of the disease under BCG treatment, such as a higher number of recurrences, higher T or higher grade, or appearance of CIS, in spite of an initial response (level of evidence: 3).

Patients with a later recurrence after completion of BCG therapy can be treated according to the risk classification (Tables 3 and 4).

Changing from BCG to intravesical chemotherapy or device-assisted chemotherapy instillations can yield responses in selected cases with non-muscle invasive BCG failure. However, experience is limited and these strategies are considered experimental. Because of the high risk of development of muscle invasive tumour in these patients (70,72) (level of evidence: 3), immediate cystectomy is strongly advocated upon BCG failure.

7.4 Recommendations for adjuvant therapy

- The type of intravesical therapy is based on the risk groups as shown in Table 4
- In patients at low risk of tumour recurrence and progression, one immediate instillation of chemotherapy is strongly recommended as the complete adjuvant treatment. (Grade of recommendation: A)
- In patients at an intermediate or high risk of recurrence and an intermediate risk of progression, one immediate instillation of chemotherapy should be followed by further instillations of chemotherapy or a minimum of 1 year of BCG. (Grade of recommendation: A)
- If 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. The optimal schedule and the duration of the chemotherapy instillations remain unclear, but it should probably be given for 6 to 12 months. (Grade of recommendation: B)
- In patients at high risk of tumour progression, after an immediate instillation of chemotherapy, intravesical BCG for at least 1 year is indicated. (Grade of recommendation: A)

- Immediate radical cystectomy may be offered to patients at highest risk of tumour progression. In patients with BCG failure, cystectomy is recommended. (Grade of recommendation: C)
- The absolute risks of recurrence and of progression do not always indicate the risk at which a certain therapy is optimal. The choice of therapy may be considered differently according to what risk is acceptable for the individual patient and the urologist.

8. CYSTECTOMY FOR NON-MUSCLE INVASIVE BLADDER CANCER

Many experts consider it is reasonable to propose immediate cystectomy to those patients with non-muscle invasive tumour who are at high risk of progression. According to the risk tables of the EORTC (see Tables 3 and 4) these are:

- multiple recurrent high-grade tumours
- high-grade T1 tumours
- high-grade tumours with concomitant CIS.

Cystectomy is advocated in patients with non-muscle invasive BCG failure as mentioned above. Delaying cystectomy in these patients may lead to decreased disease-specific survival (73).

9. FOLLOW-UP OF PATIENTS WITH TaT1 BLADDER TUMOURS

Because of the risk of recurrence and progression, patients with TaT1 bladder tumours need be followed; however, the frequency and duration of cystoscopies should reflect the individual patient's degree of risk. Using risk tables (see Tables 3 and 4), we are able to predict the short-term and long-term risks of both recurrence and progression in individual patients and can adapt the follow-up schedule accordingly (44):

a. The prompt detection of muscle invasive and high-grade non-muscle invasive recurrences is critical since a delay in diagnosis and therapy threatens a patient's life.

b. Tumour recurrence in the low-risk group is nearly always low stage and low grade. Small, non-invasive (Ta), low-grade papillary recurrences do not present an immediate danger to the patient and their early detection is not essential for successful therapy (74-81) (level of evidence: 2b).

c. The result of the first cystoscopy after TUR at 3 months is a very important prognostic factor for recurrence and for progression (44,72,82,83) (level of evidence: 1a). The first cystoscopy should thus always be performed 3 months after TUR in all patients with TaT1 bladder tumour.

Randomized studies investigating the possibility of safely reducing follow-up cystoscopies are lacking. The following recommendations are therefore based only on retrospective experience.

9.1 Recommendations for follow-up cystoscopy

- Patients with tumours at low risk of recurrence and progression should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years. (Grade of recommendation: C)
- Patients with tumours at high risk of progression should have a cystoscopy and urinary cytology at 3 months. If negative, the following cystoscopies and cytologies should be repeated every 3 months for a period of 2 years, every 4 months in the third year, every 6 months thereafter until 5 years, and yearly thereafter. A yearly exploration of the upper tract is recommended. (Grade of recommendation: C)
- Patients with intermediate-risk of progression (about one-third of all patients) should have an in-between follow-up scheme using cystoscopy and cytology, adapted according to personal and subjective factors. (Grade of recommendation: C)

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11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

5-ALA	5-aminolaevulinic acid
ASR	age-standardized rate
BCG	bacillus Calmette-Guérin
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
HAL	hexaminolaevulinic acid
ISUP	International Society of Urological Pathology
IVU	intravenous urography
PUNLMP	papillary urothelial neoplasms of low malignant potential
TNM	tumour, node, metastasis
TUR	transurethral resection
UICC	Union International Contre le Cancer
US	ultrasonography
WHO	World Health Organization

Conflict of interest

All members of the Non-Muscle Invasive Bladder Cancer guidelines writing panel have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. 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.