Guidelines on TaT1 (Non-muscle invasive) Bladder Cancer

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European Association of Urology

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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).
- Prognostic factors for TaT1 tumours.
- Muscle-invasive bladder tumours.

Each of the separate guidelines have been published in European Urology (2-4). This overview represents the updated EAU guidelines on TaT1 (non-muscle invasive) bladder cancer.

1.2 Introduction

Approximately 75-85% of patients with bladder cancer present with disease confined to the mucosa (stage Ta-CIS) or submucosa (stage T1). The management of non-muscle invasive bladder cancer has become more complex with regard to initial investigation, treatment and follow-up.

2. CLASSIFICATION

The tumour node metastases (TNM) 2002 classification approved by the Union International Contre le Cancer (UICC) was widely accepted (Table 1) (5) and differs from the TNM 1997 and TNM 1992 classifications in the T2 stage, which now includes bladder wall infiltration of different depth (T2a inner half, T2b outer half).

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	

2.1 Histological grading of superficial bladder tumours

In 1998, a new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification [6]). This new classification system was published by the WHO in 2004 (7) (Table 2). The detailed histological description

of the various grades, employing specific cytological and architectural criteria, is a major contribution of the WHO/ISUP classification (7). A website (www.pathology.jhu.edu/bladder) illustrating examples of various grades was developed to further improve accuracy in using the system. The new WHO/ISUP classification differentiates between papillary urothelial neoplasms of low malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas.

2.1.1 WHO/ISUP grading

The PUNLMP are 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.

Table 2: WHO grading in 1973 and in 2004 (7,8)

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

The 2004 WHO grading classifies the tumours for papillary urothelial neoplasms of low malignant potential (PUNLMP) and urothelial carcinoma into only two grades: low grade and high grade (Table 2). The intermediate group is eliminated; this group and PUNLMP were the subject of controversy in the 1973 WHO classification. The use of the 2004 WHO classification is advocated, as this should result in a uniform diagnosis of tumours, which is better stratified 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 (9).

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.

2.2 Controversial definition of superficial and infiltrative 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 can be removed by transurethral resection (TUR), they are grouped under the heading of 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 term superficial bladder cancer is a suboptimal description.

2.3 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 (10,11). As a consequence, this working party strongly recommends that the urologist reviews histological findings with the pathologist.

2.3.1 Recommendation for use of grading system

Until the 2004 WHO grading system has been validated, the use of the old and the new WHO grading systems together is recommended (grade C recommendation)

3. 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 occur to urothelial carcinogens (12). 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.

Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer (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). The profession and/or smoking habits of patients presenting with bladder cancer should be recorded.

4. DIAGNOSIS

4.1 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.

4.2 Physical examination

Physical examination will not reveal a bladder tumour confined to the mucosa or submucosa (TaT1).

4.3 Imaging

4.3.1 Intravenous urography

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 in low-grade tumours, but increases to 7% in T1G3 tumours (16).

4.3.2 Ultrasonography

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).

4.4 Urinary cytology

Examination of a voided urine or bladder barbotage specimen for exfoliated cancer cells is particularly useful when a high-grade malignancy or CIS is present.

Positive urinary cytology may indicate urothelial tumour anywhere in the urinary tract, from the calyx, through the ureters, into the bladder and urethra. Moreover, negative voided urinary cytology does not exclude the presence of a low-grade bladder tumour. Cytological interpretation can be problematic; low cellular yields, atypia, degenerative changes, urinary tract infections, stones and intravesical instillations hamper a correct diagnosis.

4.5 Urine molecular tests

Many studies have focused on evaluating molecular urinary markers. Tests for bladder tumour antigen, nuclear matrix protein 22 (NMP 22), fibrin-degradation products, Quanticyt and Immunocyt, are now available. Most of these tests have a better sensitivity for detecting bladder cancer, but specificity is lower. Hence false-positive tests can lead to unnecessary imaging and bladder biopsies. It remains unclear whether these tests offer additional information which is useful for decision-making, treatment and prognosis of superficial bladder tumours, as data from large prospective multicentre trials are lacking (18-20). Combining these new markers may optimize their reliability. Moreover, the costs of these tests may be considerable.

4.6 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 or if urinary cytology has previously been found to be positive, diagnostic cystoscopy can be omitted, as anyway the patient will undergo TUR.

4.7 Transurethral resection of TaT1 bladder tumours

Small tumours can be resected in one chip where the chip contains the complete tumour plus a part of the underlying bladder wall. Larger tumours have to be resected in fractions. First, the exophytic tumour tissue is removed, then separately the underlying bladder wall is resected into the muscle. Without the presence of muscle, the pathologist is unable to stage the tumour as Ta, T1 or T2. In the case of large tumours, it is advised to also resect the edges of the resection area separately, as CIS may be present there. The chips of the three different resections have to be stored in three separate containers to enable the pathologist to make a correct diagnosis. Cauterization has to be avoided as much as possible to prevent tissue destruction. Necrotic and cauterized tissue hampers correct staging and grading. A complete and correct TUR is essential for the prognosis of the patient (21).

4.8 Bladder biopsies

Bladder tumours are often multifocal. Carcinoma in situ, dysplasia, inflammation, etc., may present themselves as velvet-like, reddish areas in the bladder or may be not visible at all.

If, except for a papillary tumour, the rest of the bladder mucosa has a normal aspect and if urine cytology is negative, it is not advised to routinely perform random biopsies. The likelihood of detecting CIS is extremely low and the choice of adjuvant intravesical therapy is not influenced by the biopsy result (22) (level of evidence: 2a).

However, when cytology is positive or when abnormal areas of urothelium are seen, it is advised to take ‘cold cup’ biopsies or biopsies with a resection loop. These biopsies, also termed ‘selected biopsies’, should be sent for pathological assessment in separate containers. When a tumour is located on the trigone or bladder neck, when CIS is suspected, or when cytology is positive, biopsies of the prostatic urethra have to be taken.

4.9 Fluorescence cystoscopy

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

Fluorescence cystoscopy, which is performed using blue light and a porphyrin-based photosensitizer, (hexi)-aminolaevulinic acid (HAL or ALA), will reveal areas in the bladder that are suspicious for CIS or for developing papillary tumour that cannot be seen with white-light cystoscopy (23-25). This investigational method has not yet been implemented on a regular basis in daily practice.

4.10 Second resection

Although it seems an easy procedure to remove a bladder tumour by TUR, it has been demonstrated that the occurrence of a new tumour or the presence of residual tumour are frequently observed (26) (level of evidence: 1).

A re-TUR should be performed when the initial resection has been incomplete, e.g. when multiple and/or large tumours are present or when the pathologist has reported that the specimen contains no muscle tissue. Furthermore, a re-TUR should also be performed when a TaT1, high-grade tumour has been detected at the initial TUR.

The likelihood that a TaT1G3 tumour has been understaged and is therefore a muscle-invasive tumour (26,27) is 10%. As the treatment of a TaT1G3 tumour and a T2 tumour is completely different, correct staging is important.

It has been demonstrated that a second TUR leads to reduced recurrences and improved prognosis (28) (level of evidence: 2a). There is no consensus about the timing of a second TUR, but most procedures are done between 2 and 6 weeks after the initial TUR.

4.11 Recommendations for assessment of TaT1 bladder tumours

- Renal and bladder ultrasonography and/or IVU in selected cases (grade 3 tumours)
- Cystoscopy with description of the tumour: site, appearance (a bladder diagram is recommended)
- Urine analysis
- Urine cytology
- TUR in one piece for small tumours, including a part from the underlying bladder wall
- TUR in fractions (including muscle tissue) for larger tumours
  - Selected biopsies of abnormal-looking urothelium
  - Biopsy of the prostatic urethra in case of bladder neck tumour, or suspicion of CIS.

5. ADJUVANT TREATMENT

5.1 One, immediate, post-operative instillation

Although a state-of-the-art TUR by itself could eradicate a Ta,T1 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 (result of cystoscopy 3 months after TUR) indicates that TUR is incomplete or provokes recurrences in a considerable percentage of patients (21). It is therefore necessary to treat every patient adjuvantly with intravesical chemotherapy.

A meta-analysis (29) (level of evidence: 1a) of seven randomized trials (1,476 patients with a median follow-up of 3.4 years) has demonstrated that one immediate instillation of chemotherapy after TUR decreases the relative risk of recurrence by 40%.

Both single and multiple tumours benefit from a single instillation only. 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 within 24 hours, the risk of recurrence increased by twofold (30).

There is no superior drug with regard to efficacy. Mitomycin C, epirubicin and doxirubicin have all shown a beneficial effect (29).

Although it has been advocated in the past to only give one, immediate, post-operative instillation in solitary, low-grade tumours, it is now recommended to give the instillation in every patient. However, severe complications have been reported in patients in whom extravasation of the drug occurred (31). Thus, an immediate instillation should not be given in case of overt or suspected intra- or extra-peritoneal perforation, which is most likely to appear in extensive TUR procedures.

The meta-analysis demonstrated that, in every 100 patients, 12 TURs may be avoided with one post-operative instillation. This means 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.

5.2 Additional adjuvant intravesical instillations

The need for further adjuvant intravesical therapy depends on the prognostic risk of the superficial bladder tumours. A single immediate instillation optimally reduces the recurrence rate in patients belonging to the low-risk group (29) (level of evidence: 1) and may be considered as the standard treatment for these patients. 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 (32,33) (level of evidence: 1). It has been calculated from the data of five randomized trials (33) that the reduction of recurrence lasts for a period of approximately 500 days. The choice between chemotherapy or immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. Adjuvant chemotherapy bladder instillations are effective in preventing recurrence in low-grade tumours. In high-grade tumours, bacillus Calmette-Guerin (BCG) therapy has proven to be superior to intravesical chemotherapy. Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, tumour progression (34,35) (level of evidence: 1a). A meta-analysis of European Organization for Research and Treatment of Cancer (EORTC) and Medical Research Council (MRC) data (36) (level of evidence: 1), comparing intravesical chemotherapy versus TUR alone, demonstrated that chemotherapy does prevent recurrence but not progression.

It is still controversial how long and how frequent intravesical instillations have to be given. The EORTC demonstrated that administrating intravesical chemotherapy monthly for 1 year versus monthly for a period of

6 months did not reduce the recurrence rate when the first instillation was given immediately after TUR (37) (level of evidence: 2). This observation was confirmed by a Japanese study (38) (level of evidence: 3). Another randomized trial reported reduced recurrence rates after 1 year of treatment with epirubicin (19 instillations) compared to only 3 months (9 instillations) (39) (level of evidence: 3). These conflicting data indicate that the optimal instillation scheme is unknown.

5.3 Optimizing intravesical chemotherapy

One randomized trial has demonstrated that adapting the urinary pH, decreasing the urinary excretion and buffering the intravesical solution reduce the recurrence rate (40) (level of evidence: 2a).
Another randomized trial documented that concentration was more important than the duration of the treatment (41) (level of evidence: 2a). 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.

5.4 Intravesical BCG instillations (immunotherapy)

5.4.1 Indications for BCG

Although BCG is considered to be a very effective treatment, consensus exists that not every patient with superficial bladder cancer should be treated with BCG due to its increased risk of toxicity. Ultimately, the choice of treatment will depend upon the patient's risk of recurrence and progression as explained below in Section 5.5. The use of BCG will not alter the natural course of the disease in low-risk patients and may be considered to be over-treatment for this category.

In patients with high-risk tumours for whom a cystectomy is not carried out, no controversy exists about how to treat these patients. In multiple T1G3 tumours, Ta-T1G3 tumours with or without CIS, and CIS alone, where 15% or more of the patients will progress, the advantages of intravesical BCG are more pronounced than in intermediate-risk patients, who are at a lower risk of progression (42,43) (level of evidence: 1).

The treatment of the remaining intermediate-risk tumours (multifocal T1G1, TaG2 and single T1G2 tumours) is more controversial. It consists of complete TUR followed by intravesical chemotherapy or intravesical BCG. The major issue in intermediate-risk tumours is to prevent recurrence and progression, of which recurrence is by far the most likely. Millan-Rodriguez et al. found that, while tumour will recur in about 45% of these patients, the likelihood of progression to muscle-invasive disease is low in these patients at approximately 1.8% (44).

In Section 5.5 (see below), the calculation of risk for tumour recurrence and progression, both short term and long term, are explained.

5.4.2 BCG can delay or prevent progression to muscle-invasive disease

Although BCG is superior to chemotherapy in preventing recurrences (45), controversy existed until recently as to whether BCG could delay or prevent progression to muscle-invasive disease. A meta-analysis carried out by the EORTC has provided a clinically relevant answer to this question (34) (level of evidence: 1). A total of 24 randomized trials were identified with follow-up information on progression for 4,863 patients. 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 risk of progression with BCG treatment ($p = 0.0001$). The size of the reduction is similar in patients with Ta,T1 papillary tumours and in those with CIS.

5.4.3 Maintenance therapy is necessary for optimal efficacy

In this same meta-analysis (34), only patients receiving maintenance BCG benefited. In the four trials where no maintenance was given, no reduction of progression was observed. In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the risk of progression was observed ($p = 0.00004$). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective. In their meta-analysis, Bohle et al. (45) concluded that at least 1 year of maintenance BCG was required to show the superiority of BCG over mitomycin C in preventing recurrence.

5.4.4 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. Early publications reporting deaths due to BCG sepsis and indicating that BCG-induced cystitis occurs in up to 90% of patients have strongly compromised the use of BCG.

However, with increased experience in applying BCG, the side-effects now appear to be less prominent and few, if any, deaths due to BCG therapy have been reported in recent literature. Serious side-effects are encountered in less than 5% of patients and can be effectively treated in virtually all cases (46) (level of evidence: 2).

5.4.5 The optimal schedule for BCG

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 (47). The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown.

5.4.6 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 (48,49) (level of evidence: 2). Although fewer patients reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar in the standard and reduced dose groups. Further research is required to determine the optimal dose of BCG, both for induction instillations and for maintenance (50).

5.4.7 Recommendations for the use of BCG

- BCG is superior to chemotherapy for preventing recurrences
- Patients with intermediate-risk and high-risk tumours are suitable for BCG therapy
- BCG delays, or prevents, progression to muscle-invasive bladder cancer
- Maintenance therapy is necessary for optimal efficacy, but the optimal schedule and dose have not yet been defined
- At least 1 year of maintenance therapy is advised.

5.5 Predicting recurrence and progression in TaT1 tumours

The classic way to categorize patients with TaT1 tumours into risk categories is to use prognostic factors derived from multivariate analyses. In such a way, it should be possible to divide patients into low-risk (50%), intermediate-risk (35%) and high-risk (15%) groups (44). When using these risk groups, however, no separation is 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 for 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 EORTC developed a scoring system and risk tables (4). 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.

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 CIS
- tumour grade.

The probability for recurrence and progression at 1 year varied from 15-61% and 0.2-17%, respectively. After 5 years of follow-up, recurrence and progression rates ranged from 31% to 78% and from 0.8-45% respectively (Tables 3 and 4).

Table 3: Weighting used to calculate recurrence and progression scores

Factor	Recurrence	Progression
Number of Tumours		
Single	0	0
2 to 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
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;* rec/yr = recurrence per year.

Table 4: Probability of recurrence and progression according to score

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

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

Using these tables, the urologist can discuss the various options with the patient, which may range from one post-operative instillation of chemotherapy only, adjuvant intravesical chemotherapy, adjuvant intravesical BCG, or in the worst cases, cystectomy.

5.5.1 Recommendations for intravesical chemotherapy or BCG

- When patients are at low to moderate risk of recurrence and very low risk of progression, a single immediate dose of chemotherapy is strongly recommended as the complete adjuvant treatment
- When patients are at low to moderate risk of progression, regardless of risk of recurrence, a single immediate post-operative dose of chemotherapy should be followed by either more chemotherapeutic instillations for a duration of at least 6-12 months (maintenance) or intravesical BCG instillations for at least 1 year (maintenance)
- When patients are at high risk of progression, intravesical BCG (at least 1 year of maintenance) or immediate radical cystectomy may be offered
- The absolute risks of recurrence and of progression do not exactly indicate at what risk 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.

5.6 Treatment of failures of instillation therapy

Failure of adjuvant intravesical therapy is poorly defined. While progression to muscle-invasive disease is the trigger for cystectomy in most cases, there are other features that may indicate the failure of intravesical instillations.

The treatment can be considered to fail when higher grade or T category or carcinoma in situ (Tis) appear during therapy. If a recurrence (even of the same grade and T category) is present at both 3 months and 6 months, the therapy can also be considered to be a failure because only a few patients will respond to further intravesical therapy (51) (level of evidence: 3). A recurrence at 3 months is not considered to be a failure because additional treatment provokes complete remission in about one-fifth of patients.

Changing from BCG to chemotherapy can give further remissions in selected cases. However, in high-grade papillary tumours, considerable time is lost in the majority of patients and cystectomy is advocated because of the high risk of development of muscle-invasive tumour and even metastases at this stage of the disease.

The time to response to intravesical therapy is not defined. Although it is known that BCG immunotherapy needs some time to evoke an immune response, it is unknown how long the clinician may wait for a response without jeopardizing the patient. Delaying cystectomy might lead to progression, metastases and death from bladder cancer.

Patients with no response to BCG at 6 months after starting BCG should be offered radical cystectomy. Furthermore, the appearance of new superficial tumours every 3 months, the consequent TUR, the ongoing intravesical instillations, etc., may lead to a bladder of such low quality in terms of capacity, urge, pain, etc., that, in selected cases, a patient should undergo a cystectomy.

5.7 Follow-up of patients with TaT1 bladder tumours

As a result of education, many urologists perform life-long, frequent, follow-up cystoscopies for patients with TaT1 bladder tumours. This is not necessary for two reasons (52):

About half of all patients with TaT1 bladder cancer have a very low risk for recurrence and a negligible risk for progression.

The likelihood that a low risk tumour recurs is not high, but once a recurrence appears, it is nearly always low stage and low grade. Not treating, or overlooking such low-risk tumours will not harm the patient (53-58). However, the opposite is true for patients with poor prognostic factors (T1G3, CIS).

The result of the first cystoscopy after TUR at 3 months is a very important prognostic factor for recurrence and for progression. Randomized studies investigating the possibility of safely reducing follow-up cystoscopies are lacking. Therefore, the following recommendations are not based on evidence-based data but on retrospective experience.

5.7.1 Recommendations for follow-up cystoscopy

- Patients with low-risk (TaG1) tumours (50% of all patients) should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years
- High-risk patients (15% of all patients) should have a cystoscopy at 3 months. If negative, the following cystocopies 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 IVU should be recommended
- Patients with intermediate-risk factors (about one-third of all patients) should have an in-between follow-up scheme, adapted according to personal and subjective factors.

6. REFERENCES

1. Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C; European Association of Urology (EAU) Working Group on Oncological Urology. Guidelines on bladder cancer. Eur Urol 2002;24:105-112. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12074395&query_hl=13&itool=pubmed_docsum
2. Oosterlinck W, Solsona E, van der Meijden APM, Sylvester R, Boehle A, Rintala E, Lobel B; European Association of Urology. EAU guidelines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. Eur Urol 2004;46:147-154. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15245806&query_hl=7&itool=pubmed_docsum

3. van der Meijden APM, Sylvester R, Oosterlinck W, Solsona E, Boehle A, Lobel B, Rintala E; 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;48:363-371. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15994003&query_hl=15&itool=pubmed_docsum
4. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes A, Bouffioux C, Denis L, Newling D, Kurth K. Predicting recurrence and progression in individual patients with stage TaT1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006; 49:466-477. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16442208&query_hl=17&itool=pubmed_docsum
5. Sobin DH, Wittekind Ch., eds. pp. 199-202 In: *TNM classification of malignant tumours*. 6th edn. New York: Wiley-Liss, 2002.
6. Epstein JI, Amin MB, Reuter VR, Mostofi FK. 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;22:1435-48. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9850170&query_hl=13&itool=pubmed_docsum
7. Sauter G, Algaba F, Amin M, Busch C, Cheville J, Gasser T, Grignon DJ, Hofstadter F, Lopez-Beltran A, Epstein JI. 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.
8. Mostofi FK, Davis CJ, Sesterhenn IA. Histological typing of urinary bladder tumours. In: *World Health Organization international histologic classification of tumours*. 2nd edn. Heidelberg: Springer-Verlag, 1999.
9. Lopez-Beltran A, Montironi R. Non-invasive urothelial neoplasms: according to the most recent WHO classification. Eur Urol 2004;46:170-176. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15245809&query_hl=23&itool=pubmed_docsum
10. 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;168:968-972. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12187201&query_hl=28&itool=pubmed_docsum
11. Bol M, Baak J, Buhr-Wildhagen S, Kruse AJ, Kjellevold K, Janssen E, Mestad O, Ogreid P. Reproducibility and prognostic variability of grade and lamina propria invasion in stages Ta, T1 urothelial carcinoma of the bladder. J Urol 2003;169:1291-1294. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1262934 5&query_hl=25&itool=pubmed_docsum
12. McCahy PJ, Harris CA, Neal E. The accuracy of recording of occupational history in patients with bladder cancer. Br J Urol 1997;79:91-93. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9043504&query_hl=31&itool=pubmed_docsum
13. Zeegers MP, Tan FE, Dorant E, van den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. Cancer 2000;89:630-639. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10931463&query_hl=34&itool=pubmed_docsum
14. Aveyard P, Adab P, Cheng K, Wallace D, Hey K, Murphy M. Does smoking status influence the prognosis of bladder cancer ? A systematic review. BJU Int 2002;90:228-239. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1213305 7&query_hl=32&itool=pubmed_docsum
15. Goessl C, Knispel HH, Millar K, Klan R. Is routine excretory urography necessary at first diagnosis of bladder cancer? J Urol 1997;157:480-481. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8996338&query_hl=40&itool=pubmed_docsum
16. Herranz-Amo F, Diez-Cordero JM, Verdu-Tartajo F, Bueno-Chomon G, Leal-Hernandez F, Bielsa-Carillo A. Need for intravenous urography in patients with primary transitional carcinoma of the bladder. Eur Urol 1999;36:221-224. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10450006&query_hl=43&itool=pubmed_docsum

17. Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. Long-term follow-up of a bladder carcinoma cohort: routine followup urography is not necessary. J Urol 1998;160:45-48. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9628602&query_hl=50&itool=pubmed_docsum
18. Glas A, Roos D, Deutekom M, Zwinderman A, Bossuyt P, Kurth K. Tumor markers in the diagnosis of primary bladder cancer. A systematic review. J Urol 2003;169:1975-1982. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12771702&query_hl=53&itool=pubmed_docsum
19. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analysis. Urology 2003;61:109-118. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12559279&query_hl=59&itool=pubmed_docsum
20. Van Rhijn BW, van der Poel HG, van der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. Eur Urol 2005;47:736-748. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15925067&query_hl=56&itool=pubmed_docsum
21. Brausi M, Collette L, Kurth K, van der Meijden A, Oosterlinck W, Witjes JA, Newling D, Bouffioux C, Sylvester R; 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;41:523-531. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12074794&query_hl=62&itool=pubmed_docsum
22. van der Meijden A, Oosterlinck W, Brausi M, Kurth KH, Sylvester R, de Balincourt C. Significance of bladder biopsies in Ta,T1 bladder tumors: a report of the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. Eur Urol 1999;35:267-271. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10419345&query_hl=65&itool=pubmed_docsum
23. Schmidbauer J, Witjes F, Schmeller N, Donat R, Susani M, Marberger M; Hexvix PCB301/01 Study Group. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. J Urol 2004;171:135-138. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14665861&query_hl=69&itool=pubmed_docsum
24. Jichlinski P, Guillou L, Karlsen SJ, Malmstrom PU, Jocham D, Brennhovd B, Johansson E, Gartner T, Lange N, van den Bergh H, Leisinger HJ. Hexyl aminolevulinate fluorescence cystoscopy: a new diagnostic tool for photodiagnosis of superficial bladder cancer - a multicenter study. J Urol 2003;170:226-229. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12796694&query_hl=71&itool=pubmed_docsum
25. Zaak D, Kriegmair M, Stepp H, Baumgartner R, Oberneder R, Schneede P, Corvin S, Frimberger D, Knuchel R, Hofstetter A. Endoscopic detection of transitional cell carcinoma with 5-aminolevulic acid: results of 1012 fluorscenic endoscopies. Urology 2001;57:690-694. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11306382&query_hl=84&itool=pubmed_docsum
26. Miladi M, Peyromaure M, Zerbib M, Saighi D, Debre B. The value of a second transurethral resection in evaluating patients with bladder tumours. Eur Urol 2003;43:241-245. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12600426&query_hl=86&itool=pubmed_docsum
27. Jakse G, Algaba F, Malmstrom PU, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? Eur Urol 2004;45:539-546. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15082193&query_hl=89&itool=pubmed_docsum
28. 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;165:808-810. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11176474&query_hl=94&itool=pubmed_docsum
29. Sylvester R, Oosterlinck W, van der Meijden A. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186-2190. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15126782&query_hl=97&itool=pubmed_docsum

30. Kaasinen E, Rintala E, Hellstrom P, Viitanen J, Juusela H, Rajala P, Korhonen H, Liukkonen T; FinnBladder Group. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol 2002;42:167-174. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12160589&query_hl=10&itool=pubmed_docsum
31. Oddens JR, van der Meijden A, Sylvester R. One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? Eur Urol 2004;46:336-338. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15306104&query_hl=102&itool=pubmed_docsum
32. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. J Urol 1999;161:1120-1123. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10081851&query_hl=107&itool=pubmed_docsum
33. Hinotsu S, Akaza H, Ohashi Y, Kotake T. Intravesical chemotherapy for maximum prophylaxis of new early phase superficial bladder carcinoma treated by transurethral resection: a combined analysis of trials by the Japanese Urological Cancer Research Group using smoothed hazard function. Cancer 1999;86:1818-1826. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10547556&query_hl=109&itool=pubmed_docsum
34. Sylvester RJ, van der Meijden, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a combined analysis of the published results of randomized clinical trials. J Urol 2002;168:1964-1970. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12394686&query_hl=114&itool=pubmed_docsum
35. Bohle A, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 2004;63:682-687. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15072879&query_hl=125&itool=pubmed_docsum
36. Pawinski A, Sylvester R, Kurth KH, Bouffioux C, van der Meijden A, Parkmar MK, Bijnens L. A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of TaT1 bladder cancer. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Part on Superficial Bladder Cancer. J Urol 1996;156:1934-1941. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8911360&query_hl=127&itool=pubmed_docsum
37. Bouffioux C, Kurth K, Bono A, Oosterlinck W, Kruger CB, De Pauw M, Sylvester R. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol 1995;153:934-941. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7853578&query_hl=129&itool=pubmed_docsum
38. Nomata K, Noguchi M, Kanetake M, Tsuda N, Hayashi M, Yamashita S, Sakuragi T, Kusaba Y, Shindo K; Nagasaki Clinical Research Group for Bladder Cancer. Intravesical adjuvant chemotherapy for superficial transitional bladder cancer: results of a randomised trial with epirubicin comparing short and long-term maintenance treatment. Cancer Chemother Pharmacol 2002;50:266-270. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12357299&query_hl=5&itool=pubmed_docsum
39. Koga G, Kuroiwa K, Yamaguchi A. Osada Y, Tsuneyoshi M, Naito S. A randomized controlled trial of short- term versus long-term prohylactic intravesical instillation chemotherapy for recurrence after transurethral resection of Ta/T1 transitional cell carcinoma of the bladder. J Urol 2004;171:153-157. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14665865&query_hl=8&itool=pubmed_docsum

40. Au JL, Baladament RA, Wientjes MG, Young DC, Warner JA, Venema PL, Pollifrone DL, Harbrecht JD, Chin JL, Lerner SP, Miles BJ; International Mitomycin C Consortium. Methods to improve efficacy of intravesical mitomycin C: results of an randomized phase III trial. J Natl Cancer Inst 2001;93:597-604. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11309436&query_hl=12&itool=pubmed_docsum
41. Kuroda M, Niijima T, Kotake T, Akaza H, Hinotsu S; 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;45:600-605. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15082202&query_hl=14&itool=pubmed_docsum
42. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int 2004;93:485-490. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15008714&query_hl=5&itool=pubmed_docsum
43. Huncharek, Kupelnick B. Impact of intravesical chemotherapy versus BCG immunotherapy on recurrence of superficial transitional cell carcinoma of the bladder. Am J Clin Oncol 2003;26:402-407. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12902895&query_hl=18&itool=pubmed_docsum
44. Millan-Rodriguez F, Chéchile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J Urol 2000;163:73-78. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10604317&query_hl=20&itool=pubmed_docsum
45. Bohle 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;169:90-95. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12478111&query_hl=22&itool=pubmed_docsum
46. van der Meijden AP, Sylvester RJ, Oosterlinck W, Hoeltl W, Bono AV; EORTC Genito-Urinary Tract Cancer Group. Maintenance bacillus Calmette-Guerin for Ta, T1 bladder tumors is not associated with increase toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. Eur Urol 2003;44:429-434. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14499676&query_hl=24&itool=pubmed_docsum
47. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, Sarasody MF, Bohl RD, Grossman HB, Beck TM, Leimert JT, Crawford ED. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124-1129. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10737480&query_hl=26&itool=pubmed_docsum
48. Martinez-Pineiro JA, Flores N, Isorna S, Solsona E, Sebastian JL, Pertusa C, Rioja LA, Martinez-Pineiro L, Vela R, Camacho JE, Nogueira JL, Pereira I, Resel L, Muntanola P, Galvis F, Chesa N, de Torres JA, Carballido J, Bernuy C, Arribas S, Madero R; for CUETO (Club Urologico Espanol de Tratamiento Oncologico). Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guerin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int 2002;89:671-680. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11966623&query_hl=31&itool=pubmed_docsum
49. Martinez-Pineiro JA, Martinez-Pineiro L, Solsona E, Rodriguez RH, Gomez JM, Martin MG, Molina JR, Collado AG, Flores N, Isorna S, Pertusa C, Rabadan M, Astobieta A, Camacho JE, Arribas S, Madero R; Club Urologico Espanol de Tratamiento Oncologico (CUETO). Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005;174:1242-1247. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16145378&query_hl=3&itool=pubmed_docsum

50. Zlotta AR, van Vooren JP, Huygen K, Drowart A, Decok M, Pirson M, Jurion F, Palfliet K, Denis O, Simon J, Schulmann CC. What is the optimal regimen for BCG intravesical therapy ? Eur Urol 2000;37:470-477.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10765079&query_hl=32&itool=pubmed_docsum
51. Herr H, Dalbagni G. Defining bacillus Calmette-Guerin refractory superficial bladder tumors. J Urol 2003; 169:1706-1708.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12686813&query_hl=34&itool=pubmed_docsum
52. Oge O, Erdem E, Atsu N, Ahin A, Ozen H. Proposal for changes in cystoscopic follow-up of patients with low-grade pTa bladder tumor. Eur Urol 2000;37:271-274.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10720851&query_hl=36&itool=pubmed_docsum
53. Holmäng S, Andius P, Hedelin H, Wester K, Busch C, Johansson SL. Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol 2001;165;1124-1128.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11257652&query_hl=38&itool=pubmed_docsum
54. Fujii Y, Kawakami S, Koga F, Nemoto T, Kihara K. Long-term outcome of bladder papillary urothelial neoplasms of low malignant potential. BJU Int. 2003;92:559-562.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14511033&query_hl=40&itool=pubmed_docsum
55. Leblanc B, Duclos AJ, Bénard F, Côté J, Valiquette L, Paquin JM, Mauffette F, Faucher R, Perreault JP. Long-term follow-up of initial Ta grade 1 transitional cell carcinoma of the bladder. J Urol 1999;162;1946-1950.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10569544&query_hl=42&itool=pubmed_docsum
56. Zieger K, Wolf H, Olsen PR, Hojgaard K. Long-term follow-up of non-invasive bladder tumours (stage Ta): recurrence and progression. BJU Int 2000;85:824-828.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10792160&query_hl=47&itool=pubmed_docsum
57. Borhan A, Reeder JE, O'Connell MJ, Wright KO, Wheeless LL, di Sant' Agnese PA, McNally ML, Messing EM. Grade progression and regression in recurrent urothelial cancer. J Urol 2003;169:2106-2109.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12771728&query_hl=49&itool=pubmed_docsum
58. Soloway M, Bruck DS, Kim SS. Expectant management of small recurrent, non-invasive papillary bladder tumours. J Urol 2003;170:438-441.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12853794&query_hl=53&itool=pubmed_docsum

7. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

ALA	aminolaevulinic acid
BCG	bacillus Calmette-Guérin
CIS	carcinoma in situ
CUETO	Club Urologico Espanol de Tratamiento Oncologico (Spanish Oncology Group)
EAU	European Association of Urology
EORTC	European Organization for Research and Treatment of Cancer
HAL	hexi-aminolaevulinic acid
ISUP	International Society of Urological Pathology
IVU	intravenous urography
MRC	Medical Research Council
NMP 22	nuclear matrix protein 22
PUNLMP	papillary urothelial neoplasms of low malignant potential
SBC	superficial bladder cancer
TCC	transitional cell carcinoma
TNM	tumour, node, metastasis
TUR	transurethral resection
UICC	Union International Contre le Cancer
US	ultrasonography
WHO	World Health Organization