



Guidelines

EAU Guidelines on Non–Muscle-Invasive Urothelial Carcinoma of the Bladder, the 2011 Update

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Abstract

Context and objective: To present the 2011 European Association of Urology (EAU) guidelines on non–muscle-invasive bladder cancer (NMIBC).

Evidence acquisition: Literature published between 2004 and 2010 on the diagnosis and treatment of NMIBC was systematically reviewed. Previous guidelines were updated, and the level of evidence (LE) and grade of recommendation (GR) were assigned.

Evidence synthesis: Tumours staged as Ta, T1, or carcinoma in situ (CIS) are grouped as NMIBC. Diagnosis depends on cystoscopy and histologic evaluation of the tissue obtained by transurethral resection (TUR) in papillary tumours or by multiple bladder biopsies in CIS. In papillary lesions, a complete TUR is essential for the patient's prognosis. Where the initial resection is incomplete or where a high-grade or T1 tumour is detected, a second TUR should be performed within 2–6 wk.

In papillary tumours, the risks of both recurrence and progression may be estimated for individual patients using the scoring system and risk tables. The stratification of patients into low-, intermediate-, and high-risk groups—separately for recurrence and progression—is pivotal to recommending adjuvant treatment. For patients with a low risk of tumour recurrence and progression, one immediate instillation of chemotherapy is recommended. Patients with an intermediate or high risk of recurrence and an intermediate risk of progression should receive one immediate instillation of chemotherapy followed by a minimum of 1 yr of bacillus Calmette–Guérin (BCG) intravesical immunotherapy or further instillations of chemotherapy. Papillary tumours with a high risk of progression and CIS should receive intravesical BCG for 1 yr.

Cystectomy may be offered to the highest risk patients, and it is at least recommended in BCG failure patients. The long version of the guidelines is available from the EAU Web site (www.uroweb.org).

Conclusions: These abridged EAU guidelines present updated information on the diagnosis and treatment of NMIBC for incorporation into clinical practice.

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1. Introduction

The first European Association of Urology (EAU) guidelines on bladder cancer were published in 2002 [1]. Since then the guidelines have been continuously updated, and the most recent version is available from the EAU Web site, www.uroweb.org. An overview of the updated 2011 EAU guidelines on non-muscle-invasive bladder cancer (NMIBC) (Ta, T1, and carcinoma in situ [CIS]) is provided here.

2. Evidence acquisition

The panel members performed a systematic literature search for each section of the guidelines. Medline, Web of Science, and Embase databases were searched for original and review articles published between 2004 and 2010. Panel members selected records with the highest level of evidence according to a modified classification system from the Oxford Centre for Evidence-Based Medicine levels of evidence (LEs) [2]. Recommendations were graded to provide transparency regarding the underlying LE for each recommendation given.

3. Epidemiology

Bladder cancer is the most common malignancy of the urinary tract. The worldwide age standardised rate (ASR) is 10.1 per 100 000 for men and 2.5 per 100 000 for women. In Europe, the highest incidence of bladder cancer (ASR) has been reported in the western region (23.6 in men and 5.4 in women) and in the southern region (27.1 in men and 4.1 in women), followed by northern Europe (16.9 in men and 4.9 in women). The lowest incidence has been observed in eastern European regions (14.7 in men and 2.2 in women) [3].

The global world mortality rate is 4 per 100 000 among men and 1.1 per 100 000 among women. In Europe, bladder cancer mortality rates have declined over the last decade to about 16% in men and 12% in women [4]. Approximately 75–85% of patients with bladder cancer present with disease that is confined to the mucosa (Ta or CIS) or submucosa (T1).

4. Risk factors

Urologists should be aware of the various types of occupational exposures that may be related to urothelial carcinogens [5]. Aromatic amines were recognised first. At-risk groups include workers in the following industries: printing, iron and aluminium processing, industrial painting, and gas- and tar manufacturing (LE: 3). Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer and leads to higher mortality rates [6] (LE: 3).

5. Classification

The Tumour, Node, Metastasis (TNM) classification approved by the Union Internationale Contre le Cancer, which was

Table 1 – 2009 TNM classification of urinary bladder cancer

| | |
|----------------------|--|
| T Primary tumour | |
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Ta | Noninvasive papillary carcinoma |
| Tis | Carcinoma in situ: 'flat tumour' |
| T1 | Tumour invades subepithelial connective tissue |
| T2 | Tumour invades muscle |
| | T2a Tumour invades superficial muscle (inner half) |
| | T2b Tumour invades deep muscle (outer half) |
| T3 | Tumour invades perivesical tissue: |
| | T3a Microscopically |
| | T3b Macroscopically (extravesical mass) |
| T4 | Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall |
| | T4a Tumour invades prostate, uterus, or vagina |
| | T4b Tumour invades pelvic wall or abdominal wall |
| N Lymph nodes | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral) |
| N2 | Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral) |
| N3 | Metastasis in a common iliac lymph node(s) |
| M Distant metastasis | |
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

updated in 2009, is used in these guidelines (Table 1) [7]. The new classification for grading NMIBCs proposed by the World Health Organisation (WHO) and the International Society of Urological Pathology was published by the WHO in 2004 (Table 2) [8]. New categories were defined among flat and papillary lesions. Among papillary lesions, they are papillary urothelial neoplasms of low malignant potential (PUNLMPs) and low-grade and high-grade urothelial carcinomas. PUNLMPs are lesions that do not have the cytologic features of malignancy but show normal urothelial cells in a papillary configuration. They have a negligible

Table 2 – World Health Organisation grading in 1973 and in 2004

| | |
|---|--|
| 1973 WHO grading | |
| Urothelial papilloma: | |
| | Grade 1: well differentiated |
| | Grade 2: moderately differentiated |
| | Grade 3: poorly differentiated |
| 2004 WHO grading | |
| Flat lesions: | |
| | Hyperplasia (flat lesion without atypia or papillary) |
| | Reactive atypia (flat lesion with atypia) |
| | Atypia of unknown significance |
| | Urothelial dysplasia |
| | Urothelial CIS |
| Papillary lesions: | |
| | Urothelial papilloma (which is a completely benign lesion) |
| | Papillary urothelial neoplasm of low malignant potential |
| | Low-grade papillary urothelial carcinoma |
| | High-grade papillary urothelial carcinoma |
| WHO = World Health Organisation; CIS = carcinoma in situ. | |

risk for progression but have a tendency to recur. The intermediate grade (grade 2), which was the subject of controversy in the 1973 WHO classification, was removed.

The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. However, attempts to demonstrate better prognostic value of one system over another have yielded controversial results [9–11]. Most clinical trials published to date on TaT1 bladder tumours used the 1973 WHO classification, and therefore these guidelines are based on this scheme. Both classifications can be used until more prospective trials validate the prognostic role of the WHO 2004.

Despite well-defined criteria, there is interobserver variability in classifying dysplasia versus CIS, stage T1 versus Ta tumours, and grading of the tumours [12]. Consequently, a review of slides is recommended, particularly for T1, CIS, and high-grade lesions.

5.1. *Specific characteristics of carcinoma in situ and its clinical classification*

CIS is a flat, high-grade, noninvasive urothelial carcinoma. It can occur in the bladder, in the upper urinary tract, and in the prostatic ducts and urethra. Bladder CIS is classified into one of three different clinical types [13]: (1) primary, isolated CIS with no previous or concurrent exophytic tumours; (2) secondary, CIS detected during the follow-up of patients with a previous tumour; and (3) concurrent, CIS in the presence of exophytic tumours.

6. **Diagnosis**

Haematuria is the most common finding in NMIBC. Lower urinary tract symptoms may appear in patients with CIS.

6.1. *Imaging*

Intravenous urography (IVU) is used to detect filling defects and dilation in the upper urinary tract that can indicate the presence of urothelial tumour. Large exophytic tumours may be seen as filling defects in the bladder. The need to perform routine IVU is now questioned because of the low incidence of significant findings [14,15] (LE: 3). The incidence of simultaneous upper urinary tract tumours is low (1.8%) but increases to 7.5% in tumours located in the trigone [14]. The risk of tumour recurrence in the upper urinary tract during follow-up is increased in multiple and high-risk tumours [15].

Computed tomography (CT) urography is used as an alternative to conventional IVU. In muscle-invasive tumours of the bladder and in upper urinary tract tumours, CT urography provides more information than IVU (LE: 4).

Transabdominal ultrasound (US) allows the characterisation of renal masses, the detection of hydronephrosis, and the visualisation of intraluminal masses in the bladder. It can be a useful investigative tool in patients with haematuria to detect obstruction; however, it cannot exclude the presence of upper urinary tract tumours (LE: 3).

Imaging (IVU, CT urography, or US) has no role in the diagnosis of CIS.

6.2. *Urinary cytology*

Examining voided urine or bladder washing specimens for exfoliated cancer cells has high sensitivity in high-grade tumours but low sensitivity in low-grade tumours (LE: 2b) [16]. Therefore, it is useful when a high-grade tumour or CIS is present; however, a negative result cannot exclude the presence of a low-grade cancer.

Positive urinary cytology may indicate a urothelial tumour anywhere in the urinary tract. Cytologic interpretation is user dependent [17]. Cytology evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations. With experienced cytologists, the specificity exceeds 90% [16] (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because cytolysis may be present.

6.3. *Urine molecular tests*

Numerous urinary tests for the diagnosis of bladder cancer based on the detection of soluble or cell-associated markers have been developed [16,18]. Three tests are particularly promising, namely, NMP22, UroVysion, and ImmunoCyt [19–21]. Although most of the tests have better sensitivity than urinary cytology, their specificity is lower (LE: 2b). None of them have been accepted as a standard diagnostic procedure in routine urology to date.

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

6.3.1. *Screening of the population at risk of non-muscle-invasive bladder cancer*

Use of the haematuria dipstick, NMP22, or UroVysion for bladder cancer screening in high-risk populations has been reported [22]. However, concerns about feasibility and cost effectiveness mean that the routine application of screening has not yet been established.

6.3.2. *Exploration of patients after haematuria or other symptoms suggestive of bladder cancer*

None of the urinary tests can replace cystoscopy. However, urinary cytology or markers can be used as an adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, the method should have high sensitivity and specificity for high-grade tumours. Urinary cytology is highly specific and sensitive in this regard, and urinary markers are even more sensitive but less specific [16,18].

6.3.3. *Facilitate surveillance of non-muscle-invasive bladder cancer to reduce the number of cystoscopies*

To reduce the number of cystoscopies [16,23], tests should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology is its low sensitivity for low-grade recurrences. Several urinary markers have higher sensitivity, which is still not sufficient. Urinary cytology or markers cannot safely replace cystoscopy in this setting.

6.4. Cystoscopy

The diagnosis of bladder cancer depends on a cystoscopic examination and histologic evaluation of the resected tissue. The diagnosis of CIS is made using the combination of cystoscopy, urine cytology, and histologic evaluation of multiple bladder biopsies [13].

Cystoscopy is initially performed in the office, using flexible instruments. If a bladder tumour has been visualised in earlier imaging studies, a diagnostic cystoscopy can be omitted.

A careful description of the cystoscopy 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.

6.5. Transurethral resection

The goal of transurethral resection (TUR) in TaT1 bladder tumours is to make the correct diagnosis and remove all visible lesions. Small tumours (<1 cm) can be resected en bloc. The specimen should contain 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. Cauterisation must be avoided as much as possible during the resection procedure to prevent tissue destruction.

The pathologic report should specify the grade of the lesion, the depth of tumour invasion into the bladder wall,

and whether the lamina propria and muscle are present in the specimen [24]. A complete and correct TUR is essential for the prognosis of the patient [25].

6.6. Bladder and prostatic urethra biopsies

CIS can present as a velvet-like reddish area that is indistinguishable from inflammation, or it may not be visible at all. When abnormal areas of the urothelium are seen, it is advised to take “cold cup” biopsies or biopsies with a resection loop. Biopsies from normal-looking mucosa, so-called random biopsies (R-biopsies), should be performed in patients with positive urinary cytology in the absence of visible tumour in the bladder. In patients with TaT1 tumours, R-biopsies are not routinely recommended. The likelihood of detecting CIS in low-risk tumours is extremely low (<2%) [26] (LE: 2a). R-biopsies should be performed in TaT1 tumours when cytology is positive or when the exophytic tumour appears nonpapillary. It is recommended to take R-biopsies from the trigone, bladder dome, and from the right, left, anterior, and posterior bladder walls. Material obtained by random or directed biopsies must be sent for pathologic assessment in separate containers.

The involvement of the prostatic urethra and ducts in male patients with NMIBC has been reported. The risk seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours [27] (LE: 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 from abnormal areas and from the precollicular area between the 5 o'clock and 7 o'clock positions using a resection loop.

Table 3 – Recommendations for the diagnosis of non-muscle-invasive bladder cancer

| Recommendations | GR |
|---|----|
| The renal and bladder US may be used during initial workup in patients with haematuria. | C |
| At the time of initial diagnosis of bladder cancer, CT urography or IVU should be performed only in selected cases (eg, tumours located in the trigone). | B |
| Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or by any other noninvasive test. | A |
| Cystoscopy should describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities. A bladder diagram is recommended. | C |
| Voided urine cytology or urinary markers are advocated to predict high-grade tumour before TUR. | C |
| It is recommended to perform TUR in one piece for small papillary tumours (<1 cm), including part of the underlying bladder wall. | B |
| It is recommended to perform TUR in fractions (including muscle tissue) for tumours >1 cm in diameter. | B |
| It is recommended to take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and from right, left, anterior, and posterior bladder walls) are recommended only when cytology is positive or when exophytic tumour has a nonpapillary appearance. | C |
| Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection. The biopsy should be taken from the precollicular area between 5 and 7 o'clock positions using a resection loop. | C |
| If equipment is available, fluorescence-guided biopsy when bladder CIS is suspected (eg, positive cytology, recurrent tumour with previous history of a high-grade lesion). | B |
| A second TUR should be performed 2–6 wk after the initial resection when the latter is incomplete (in large and multiple tumours, no muscle in the specimen) or when an exophytic high-grade and/or T1 tumour is detected. | A |
| The pathologic report should specify the grade, the depth of tumour invasion, and whether the lamina propria and muscle are present in the specimen. | A |

GR = grade; US = ultrasound; CT = computed tomography; IVU = intravenous urography; TUR = transurethral resection; CIS = carcinoma in situ.

6.7. Photodynamic diagnosis (fluorescence cystoscopy)

Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (5-ALA) or hexaminolevulinic acid (HAL). Fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly CIS. The additional detection rate of PDD was 20% for all tumours and 23% for CIS in a cumulative analysis of prospective trials [28] (LE: 2a). However, false positivity can be induced by inflammation, recent TUR, or bacillus Calmette-Guérin (BCG) intravesical instillation during the previous 3 mo.

The benefit of 5-ALA fluorescence-guided TUR for recurrence-free survival has been considered. Cumulative analysis of three trials has shown that recurrence-free survival was 15.8–27% higher at 12 mo in the fluorescence-guided TUR groups compared with the white light cystoscopy alone groups [28] (LE: 2a). However, a large Swedish study could not detect any advantage in using 5-ALA fluorescence-guided TUR [29]. A recent trial that compared HAL fluorescence-guided TUR with standard TUR reported an absolute reduction of no more than 9% in the recurrence rate within 9 mo in the HAL arm [30].

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

PDD should be restricted to those patients who are suspected of harbouring a high-grade tumour, particularly CIS (eg, for biopsy guidance in patients with positive cytology or with a history of high-grade tumour).

6.8. Second resection

A significant risk of residual tumour after the initial TUR of TaT1 lesions has been shown [25,31] (LE:1b). Moreover, the tumour may be understaged by the initial resection.

A second TUR should be considered if there is any suspicion that the initial resection was incomplete (eg, when multiple or large tumours are present or when the pathologist reported no muscle tissue in the specimen). Furthermore, it should be performed when a high-grade

Table 4 – Weighting used to calculate recurrence and progression scores*

| Factor | Recurrence | Progression |
|------------------------|------------|-------------|
| No. 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 per year | 2 | 2 |
| >1 recurrence per 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; WHO = World Health Organisation.

* Electronic calculator for Table 4 is available at

<http://www.eortc.be/tools/bladdercalculator/>.

non-muscle-invasive tumour or a T1 tumour was detected at the initial TUR. A second TUR can increase recurrence-free survival [32] (LE: 2a).

Second resection should be performed 2–6 wk after the initial TUR. The procedure should include a resection of the primary tumour site.

Table 3 summarises the recommendations for the diagnosis of NMIBC.

7. Predicting recurrence and progression

7.1. Prognosis of TaT1 tumours

The classic way to categorise patients with TaT1 tumours is to divide them into risk groups based on prognostic factors derived from multivariate analyses. To predict separately

Table 5 – Probability of recurrence and progression according to total score*

| Recurrence score | Probability of recurrence at 1 yr | | Probability of recurrence at 5 yr | | Recurrence risk group |
|-------------------|------------------------------------|-----------|------------------------------------|----------|------------------------|
| | % | (95% CI) | % | (95% CI) | |
| 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) | High risk |
| 10–17 | 61 | (55–67) | 78 | (73–84) | High risk |
| Progression score | Probability of progression at 1 yr | | Probability of progression at 5 yr | | Progression risk group |
| | % | (95% CI) | % | (95% CI) | |
| 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) | High risk |

CI = confidence interval.

* Electronic calculator for Table 5 is available at <http://www.eortc.be/tools/bladdercalculator/>.

the short- and long-term risks of both recurrence and progression in individual patients, a scoring system and risk tables were developed by the European Organisation for Research and Treatment of Cancer (EORTC) [33]. The EORTC database provided individual data for 2596 patients diagnosed with TaT1 tumours who did not have a second TUR or receive maintenance BCG therapy. The EORTC scoring system is based on the six most significant clinical and pathologic factors: number of tumours, tumour size, prior recurrence rate, T category, presence of concomitant CIS, and tumour grade.

Table 4 illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 5 shows the total scores stratified into four categories reflecting the probabilities of recurrence and progression at 1 and 5 yr [33]. With combining two of the four categories distinctly in recurrence and progression, the EAU working group suggests using a three-tier classification system defining low-, intermediate-, and high-risk groups (as shown in the right-most column in Table 5).

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression was recently developed by the Club Urológico Español de Tratamiento Oncológico (CUETO; Spanish Oncology Group). Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression probabilities, it is lower only in high-risk patients [34]. The lower risks in the CUETO tables may be attributable to using a more effective instillation therapy in the individual studies on which the tables are based.

7.2. Prognosis of carcinoma in situ

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [13,35]. There are no reliable prognostic factors that can be used to predict the course of CIS. Some studies have reported a worse prognosis in patients with concurrent CIS and T1 tumours compared with primary CIS, extended CIS, and those who do not respond to BCG treatment [13,36] (LE: 3).

8. Adjuvant intravesical chemotherapy

8.1. One immediate postoperative intravesical instillation

TaT1 tumours recur frequently and progress to muscle-invasive disease in a limited number of cases. It is therefore necessary to consider adjuvant therapy in all patients.

The results of a meta-analysis of seven randomised trials demonstrated that one immediate instillation of chemotherapy after TUR significantly reduced recurrence compared with TUR alone (LE: 1a) [37]. In absolute values, the reduction was 11.7%, which implies a 24.2% decrease in the corresponding relative risk. The efficacy of the single instillation has also been confirmed by two recently published studies [38,39]. In one of these, the benefit was mainly seen in primary and single tumours. When stratified according to EORTC recurrence scores, the benefit was

observed in patients with scores of 0–2 but not with scores ≥ 3 . However, the study was not sufficiently powered for subgroup analyses [39].

No prospective data are available showing that the single instillation significantly reduces recurrence rates in patients with recurrent tumours. Nevertheless, there is significant evidence from one subgroup analysis that immediate instillation might have an impact on the repeat instillation regimens for the treatment of patients who have an intermediate and high risk of recurrence [40] (LE: 2a). There are no statistically relevant data that address the role of immediate chemotherapy instillation before further BCG intravesical treatment in tumours with a high risk of progression.

In summary, one immediate instillation of chemotherapy significantly reduces the risk of recurrence of TaT1 bladder cancer. Further studies are required, however, to determine the definitive role of immediate chemotherapy before BCG or further chemotherapy instillations in intermediate- and high-risk groups.

Adjuvant chemotherapy is thought to mediate its effect by destroying circulating tumour cells or having an ablative effect on residual tumour cells at the resection site. Prevention of tumour cell implantation should be initiated within the first hours after cell seeding. In all studies, the instillation was administered within 24 h. Subgroup analysis of one study has shown that, if the first instillation was not given on the same day as TUR, there was a twofold increase in the relative risk of recurrence [40] (LE: 2a). A study in which the instillation was not given strictly on the same day did not find any advantage [41].

Mitomycin C (MMC), epirubicin, and doxorubicin have all shown comparable beneficial effects [37] (LE: 1a).

Early immediate instillation of chemotherapy is recommended in tumours at low risk of recurrence and progression as the only intravesical treatment. A single instillation is considered as the initial stage of further intravesical therapy in those presumably at intermediate risk. In tumours that presumably have a high risk of progression (solid lesions, positive urinary cytology), immediate instillation is an option because it can have a positive impact on the recurrence rate through prevention of tumour cell implantation. However, there is no doubt that subsequent BCG intravesical immunotherapy is an essential treatment option in these patients.

The instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation, which is most likely to appear in extensive TUR procedures and in situations with difficult bleeding requiring bladder irrigation. Severe complications have been reported in patients in whom extravasation of the drug occurs [42]. Clear instructions should be given to the nursing staff to control the free flow of the bladder catheter at the end of the instillation.

8.2. Additional intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on the patient's prognosis. In patients with a low risk of

recurrence (Table 5), a single immediate instillation is considered to be sufficient treatment [37] (LE: 1a). For other patients, however, it remains an incomplete treatment because the likelihood of recurrence and/or progression is considerable.

The choice between further chemotherapy or BCG immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. A meta-analysis comparing intravesical chemotherapy with TUR alone demonstrated that chemotherapy prevents recurrence but not progression [43] (LE: 1a). The efficacy of intravesical chemotherapy in reducing the risk of tumour recurrence was confirmed by two other meta-analyses in primary [44] and recurrent tumours [45].

It is still controversial how long and how frequently intravesical chemotherapy instillations should be given [46]. Nevertheless, the available evidence does not support any treatment schedule >1 yr.

8.3. Optimising intravesical chemotherapy

Adapting the urinary pH, decreasing urinary excretion, and buffering the intravesical solution can reduce the recurrence rate [47] (LE: 1b). Concentration was more important than treatment duration [48] (LE: 1b). In view of these data, it seems advisable to dissolve the drug in a buffered solution at optimal pH and to instruct the patient not to drink on the morning before instillation.

8.4. Adjuvant intravesical bacillus Calmette-Guérin immunotherapy

The superiority of BCG after TUR compared with TUR alone or TUR and chemotherapy in preventing recurrences of TaT1 tumours has been confirmed [49–56] (LE: 1a). The clinical effect is long lasting [54,55], and it was also observed in a separate analysis of patients with intermediate-risk tumours [55].

A recently published meta-analysis [56] evaluated individual data from 2820 patients who were enrolled in nine randomised studies that compared MMC with BCG. In the BCG maintenance trials, a 32% reduction in the risk of recurrence was found for BCG compared with MMC ($p < 0.0001$), whereas BCG without maintenance was less effective than MMC.

Data from two meta-analyses demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [57,58] (LE: 1a). The EORTC meta-analysis demonstrated a reduction of 27% in the odds of progression with BCG maintenance treatment ($p = 0.0001$) [57]. A recent randomised study with a long-term observation period demonstrated significantly fewer distant metastases and better overall and disease-specific survival in patients treated with BCG compared with epirubicin [55]. On the contrary, a meta-analysis of individual patient data was unable to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [56].

In summary, despite these conflicting results, most of the data were able to show a reduction in the risk of progression

in tumours with high and intermediate risk if BCG including a maintenance schedule was used.

8.5. The optimal bacillus Calmette-Guérin

For optimal efficacy, BCG should be given on a maintenance schedule [52,56–58] (LE: 1a). The observations from the EORTC meta-analysis revealed that only patients receiving maintenance BCG benefitted. In the four trials where no maintenance BCG 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 ($p = 0.00004$). However, the meta-analysis was unable to determine which BCG maintenance schedule was the most effective [57]. The conclusions of other meta-analyses stated that at least 1 yr of maintenance BCG was required to show the superiority of BCG over MMC in preventing recurrence or progression [52,58].

Induction BCG instillations are classically given according to the empirical 6-weekly induction schedule, and many different maintenance schedules have been used with up to 30 instillations given over 3 yr [59]. The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown.

To reduce toxicity, one-third and one-quarter doses of BCG have been proposed. No overall difference in BCG efficacy was found when the one-third dose was compared with the full dose. However, there was a suggestion that a full dose of BCG may be more effective in multifocal disease [60] (LE: 1b). Although fewer patients reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar. A further reduction of BCG to one-sixth dose was associated with decreased efficacy but with equal toxicity [61].

8.6. Bacillus Calmette-Guérin toxicity

The use of BCG has been compromised because of tolerability issues, namely, deaths due to BCG sepsis and BCG-induced cystitis. However, with increased experience in using BCG, the side effects now appear to be less prominent. Fewer than 5% of patients experience serious side effects with BCG use [62] (LE: 1b). Major complications can appear after systemic absorption of the drug. BCG should not be administered during the first 2 wk after TUR, in patients with haematuria or urinary tract infection, after traumatic catheterisation, or in immunocompromised patients (LE: 2b). The management of side effects after BCG therapy should reflect their type and grade [63].

8.7. Indications for bacillus Calmette-Guérin

There is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. BCG use does not alter the natural course of tumours with a low risk of recurrence (Table 5) and may be considered overtreatment for this category of patients. In patients with tumours with a high risk of progression, BCG including a maintenance

Table 6 – Treatment recommendations in TaT1 tumours according to risk stratification

| Risk category | Low | Intermediate | High |
|---------------|--|--|---|
| Recurrence | One immediate instillation of chemotherapy | One immediate instillation of chemotherapy, followed by further instillations, either chemotherapy or a minimum 1 yr of BCG (the final choice is determined by the risk of tumour progression) | One immediate instillation of chemotherapy, followed by further instillations, either chemotherapy or a minimum of 1 yr of BCG (the final choice is determined by the risk of tumour progression) |
| Progression | One immediate instillation of chemotherapy (it can be followed by further chemotherapy instillations if the patient has an intermediate risk of recurrence at the same time) | One immediate instillation of chemotherapy, followed by a minimum of 1 yr of BCG or further chemotherapy instillations | Intravesical BCG for at least 1 yr or immediate cystectomy |

BCG = bacillus Calmette-Guérin.

schedule is recommended. BCG with 1-yr maintenance is more effective than chemotherapy for preventing recurrence in patients with an intermediate or high risk of recurrence and intermediate risk of progression; however, BCG has more side effects than chemotherapy. For this reason both BCG with maintenance and intravesical chemotherapy remain a treatment option. The final choice should reflect the individual patient's risk and the efficacy and tolerability of each treatment modality. Tables 6 and 7 summarise the recommendations for intravesical therapy in TaT1 tumours.

8.8. Specific aspects of treatment of carcinoma in situ

CIS cannot be resolved by endoscopic procedure alone. Histologic diagnosis of CIS must be followed by further treatment, either intravesical instillations or radical cystectomy (LE: 2). No consensus exists about whether conservative therapy (intravesical BCG instillations) or aggressive therapy (cystectomy) should be performed. Tumour-specific survival rates after early cystectomy for CIS are excellent, but up to 40–50% of patients may be overtreated [13].

8.8.1. Intravesical treatment of bladder carcinoma in situ

Retrospective evaluations have reported a complete response rate of 48% with intravesical chemotherapy and

72–93% with BCG (LE: 2a). The results of a meta-analysis of clinical trials in CIS patients that compared intravesical BCG with chemotherapy showed a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG (odds ratio [OR]: 0.41; $p = 0.0001$). Clinical trials that compared BCG with MMC showed that the long-term benefit of BCG was smaller, but BCG was superior to MMC in BCG maintenance studies (OR: 0.57; $p = 0.04$) [64].

The EORTC meta-analysis of tumour progression in a subgroup of 403 CIS patients showed that BCG reduced the risk of progression by 35% compared with intravesical chemotherapy or different immunotherapy [57] (LE: 1a).

In summary, when compared with chemotherapy, BCG treatment increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression in CIS patients (LE: 1a).

8.8.2. Treatment of extravesical carcinoma in situ

Patients with CIS in the epithelial lining of the prostatic urethra can be treated with intravesical instillations of BCG. Previous TUR of the prostate can improve the contact of BCG with the prostatic urethra [65] (LE: 3). In patients with prostatic duct involvement, radical surgery should be considered [65] (LE: 3). Table 7 summarises the recommendations for therapy of CIS.

Table 7 – Recommendations for adjuvant therapy in TaT1 tumours and for treatment of carcinoma in situ

| Recommendations | GR |
|--|----|
| The type of adjuvant therapy should be based on the risk groups specified in Table 5. | A |
| In patients at low risk of tumour recurrence and progression, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment. | A |
| In patients with TaT1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, one immediate instillation of chemotherapy should be followed by a minimum 1 yr of BCG treatment or by further instillations of chemotherapy. | 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 no more than 1 yr. | B |
| In patients at high risk of tumour progression, intravesical BCG for at least 1 yr is recommended. | A |
| In patients with bladder CIS, intravesical BCG is recommended for at least 1 yr. | A |
| In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillations of BCG may be a suitable option. | C |
| For patients at high risk of tumour progression, immediate cystectomy may be offered. | C |
| Cystectomy is recommended for patients with BCG failure. | B |

GR = grade; BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; TUR = transurethral resection.

Table 8 – Recommendations for follow-up of non-muscle-invasive bladder cancer in patients after transurethral resection

| Recommendations | GR |
|--|----|
| Patients with TaT1 tumours at low risk of recurrence and progression should have a cystoscopy at 3 mo. If negative, the following cystoscopy is advised 9 mo later and then yearly for 5 yr. | C |
| Patients with TaT1 tumours at high risk of progression and those with CIS should have a cystoscopy and urinary cytology at 3 mo. If negative, the following cystoscopy and cytology should be repeated every 3 mo for a period of 2 yr, every 6 mo thereafter until 5 yr, and then yearly. Yearly imaging of the upper tract is recommended. | C |
| Patients with TaT1 tumours at intermediate risk of progression (about a third of all patients) should have an intervening follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors. | C |
| During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended. | B |
| GR = grade; CIS = carcinoma in situ; PDD = photodynamic diagnosis; CT = computed tomography. | |

8.9. Treatment of failures of intravesical therapy

Patients with non-muscle-invasive recurrences after intravesical chemotherapy can benefit from BCG instillations (LE: 1a). Treatment with BCG is considered to have failed in the following situations: (1) where muscle-invasive tumour is detected during follow-up; (2) when high-grade non-muscle-invasive tumour is present at both 3 and 6 mo [66]. In patients with tumour present at 3 mo, an additional BCG course can achieve complete response in >50% of cases [13,66] but increases the risk of progression [67,68]; and (3) any deterioration of the disease under BCG treatment, such as a higher number of recurrences, higher T stage or higher grade, or the appearance of CIS, despite an initial response (LE: 3).

Changing from BCG to intravesical chemotherapy, device-assisted chemotherapy instillations, or additional interferon α -2b can yield responses in selected cases with non-muscle-invasive BCG treatment failure. However, these strategies are considered experimental. Due to an increased risk of developing muscle-invasive tumour [66–68] (LE: 3), cystectomy is strongly advocated following early BCG failure in fit patients.

Patients with recurrence at >1 yr after completion of BCG therapy can be treated according to the risk classification defined in Tables 4, 5, and 6.

9. Cystectomy for non-muscle-invasive bladder cancer

Immediate cystectomy can be considered for those patients who are at high risk of progression. According to the EORTC tables (Tables 4 and 5), these patients have multiple recurrent high-grade tumours, high-grade T1 tumours, and high-grade tumours with concurrent CIS. Cystectomy is advocated in patients with BCG failure. Delaying cystectomy in these patients may lead to decreased disease-specific survival [69].

10. Follow-up

Patients need to be followed up because of the risk of recurrence and progression; however, the frequency and duration of cystoscopies and upper urinary tract investigations should reflect the degree of risk [33]. When planning a

follow-up schedule, the following aspects should be considered:

- Prompt detection of muscle-invasive and high-grade non-muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life threatening.
- Tumour recurrence in the low-risk group is nearly always low stage and low grade. Small noninvasive (Ta), low-grade papillary recurrences do not present an immediate danger to the patient, and early detection is not essential for successful therapy [70] (LE: 2b). In these patients, fulguration of small papillary recurrences on an outpatient basis is considered a safe treatment option [71] (LE: 3).
- The result of the first cystoscopy after TUR at 3 mo is a very important prognostic factor for recurrence and progression [33,67,72] (LE: 1a). The first cystoscopy should always be performed 3 mo after TUR.
- The risk of upper urinary tract recurrence increases in patients with multiple and high-risk tumours [15] (LE: 3).

Table 8 lists the recommendations for the follow-up schedule of NMIBC.

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