GUIDELINES ON NON-MUSCLE INVASIVE (Ta, T1, CIS) BLADDER CANCER

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Introduction

The EAU Working Group has published guidelines on non-muscle-invasive bladder cancer (NMIBC). It comprises Ta and T1 tumours as well as carcinoma *in situ* (CIS).

Staging and classification systems

The TNM Classification of Malignant Tumours, 7th Edition, 2009 will apply (Table 1).

Table 1: TNM Classification 2009	
T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N - Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Carcinoma *in situ* classification

CIS is classified into the following clinical types:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

Currently, two grading systems for NMIBC are available, WHO 1973 and WHO 2004 (Table 2).

The prognostic value of both WHO 1973 and 2004 grading systems has been confirmed. The WHO 2004 system has not yet been fully incorporated into prognostic models. Most clinical trials published to date on Ta, T1 bladder tumours have been performed using the 1973 WHO classification, and the following guidelines are therefore based on this version.

Table 2: WHO 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 system** *Papillary lesions:* • Urothelial papilloma (completely benign lesion) • Papillary urothelial neoplasm of low malignant potential (PUNLMP) • Low-grade (LG) papillary urothelial carcinoma • High-grade (HG) papillary urothelial carcinoma *Flat lesions:* • Hyperplasia (flat lesion without atypia or papillary aspects) • Reactive atypia (flat lesion with atypia) • Atypia of unknown significance • Urothelial dysplasia • Urothelial CIS is always high-grade

Diagnosis

A comprehensive patient history is mandatory. Haematuria is the most common finding. Physical examination will not reveal NMIBC.

Guidelines for primary assessment of NMIBC	GR
Patient history should be taken.	A
Renal and bladder US may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of NMIBC, CT urography (or IVU) should be performed only in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	B
Cystoscopy is recommended in all patients with symptoms suggestive of BC. It cannot be replaced by cytology or by any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Voided urine cytology is advocated to predict HG tumour before TURB.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C

BC = bladder cancer; CT = computed tomography; GR = grade of recommendation; HG = high-grade; IVU = intravenous urography; US = ultrasound; NMIBC = non-muscle invasive bladder cancer; TURB = transurethral resection of the bladder.

Papillary (Ta, T1) tumours

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue.

Transurethral resection (TURB) of Ta, T1 tumours

TURB is a crucial procedure in the diagnosis and treatment of BC. It should be performed systematically in individual steps

(see recommendations below). The strategy of resection depends on the size of the lesion.

In selected cases, due to the risk of tumour persistence and understaging after initial TURB, a second resection (2nd TURB) is recommended.

Carcinoma *in situ*

CIS is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies. Carcinoma *in situ* cannot be eradicated by TURB and further treatment is mandatory.

Guidelines for TURB and/or biopsies, tumour classification and pathology report	**GR**
TURB should be performed systematically in individual steps: • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • protocol formulation; • surgical report formulation – precise description of the specimen for pathological evaluation.	C
Individual steps:	
Perform resection in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B

Perform resection in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area for tumours > 1 cm in diameter.	B
Avoid cauterization as much as possible during TURB to avoid tissue deterioration.	C
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended only when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance).	C
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, the cold-cup biopsy with forceps can be used.	C
If equipment is available, use fluorescence-guided (PDD) biopsy instead of random biopsies when bladder CIS or HG tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a HG lesion).	B
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C

TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC , CIS in the bladder (random biopsies or PDD targeted biopsies) and tumour in the prostatic urethra (prostatic urethra biopsy).	C
Perform a second TURB in the following situations: • after incomplete initial TURB; • if there is no muscle in the specimen after initial resection, with the exception of Ta G1 tumours and primary CIS; • in all T1 tumours; • in all G3 tumours, except primary CIS.	A
If indicated, perform a second TURB within 2-6 weeks after initial resection. It should include resection of the primary tumour site.	C
Classification and pathological report	
For classification of the depth of tumour invasion (staging) use the 2009 TNM system.	A
For histological classification, use both the 1973 and 2004 WHO grading.	A
Do not use the term "Superficial BC".	A
Whenever using the terminology NMIBC in individual cases, mention the tumour stage and grade.	A
The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathological report should specify the presence of LVI or unusual (variant) histology.	C

In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

BC = bladder cancer; CIS = carcinoma in situ; CT = computed tomography; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; TNM = Tumour, Node, Metastasis; TURB = transurethral resection of the bladder; WHO = World Health Organisation.

Predicting disease recurrence and progression

After TURB, patients should be stratified, according to prognostic factors, into risk groups which will facilitate treatment recommendations. Their definition, which takes into account the EORTC risk tables probabilities of recurrence and especially progression, can be found in Table 3. For individual prediction of the risk of tumour recurrence and progression at different intervals after TURB, application of EORTC risk tables and calculator (http://www.eortc.be/tools/bladdercalculator/) is strongly recommended.

For BCG-treated patients, a scoring model was created by the Club Urológico Español de Tratamiento Oncológico (CUETO). The CUETO risk calculator is available at: http://www.aeu.es/Cueto.html.

Table 3: Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, LG/G1,< 3 cm, no CIS	One immediate instillation of chemotherapy.
Intermediate-risk tumours	All cases between categories of low and high risk	One immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1-year full-dose BCG.
High-risk tumours	Any of the following: • T1 tumours; • HG/G3 tumours; • CIS; • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be presented).	Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest-risk tumours).

Subgroup of highest-risk tumours	T1G3 associated with concurrent bladder CIS, multiple and/or largeT1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, unusual histology of urothelial carcinoma, LVI.	Radical cystectomy (RC) should be considered.
		In those who refuse RC, intravesical full-dose BCG instillations for 1-3 years.
	BCG failures	Radical cystectomy is recommended.

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

Recommendations for stratification of NMIBC	**GR**
Stratify patients into three risk groups.	B
Apply the EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B
In patients treated with BCG, use the CUETO risk tables for individual prediction of the risk of tumour recurrence and progression.	B

BCG = Bacillus Calmette-Guérin; CUETO = Club Urológico Español de Tratamiento Oncológico; GR = grade of recommendation; EORTC = European Organization for Research and Treatment of Cancer; TURB = transurethral resection of the bladder.

Disease management

Adjuvant treatment

Since there is considerable risk for recurrence and/or progres-

sion of tumours after TURB, adjuvant intravesical therapy is recommended for all stages (Ta, T1, and CIS).

Immediate single post-operative instillation of chemotherapy within 6 hours after TURB is recommended in tumours presumed to be at low or intermediate risk, except in cases of bladder perforation or severe bleeding. The choice of drug (mitomycin C, epirubicin, or doxorubicin) is optional.

Further chemotherapy instillations can improve RFS in intermediate-risk tumours, but do not prevent progression. These instillations are associated with minor side-effects.

Intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) (induction and maintenance) is superior to intravesical chemotherapy in reducing recurrences and in preventing or delaying progression to muscle-invasive bladder cancer. However, intravesical BCG is more toxic.

The individual choice of further intravesical adjuvant therapy depends on the patient's risk (Table 3).

In patients at highest risk of progression, radical cystectomy (RC) should be considered. Patients with BCG failure are unlikely to respond to further BCG therapy; RC is therefore the preferred option.

Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS	**GR**
Smokers with confirmed NMIBC should be counseled to stop smoking.	B
The type of intravesical therapy should be based on risk groups.	A
In patients with tumours presumed to be at low- or intermediate risk, one immediate chemotherapy instillation is recommended.	A

In patients with low-risk tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with intermediate-risk tumours, one immediate instillation of chemotherapy should be followed by 1-year full-dose BCG treatment, or by further instillation of chemotherapy for a maximum of 1 year. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconvenience.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG can be offered.	C
In patients at highest risk of tumour progression, immediate radical cystectomy should be considered.	C
In patients with BCG failure, radical cystectomy is indicated.	B
Intravesical chemotherapy	
One immediate instillation should be administered within 24 hours after TURB.	C
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extra-peritoneal perforation (after extensive TURB, or bleeding requiring bladder irrigation).	C
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C

The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined, but it should not exceed 1 year.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug by reducing fluid intake before and during instillation.	B
The length of an individual instillation should be 1-2 hours.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first 2 weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	C
The management of side effects after BCG intravesical instillation should reflect their type and grade.	C

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

Follow-up

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed up. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk.

When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial because a delay in

diagnosis and therapy can be life-threatening.

- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy. Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden.
- The first cystoscopy after TURB at 3 months is a very important prognostic indicator for recurrence and progression. Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with Ta, T1 tumours and CIS.
- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low.
- Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered.
- In tumours originally intermediate- or high-risk, recurrences after 10 years tumour-free are not unusual. Therefore, life-long follow-up is recommended.
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT).
- The risk of UUT recurrence increases in patients with multiple and high-risk tumours.
- Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy). It supports the adjunctive role of urine tests during follow-up.

The following recommendations are based on retrospective experience only.

Recommendations for follow-up	GR
The follow-up of Ta, T1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	C
Patients with intermediate-risk Ta tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
Consider R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 months) in patients with CIS.	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

CIS = carcinoma in situ; CT-IVU = computed tomography intravenous urography; GR = grade of recommendation; IVU = intravenous urography; PDD = photodynamic diagnosis; R-biopsies = random biopsies.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-80-9), available to all members of the European Association of Urology at their website: http://www.uroweb.org.