EAU GUIDELINES ON NON-MUSCLE INVASIVE (TaT1, CIS) BLADDER CANCER

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Introduction

The EAU Working Group has published guidelines on Non-muscle-invasive bladder cancer (NMIBC), TaT1 tumours and carcinoma *in situ* (CIS).

Staging and classification systems

The 2017 TNM (Tumour, Node, Metastasis Classification) is used for staging (Table 1). For grading, both the 1973 and 2004 WHO Grading classifications are used (Table 2).

Table 1: TNM Classification 2017

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	Microscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional 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 regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	

M - Distant Metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastases

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.

Carcinoma *in situ*

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma, and 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.

Table 2: WHO grading in 1973 and in 2004

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading system *(Papillary lesions)*
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

Recommendations for bladder cancer classification	GR
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	A
Use both the 1973 and 2004/2016 WHO grading systems for histological classification.	A
Do not use the term "superficial bladder cancer".	A
Mention the tumour stage and grade whenever the terminology NMIBC is used in individual cases.	A

Diagnosis

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

Recommendations for the primary assessment of non-muscle-invasive bladder cancer	GR
Take a patient history.	A
Renal and bladder ultrasound may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of non-muscle-invasive bladder cancer (NMIBC), perform computed tomography urography (or intravenous urography [IVU]) in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	B
Perform cystoscopy in all patients with symptoms suggestive of bladder cancer. 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 as an adjunct to cystoscopy to detect high-grade tumour.	C

Perform cytology on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C
Repeat urine cytology in patients with suspicious initial cytology results.	C

Papillary (TaT1) tumours

The diagnosis of papillary bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the tissue resected during transurethral resection (TURB). TURB is a crucial procedure in the diagnosis and treatment of TaT1 tumours and 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*

Carcinoma *in situ* 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.

Recommendations for transurethral resection of the bladder (TURB), biopsies and pathology report	GR
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	A
Perform TURB 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 the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen for pathology evaluation.	C
Performance of individual steps	
Perform *en-block* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	B
Avoid cauterisation 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 wall) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance). If equipment is available, perform photodynamic diagnosis (PDD)-guided biopsies.	B

Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* (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.	B
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, cold-cup biopsy with forceps can be used.	C
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
The 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 an upper tract urothelial carcinoma, CIS in the bladder (random biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (prostatic urethra biopsy).	C
Perform a second TURB in the following situations: • after (suspicion of) incomplete initial TURB (in case of any doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours.	A

If indicated, perform a second TURB within two-six weeks after initial resection. This second TURB should include resection of the primary tumour site.	C
Register the results of a second TURB as it reflects the quality of the initial resection.	A
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	A
Pathological report	
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 lymphovascular invasion or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

Predicting disease recurrence and progression

After TURB, patients should be stratified, according to prognostic factors, into risk groups which will facilitate treatment recommendations (see 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 bacillus Calmette-Guérin-(BCG) treated patients, scoring models have been created by the CUETO and the EORTC. The CUETO risk calculator is available at: http://www.aeu.es/Cueto.html.

Table 3: Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG*), < 3 cm, no carcinoma *in situ* (CIS)	One immediate instillation of chemotherapy.
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high risk).	In patients with previous low recurrence rate (≤ one recurrence/year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after transurethral resection of the bladder (TURB). In all patients: either one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus three-weekly instillations at three, six and twelve months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.

High-risk tumours	Any of the following: • T1 tumour; • G3 (HG**) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present).	Intravesical full-dose BCG instillations for one-three years or cystectomy (in highest-risk tumours - see below).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or largeT1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.	Radical cystectomy should be considered in those who refuse intravesical full-dose BCG instillations for one-three years.
	BCG failures	Radical cystectomy is recommended.

**Low grade is a mixture of G1 and G2.*
*** High grade is a mixture of some G2 and all G3.*

Recommendations for stratification of non-muscle-invasive bladder cancer	GR
Stratify patients into three risk groups (see Table 3).	B
Apply the EORTC risk tables and calculator for the prediction of the risk of tumour recurrence and progression in different intervals after transurethral resection of the bladder, in individual patients.	B
Use the CUETO risk tables and the new EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	B

Disease management

Adjuvant treatment

Since there is considerable risk for recurrence and/or progression of tumours after TURB, adjuvant intravesical therapy is recommended for all stages (TaT1, and CIS).

- **Immediate single post-operative instillation of chemotherapy** within six hours after TURB can reduce recurrence rate in patients with low-risk and selected intermediate-risk tumours. The difference of efficacy between individual drugs (mitomycin C, epirubicin, or doxorubicin) has not been confirmed.
- **Further chemotherapy** instillations can improve recurrence-free survival in intermediate-risk tumours, but do not prevent progression. These instillations are associated with minor side-effects.
- **Intravesical immunotherapy with 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 should be considered. Patients with BCG failure are unlikely to respond to further BCG therapy; radical cystectomy is therefore the preferred option.

Recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS	**GR**
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking	B
The type of further therapy after TURB should be based on risk groups.	A
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate-risk with previous low recurrence rate (≤ one recurrence/ year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	A
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus three-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. 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 one-three years (induction plus three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months) is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconveniences.	A

In patients with CIS in the epithelial lining of the prostatic urethra, transurethral resection of the prostate followed by intravesical instillation of BCG can be offered.	C
Discuss immediate radical cystectomy with patients at highest risk of tumour progression.	C
Offer radical cystectomy (RC) to patients with BCG failure.	B
In patients with BCG failure, who are not candidates for RC due to comorbidities, use preservation strategies (device-assisted instillations of chemotherapy, intravesical chemotherapy, intravesical immunotherapy).	C
Intravesical chemotherapy	
When given, a single immediate instillation of chemotherapy should be administered within 24 hours after TURB, preferably within two hours.	C
A single immediate instillation of chemotherapy should be omitted in any case of overt or suspected bladder perforation 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 one 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 one-two hours.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two 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 (see recommendations in long text).	C

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. Small, TaLG/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 three months is a

very important prognostic indicator for recurrence and progression. Therefore, the first cystoscopy should always be performed three months after TURB in all patients with TaT1 tumours and CIS.

- In tumours at low risk, the risk of recurrence after five 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 ten 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 upper urinary tract in both genders).
- The risk of upper urinary tract 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.
- In patients initially diagnosed with TaLG/G1-2 BC, ultrasound of the bladder may be a mode of surveillance in case cystoscopy is not possible or refused by the patient.

Recommendations for follow-up in patients after transurethral resection of the bladder	GR
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five 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 (computed tomography-intravenous urography [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 random (R)-biopsies or photodynamic diagnosis (PDD)-guided biopsies after intravesical treatment (at three or six months) in patients with CIS.	C
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

In patients initially diagnosed with TaLG/G1-2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	C

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-91-5), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.