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 2004/2016 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	Macroscopically (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 2004/2016 grading systems has been confirmed. As the WHO 2004/2016 system has not yet been fully incorporated into prognostic models, long-term individual patient data using both classification systems are needed.

Carcinoma *in situ*

Carcinoma *in situ* 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 2004/2016

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004/2016 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

Variants of urothelial carcinoma and lymphovascular invasion

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, sarcomatoid) have a worse prognosis than pure HG urothelial carcinoma. The presence of lymphovascular invasion (LVI) in transurethral resection of the bladder (TURB) specimens is associated with worse prognosis.

Recommendations for bladder cancer classification	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO grading systems.	Strong
Do not use the term "superficial bladder cancer".	Strong

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	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography (CT)-intravenous urography during the initial work-up in patients with haematuria.	Strong

Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong

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 TURB. Transurethral resection of the bladder is a crucial procedure in the diagnosis and treatment of TaT1 tumours and should be performed systematically in individual steps (see recommendations below). A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis.

The technique selected depends on the size of the lesion, its location and experience of the surgeon. 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 bladder biopsies taken from suspicious areas or as mapping biopsies from normal looking mucosa (for details, please consult the extended guidelines). 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	**Strength rating**
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.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak

Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia. This step may be omitted in case non-invasive or early treatment for invasive disease is planned; • 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.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong

Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours and in tumours with non-papillary appearance. If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma *in situ* is present or suspected, if there is positive cytology without evidence of tumour in the bladder, or if 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.	Strong
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 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.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak

The TURB protocol must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a 2nd TURB in the following situations: • after incomplete initial TURB, or in case of 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.	Strong
If indicated, perform a 2nd TURB within two to six weeks after initial resection. This 2nd TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a 2nd TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, presence of CIS, and detrusor muscle.	Strong

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 is strongly recommended: https://www.eortc.be/tools/bladdercalculator/download_disclaimer.htm.

For bacillus Calmette-Guérin (BCG)-treated patients, separate scoring models and risk groups have been created by the CUETO and the EORTC, respectively.

Recommendations for stratification of non-muscle invasive bladder cancer	Strength rating
Stratify patients into three risk groups according to Table 3.	Strong
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.	Strong
Use the CUETO risk tables and the EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	Strong

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 CIS	One immediate instillation of intra-vesical chemotherapy after TURB.
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 per year) and expected EORTC recurrence score < 5, one immediate instillation of intra-vesical chemo-therapy after TURB. In all patients either 1-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemo-therapy (the optimal schedule is not known) for a maximum of one year.

High-risk tumours	Any of the following: • T1 tumours; • 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 to three years or radical cystectomy (in highest-risk tumours - see below).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI.	Radical cystectomy (RC) should be considered. In those who refuse or are unfit for RC, intravesical full-dose BCG instillations for one to three years.

**Low grade is a mixture of G1 and G2.*

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

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.

The individual choice of further intravesical adjuvant therapy depends on the patient's risk (Table 3). In patients at highest risk of progression, RC should be considered.

Bacillus Calmette-Guérin (BCG) failure

Several categories of BCG failures, broadly defined as any disease recurrence following BCG therapy, have been proposed.

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1G3/HG tumour is present at 3 months (LE: 3).
2. If TaG3/HG tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance (LE: 4).

3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance (LE: 1b).
4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of G3/HG (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response (LE: 3).
BCG-unresponsive tumour
BCG refractory or T1Ta/HG BCG recurrence within 6 months of completion of adequate BCG exposure** or development of CIS within 12 months of completion of adequate BCG exposure (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment.

* *Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.*

** *Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

Guidelines for the treatment of BCG failure

Category	Treatment options	Strength rating
BCG-unresponsive	1. Radical cystectomy (RC).	Strong
	2. Enrollment in clinical trials assessing new treatment strategies.	Weak
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.	Weak

Late BCG-relapsing: T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to individual situation.	Strong
	2. Bladder-preserving strategies.	Weak
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.	Weak
	2. Radical cystectomy.	Weak

General recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS	**Strength rating**
Counsel smokers with confirmed NMIBC to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder should be based on the risk groups shown in Table 3.	Strong
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 per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	Strong

In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus 3-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.	Strong
In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus 3-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, side-effects and problems connected with BCG shortages.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak
Discuss immediate radical cystectomy (RC) with patients at highest risk of tumour progression.	Strong
Offer a RC to patients with BCG unresponsive tumours.	Strong

Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferentially in clinical trials).	Weak
Recommendations – technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be one to two hours.	Weak

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.	Strong

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.

Recommendations for follow-up in patients after transurethral resection of the bladder	**Strength rating**
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
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.	Weak
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.	Weak

Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	Weak
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
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.	Weak

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-07-3), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.