

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

*(Limited text update March 2022)*

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## **Epidemiology**

Bladder cancer (BC) is the 7<sup>th</sup> most commonly diagnosed cancer in the male population worldwide, while it drops to the 10<sup>th</sup> position when both genders are considered. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women.

## **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**

<b>T - Primary Tumour</b>	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : '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
<b>N – Regional Lymph Nodes</b>	
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

## 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.

## Subtypes of urothelial carcinoma and lymphovascular invasion

Some subtypes of urothelial carcinoma (micropapillary, plasmacytoid, sarcomatoid) have a worse prognosis than pure high-grade (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 classification systems.	Weak
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.

<b>Recommendations for the primary assessment of non-muscle invasive bladder cancer</b>	<b>Strength rating</b>
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography intravenous urography (CT-IVU) 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 and apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	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 BC 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 (2<sup>nd</sup> 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.

<b>Recommendations for transurethral resection of the bladder (TURB), biopsies and pathology report</b>	<b>Strength rating</b>
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
<p>Perform TURB systematically in individual steps:</p> <ul style="list-style-type: none"> <li>• bimanual palpation under anaesthesia;</li> <li>• insertion of the resectoscope, under visual control with inspection of the whole urethra;</li> <li>• inspection of the whole urothelial lining of the bladder;</li> <li>• biopsy from the prostatic urethra (if indicated);</li> <li>• cold-cup bladder biopsies (if indicated);</li> <li>• resection of the tumour;</li> <li>• recording of findings in the surgery report/record;</li> <li>• precise description of the specimen(s) for pathology evaluation.</li> </ul>	Strong
<b>Performance of individual steps</b>	
Perform <i>en-bloc</i> 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 if cytology or urinary molecular marker test is positive. 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 <i>in situ</i> is present or suspected, if there is positive cytology or urinary molecular marker test 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 a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	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 record 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 2 <sup>nd</sup> TURB in the following situations: <ul style="list-style-type: none"> <li>• after incomplete initial TURB, or in case of doubt about completeness of a TURB;</li> <li>• if there is no muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS;</li> <li>• in T1 tumours.</li> </ul>	Strong
If indicated, perform a 2 <sup>nd</sup> TURB within 2–6 weeks after the initial resection. This 2 <sup>nd</sup> TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a 2 <sup>nd</sup> 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, subtypes of urothelial carcinoma (variant histologies), presence of CIS, and detrusor muscle.	Strong



## Predicting disease recurrence and progression and defining risk groups

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 progression at different intervals after TURB, use of the 2021 EAU NMIBC Risk Calculator ([www.nmibc.net](http://www.nmibc.net)) is strongly recommended.

For bacillus Calmette-Guérin (BCG)-treated patients, separate scoring models and risk groups have been created by the CUETO and the EORTC, respectively. For prediction of tumour recurrence in individual patients, the 2006 EORTC scoring model and calculator may be used.

<b>Recommendations for stratification of non-muscle invasive bladder cancer</b>	<b>Strength rating</b>
Stratify patients into 4 risk groups according to Table 3. A patient's risk group can be determined by using the 2021 EAU risk group calculator available at <a href="http://www.nmibc.net">www.nmibc.net</a> . Android and iOS smartphone apps are also available.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours, use the EAU NMIBC 2021 risk group calculator.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with bacillus Calmette-Guérin (BCG).	Strong

Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1-3 year of maintenance, the CUETO model for 5 to 6 months of BCG).	Strong
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**Table 3: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems**

- Only one of the two grading systems (WHO 1973 or WHO 2004/2016) is required to use this table.
- If both grading systems are available in an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973, as it has better prognostic value.
- The category of low-grade (LG) tumours (WHO 2004/2016) also includes patients with tumours classified as PUNLMP.
- Additional clinical risk factors are\*:
  - o age > 70;
  - o multiple papillary tumours;
  - o tumour diameter  $\geq$  3 cm.

Risk Group	Description
Low Risk	• A primary, single, Ta/T1 LG/G1 tumour < 3 cm in diameter without CIS in a patient $\leq$ 70 years
	• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors*
Intermediate Risk	Patients without CIS who are not included in either the low-, high- or very high-risk groups

High Risk	<ul style="list-style-type: none"> <li>• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group</li> <li>• All CIS patients, EXCEPT those included in the very high-risk group.</li> </ul> <p><b>Stage, grade with additional clinical risk factors:</b></p> <ul style="list-style-type: none"> <li>• Ta LG/G2 or T1 G1, no CIS with all 3 risk factors</li> <li>• Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors</li> <li>• T1 G2 no CIS with at least 1 risk factor</li> </ul>
Very High Risk	<p><b>Stage, grade with additional clinical risk factors:</b></p> <ul style="list-style-type: none"> <li>• Ta HG/G3 and CIS with all 3 risk factors</li> <li>• T1 G2 and CIS with at least 2 risk factors</li> <li>• T1 HG/G3 and CIS with at least 1 risk factor</li> <li>• T1 HG/G3 no CIS with all 3 risk factors</li> </ul>

The scoring model is based on individual patient data, but does not consider patients with primary CIS (high-risk) or with recurrent tumours, as well as some pathologic parameters like subtypes of urothelial carcinoma (*micropapillary, plasmacytoid, sarcomatoid, small-cell, neuroendocrine*) and LVI. Nevertheless:

- Based on data from the literature, all patients with CIS in the prostatic urethra, with subtypes of urothelial carcinoma (variant histologies) or with LVI should be included in the very high-risk group.
- Patients with recurrent tumours should be included in the intermediate-, high- or very high-risk groups according to their other prognostic factors.

## 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** immediate single post-operative instillation of chemotherapy after TURB can reduce the recurrence rate in patients with low-risk and selected intermediate-risk tumours. The difference in 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 MIBC.

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

### Bacillus Calmette-Guérin failure

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

Whenever a MIBC is detected during follow-up.
<b>BCG-refractory tumour</b>
1. If T1 HG/G3 tumour is present at 3 months (LE: 3).
2. If Ta HG/G3 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). If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases (LE: 1b).
4. If HG tumour appears during BCG maintenance therapy*.
<b>BCG-relapsing tumour</b>
Recurrence of HG/G3 (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response (LE: 3).
<b>BCG-unresponsive tumour</b>
BCG-unresponsive tumours include all BCG refractory tumours and those who develop TaT1/ HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure** (LE: 4).
<b>BCG intolerance</b>
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.

<b>General recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS</b>	<b>Strength rating</b>
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. For determination of a patient's risk group use the 2021 EAU risk group calculator available at <a href="http://www.nmibc.net">www.nmibc.net</a> .	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, 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

<p>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. Immediate radical cystectomy (RC) may also be discussed with the patient.</p>	<p>Strong</p>
<p>In patients with very high-risk tumours, discuss RC. Offer intravesical full-dose BCG instillations for one to three years to those who refuse or are unfit for RC.</p>	<p>Strong</p>
<p>Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.</p>	<p>Weak</p>
<p>The definition of 'BCG unresponsive' should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations.</p>	<p>Strong</p>
<p>Offer a RC to patients with BCG-unresponsive tumours.</p>	<p>Strong</p>
<p>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; preferably within clinical trials).</p>	<p>Weak</p>

<b>Recommendations – technical aspects for treatment</b>	
<b><i>Intravesical chemotherapy</i></b>	
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
<b><i>BCG intravesical immunotherapy</i></b>	
Absolute contraindications of BCG intravesical instillation are: <ul style="list-style-type: none"> <li>• during the first two weeks after TURB;</li> <li>• in patients with visible haematuria;</li> <li>• after traumatic catheterisation;</li> <li>• in patients with symptomatic urinary tract infection.</li> </ul>	Strong



<b>Guidelines for the treatment of TaT1 tumours and carcinoma <i>in situ</i> according to risk stratification</b>	<b>Strength rating</b>
<b><i>EAU risk group: Low</i></b>	
Offer one immediate instillation of intravesical chemotherapy after TURB.	Strong
<b><i>EAU Risk Group: Intermediate</i></b>	
In all patients either 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. Offer one immediate chemotherapy instillation to patients with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB.	Strong
<b><i>EAU risk group: High</i></b>	
Offer intravesical full-dose BCG instillations for one to three years or radical cystectomy (RC).	Strong
<b><i>EAU risk group: Very High</i></b>	
Offer RC or intravesical full-dose BCG instillations for one to three years to those who refuse or are unfit for RC.	Strong

**Table 4: Treatment options for the various categories of BCG failure**

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC).
	2. Enrollment in clinical trials assessing new treatment strategies.
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG-relapsing: TaT1/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to a patient's individual situation.
	2. Bladder-preserving strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.
	2. Radical cystectomy.

BCG = *bacillus Calmette-Guérin*; CIS = *carcinoma in situ*; LG = *low-grade*.

### 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.

<b>Recommendations for follow-up in patients after transurethral resection of the bladder</b>	<b>Strength rating</b>
Base follow-up of TaT1 tumours and carcinoma <i>in situ</i> (CIS) on regular cystoscopy.	Strong
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.	Weak
Patients with high-risk and those with very high-risk tumours treated conservatively 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.	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 and very high-risk tumours.	Weak
Perform endoscopy under anaesthesia and bladder biopsies 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, and/or a urinary marker 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 978-94-92671-16-5) available to all members of the European Association of Urology at their website, <http://www.uroweb.org/guidelines/>.*