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

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M. Babjuk (chair), A. Böhle, M. Burger, E. Compérat, E. Kaasinen, J. Palou, B.W.G. van Rhijn, M. Rouprêt, S. Shariat, R. Sylvester, R. Zigeuner

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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) according to the TNM Classification of Malignant Tumours, 7th Edition, 2009 (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

CIS is classified into 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;
- Recurrent: Repeat occurrence of isolated CIS after initial successful response to intravesical treatment.

Currently two grading systems for NMIBC, WHO 1973 and WHO 2004, are available (Table 2). The majority of clinical trials published so far on NMIBC have been performed using the 1973 WHO classification, and therefore the guidelines recommendations are based on the 1973 WHO grade classification.

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
Flat lesions
Hyperplasia (flat lesion without atypia or papillary aspects)
Reactive atypia (flat lesion with atypia)
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS (always high-grade [HG])
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

Diagnosis and Initial Treatment Steps

The patient history should be taken, including all information possibly associated with bladder cancer (BC).

Papillary (Ta, T1) tumours

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

The standard initial therapy for Ta and T1 papillary bladder tumours is complete macroscopic transurethral resection (TURB), including a part of the underlying muscle. TURB should be performed systematically in individual steps, which

are described in the full version of the guidelines. Small tumours (< 1 cm) can be resected en bloc including a part of the underlying muscle. 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.

A second TURB 2-6 weeks after initial resection is recommended in the following situations:

- After incomplete initial TURB, if there was no muscle in the specimen after initial resection (with exception of Ta low grade (G1) tumours);
- In all T1 tumours and in all high grade (G3) tumours (except primary CIS).

CIS

CIS is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies. Biopsies are taken from suspect areas. In patients with positive urine cytology and no papillary tumour, multiple biopsies from normal looking mucosa including prostatic urethra (random biopsies) are recommended. If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy in these patients. Urine cytology is useful in the diagnosis and follow-up of CIS.

CIS cannot be eradicated by TURB and further treatment is mandatory.

Guidelines for primary assessment of NMIBC	GR
Patient history should be taken and recorded regarding all important information with a possible association with bladder cancer, including risk factors and suspicious symptoms.	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 bladder cancer, CT urography (or IVU) should be performed only in selected cases (e.g., 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 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 high-grade 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

TURB	
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; • bimanual palpation after resection; • protocol formulation; • formulation of order form for pathological evaluation.	C
Perform resection in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B
Perform resection in fractions (including muscle tissue) for tumours > 1 cm in diameter.	B
Biopsies should be taken 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 exophytic tumour has a non-papillary 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 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

Biopsy of the prostatic urethra should be taken from abnormal areas 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, fluorescence-guided (PDD) biopsy should be performed instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion).	B
The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers and labelled separately.	C
TURB protocol must describe all steps of the procedure, as well as the extent and completeness of resection.	C
A second TURB is recommended in the following situations: • after incomplete initial TURB; • if there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS; • in all T1 tumours; • in all G3 tumours, except primary CIS.	A
When done, a second TURB should be performed within 2-6 weeks after initial resection.	C
Classification and pathological report	
Depth of tumour invasion is classified according to the TNM system.	A

For histological classification, 1973 and 2004 WHO grading systems are used. Until the WHO 2004 is validated by more prospective trials and incorporated into prognostic models, both classifications should be used.	A
Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.	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 histology.	C

CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; US = ultrasound; TURB = transurethral resection of the bladder.

Prognostic Factors and Adjuvant Treatment

It is recommended to stratify patients according to prognostic factors into three risk groups that 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.

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 large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, micropapillary variant of urothelial carcinoma, LVI	Radical cystectomy should be considered
	BCG failures	Radical cystectomy is recommended

CIS = carcinoma in situ; HG = high-grade; LG = low-grade; LVI = lymphovascular invasion.

Since there is considerable risk for recurrence and/or progression of tumours after TURB, adjuvant intravesical therapy is recommended for all stages (Ta, T1, and CIS). Immediate postoperative 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 doxorubicine) is optional.

Intravesical chemotherapy reduces the risk of recurrence but not progression and is 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 (Table 3), radical cystectomy should be considered in patients with BCG failure

since they are unlikely to respond to further BCG therapy; radical cystectomy 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 counselled to stop smoking.	B
The type of intravesical therapy should be based on risk groups.	A
One immediate chemotherapy instillation is recommended in tumours presumed to be at low or intermediate risk.	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 Ta 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.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated.	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 (Table 3), immediate radical cystectomy should be considered.	C
In patients with BCG failure, radical cystectomy is indicated.	B
In patients with BCG failure ineligible for radical cystectomy, gemcitabine or MMC in combination with hyperthermia are options.	C

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
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined and 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 during instillation by reducing fluid intake.	B
The length of 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 macroscopic haematuria; • after traumatic catheterization; • 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; MMC = mitomycin C; TUR = transurethral resection; TURB = transurethral resection of the bladder.

Follow-up for Non-Muscle Invasive Bladder Tumours

As a result of the risk of recurrence and progression, patients with Ta, T1 bladder tumours and with CIS 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, non-invasive (Ta), LG/G1 papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy (LE: 2b). 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. The first cystoscopy should thus 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, lifelong follow-up is recommended.
- 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.

The following recommendations are only based on retrospective experience.

Recommendations for follow-up	GR
The follow-up of Ta, T1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk 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
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; IVU = intravenous urography; PDD = photodynamic diagnosis; R-biopsies = random biopsies.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-65-5), available to all members of the European Association of Urology at their website:, http://www.uroweb.org.