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

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Introduction

The EAU Working Group on Non-muscle-invasive Bladder Cancer has published a short and long version of guidelines on non-muscle-invasive bladder cancer which contains information on its background, classification, risk factors, diagnosis, prognostic factors, and treatment.

The current recommendations for non-muscle-invasive bladder cancer are ultra-short and are based on the current literature (until the end of 2012), with emphasis being placed on (evidence based) results from randomised clinical trials and meta-analyses. These guidelines can be used as a quick reference on the management of patients with non-muscle-invasive bladder cancer.

The recommendations of this working panel apply to patients with papillary stage Ta and T1 tumours as well as to carcinoma in situ (CIS), a flat neoplasm. The classification of non-muscle-invasive tumours (Ta, T1, and CIS) is given in the TNM Classification of Malignant Tumours, 7th Edition, 2009 (Table 1).

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

Characteristics of Stages Ta, T1, and CIS

Stage Ta tumours are confined to the urothelium, have a papillary configuration of their exophytic part, and do not penetrate from the urothelium into the lamina propria or detrusor muscle.

Stage T1 tumours originate from the urothelium but penetrate the basement membrane which separates the urothelium from the deeper layers. T1 tumours invade into the lamina propria, but not into the detrusor muscle.

Carcinoma in situ (CIS) is a high-grade (anaplastic) carcinoma confined to the urothelium, but with a flat non-papillary configuration. CIS appears as reddened and velvety mucosa, but is sometimes not visible. CIS can be local or diffuse. Four types of CIS are distinguishable:

- primary CIS (no previous or concurrent papillary tumours, no previous CIS);
- secondary CIS (with a history of papillary tumours, but not CIS);
- concurrent CIS (in the presence of papillary tumours in the bladder);
- recurrent CIS (repeat occurrence of isolated CIS).

Characteristics of Grade

1973 WHO Classification

Apart from their architecture, the individual cells show different degrees of anaplasia:
Grade 1: well differentiated tumour
Grade 2: moderately differentiated tumour
Grade 3: poorly differentiated tumour

2004 WHO Classification

A new classification system was initially proposed by the WHO/ISUP in 1998 and updated by the WHO in 2004. For non-

invasive urothelial neoplasias, the categories described in Table 2 are used.

Table 2: 2004 WHO Classification of non-invasive urothelial neoplasia

- Flat lesions
- Hyperplasia (flat lesion without atypia or papillary)
- Reactive atypia (flat lesion with atypia)
- Atypia of unknown significance
- Urothelial dysplasia
- Urothelial carcinoma in situ (CIS)
- Papillary lesions
- Urothelial papilloma (a completely benign lesion)
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma

The 2004 WHO grading system defines CIS as a non-papillary, i.e. a flat, lesion in which the surface epithelium contains cells that are cytologically malignant. Papillary tumours are classified as either papillary urothelial neoplasms of low malignant potential (PUNLMP) or as urothelial carcinomas, with the latter being subdivided into two grades: low grade and high grade (Table 2).

The intermediate group (G2) has been eliminated; this group was the subject of controversy in the 1973 WHO classification. Use of the 2004 WHO classification is advocated, as this should result in less diagnostic variability among pathologists. However until the 2004 WHO classification has been validated clinically, both classifications should be used.

The majority of clinical trials published so far on Ta, T1 bladder tumours have been performed using the 1973 WHO classifica-

tion, and therefore the following guidelines are based on the 1973 WHO grade classification.

Diagnosis and Initial Treatment Steps

The diagnosis mainly depends on the cystoscopic examination of the bladder, biopsy, and urine cytology. To date, molecular urinary markers have not improved the combination of cystoscopy and cytology.

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).

The diagnosis of CIS is based on the histology of biopsies from the bladder wall. 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.
Fluorescence cystoscopy is recommended in these cases as it

improves the detection rate of CIS. Urine cytology is an important tool in the diagnosis and follow-up of CIS because of its high sensitivity and specificity (over 90%).

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

Prognostic Factors and Adjuvant Treatment

TaT1 papillary tumours

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 TaT1 tumours according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, 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 • 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 radical 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	Radical cystectomy should be considered
	BCG refractory tumours	Radical cystectomy is recommended

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. The choice of further intravesical adjuvant therapy depends on the patient's risk.

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.

Recommendations for Low Risk Tumours	**GR**
Patients with a single, small, low grade Ta tumour without CIS are at low risk, they should receive:	
1. A complete TURB.	A
2. An immediate single post-operative instillation with a chemotherapeutic agent (drug optional).	A
3. No further treatment is recommended prior to disease recurrence.	A

Recommendations for Intermediate Risk Tumours	**GR**
The major issue in the management of intermediate risk tumours is to prevent recurrence and progression, of which disease recurrence is clinically the most frequent. Treatment should include:	
1. Complete TURB followed by an immediate postoperative instillation with a chemotherapeutic agent (drug optional).	A
2. A second TURB after 4-6 weeks when indicated.	B
3a Adjuvant intravesical immunotherapy with BCG, 1 year full dose;	A
Or	
3b Adjuvant intravesical chemotherapy (drug optional), schedule: optional although the duration of treatment should not exceed 1 year.	A

Recommendations for High Risk Tumours	GR
The treatment of Ta, T1 tumours at high risk should consist of:	
1. Complete TURB of papillary tumours.	C
2. A second TURB after 4-6 weeks.	B
3. Adjuvant intravesical immunotherapy with BCG (full dose). Maintenance therapy for 1-3 years is necessary although the optimal maintenance scheme has not yet been determined.	A
4. Immediate radical cystectomy may be offered to patients at highest risk of tumour progression.	C
5. In patients with BCG failure, radical cystectomy is recommended.	B

Carcinoma *in situ*

CIS has a high risk of progression to muscle-invasive disease which exceeds 50% in some studies.

BCG intravesical immunotherapy (induction and maintenance) is superior to intravesical chemotherapy in increasing the complete response rate and the overall percentage of patients remaining tumour free. Moreover, BCG reduces the risk of progression as compared to either intravesical chemotherapy or a different immunotherapy. Early radical cystectomy at the time of diagnosis provides excellent disease-free survival, but over-treatment occurs in up to 50% of patients.

Recommendations for the treatment of CIS	GR
1. In concurrent CIS, the initial strategy (TURB, early intravesical instillation, a second TURB) is based on the features of the papillary tumour.	
2. Intravesical BCG immunotherapy, full dose with 1-3 years of maintenance.	A
3. After the 6 week induction course, a second course of 6 weekly BCG instillations or maintenance cycles consisting of 3 weekly instillations may be considered in non responders since about 40-60% of these patients will respond to additional treatment with BCG.	B
4. In BCG non-responders at 6 months radical cystectomy is recommended.	B

Follow-up for non-muscle invasive bladder tumours

Patients with non-muscle-invasive bladder tumours need to be regularly followed up because of the risk of disease recurrence and progression; however, the frequency and duration of cystoscopies should reflect the degree of risk.
When planning a follow-up schedule, the following aspects should be considered:

a. The prompt detection of muscle-invasive and high-grade non-muscle-invasive recurrences is critical since a delay in diagnosis and therapy threatens a patient's life.
b. Tumour recurrence in the low-risk group is nearly always low stage and low grade. Small, non-invasive (Ta), low grade papillary recurrences do not present an immediate danger to the patient and their early detection is not essential for successful therapy. In these patients, fulguration of small papillary recurrences on an outpatient basis is considered to be a safe treatment option.
c. The result of the first cystoscopy after TURB at 3 months is

a very important prognostic factor for disease recurrence and for progression. The first cystoscopy should thus always be performed 3 months after TURB.

d. The risk of upper urinary tract recurrence increases in patients with multiple and high risk tumours.

The following recommendations are only based on retrospective experience.

Recommendations for follow-up	**GR**
The follow-up of Ta T1 tumours 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 T1 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

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-71-7), available to all members of the European Association of Urology at their website, http://www.uroweb.org.