GUIDELINES ON NON-MUSCLE INVASIVE BLADDER CANCER

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Introduction

The EAU Working Party 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 end of 2010), 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* (Tis), a flat neoplasm. The classification of non-muscle invasive tumours (Ta, T1, and Tis) 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
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 metatstases
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 presacral)
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 Tis

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 are not so deep that they reach the detrusor muscle.

Carcinoma in situ (Tis) is a high-grade (anaplastic) carcinoma confined to the urothelium, but with a flat non-papillary configuration. Unlike a papillary tumour, Tis appears as red-

dened and velvety mucosa and is slightly elevated but sometimes not visible. Tis can be local or diffuse. Three types of Tis are distinguishable;

- primary Tis (no previous or concurrent papillary tumours);
- secondary Tis (with a history of papillary tumours);
- concurrent Tis (in the presence of papillary tumours).

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 Tis 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 can be used.

The majority of clinical trials published so far on TaT1 bladder tumours have been performed using the 1973 WHO classification, 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 (TUR) including a part of the underlying muscle. A second TUR should be considered if there is a suspicion that the initial resection was incomplete, e.g. when multiple or large tumours are present, or when the pathologist reported no muscle tissue in the specimen or when a high-grade tumour or a T1 tumour was detected. The technique of TUR is described in the EAU guidelines on Non-muscle Invasive urothelial carcinoma of the bladder (Eur Urol 2008 Aug;54(2):303-14).

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

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

Prognostic Factors and Adjuvant Treatment

TaT1 papillary tumours

Since there is considerable risk for recurrence and/or progression of tumours after TUR, adjuvant intravesical therapy is recommended for all stages (Ta, T1, and Tis). All patients should receive an immediate post-operative instillation of chemotherapy within 6 hours after TUR, except in cases of bladder perforation or severe bleeding. An immediate instillation is considered as standard, the choice of drug (mitomycin C, epirubicin, or doxorubicine) is optional.

The choice of further intravesical adjuvant therapy depends on the patient's risk of recurrence and/or progression which can be assessed using the European Organization for the Research and Treatment of Cancer (EORTC) scoring system (Table 3) and risk tables (Table 4). Patients with multiple tumours, large tumours (≥ 3 cm), and highly recurrent tumours (> 1 recurrence/year) are at the highest risk of recurrence while patients with stage T1 tumours, high grade tumours, and CIS have the highest risk of progression.

Intravesical chemotherapy reduces the risk of recurrence but not progression and is associated with minor side-effects. Intravesical immunotherapy with Bacillus Calmette-Guerin (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

Patients with a single, small, low grade Ta tumour without CIS, who are at low risk for both recurrence and progression, should receive:	**GR**
1. A complete TUR.	A
2. An immediate single post-operative instillation with a chemotherapeutic agent (drug optional).	A
3. No further treatment is recommended prior to recurrence.	A

Recommendations for High Risk Tumours

Patients with TaT1 high grade tumours with or without CIS and those with CIS alone are at high risk of progression. Treatment should consist of:	**GR**
1. Complete TUR of papillary tumours followed by an immediate post-operative instillation with a chemotherapeutic agent (drug optional).	C
2. A second TUR after 4–6 weeks.	B
3. Adjuvant intravesical immunotherapy with BCG (full dose or reduced dose in case of side-effects). Maintenance therapy for at least 1 year is necessary although the optimal maintenance scheme has not yet been determined.	A
4. Immediate cystectomy may be offered to patients at highest risk of tumour progression.	C
5. In patients with BCG failure, cystectomy is recommended.	B

Recommendations for Intermediate Risk Tumours

In the remaining intermediate risk patients, adjuvant intravesical therapy is necessary but no consensus exists regarding the optimal drug and the most appropriate scheme.

BCG is more effective than chemotherapy in both reducing recurrence and progression but it is associated with more systemic and local side-effects.

The major issue in the management of intermediate risk tumours is to prevent recurrence and progression, of which recurrence is clinically the most frequent. Treatment should include:	**GR**
1. Complete TUR followed by an immediate post-operative instillation with a chemotherapeutic agent (drug optional).	A
2. A second TUR after 4–6 weeks when the initial resection was incomplete.	B
3a Adjuvant intravesical chemotherapy (drug optional), schedule: optional although the duration of treatment should not exceed 1 year.	A
Or	
3b Adjuvant intravesical immunotherapy with BCG (full dose or reduced dose in case of side-effects). Maintenance therapy for at least 1 year is necessary although the optimal maintenance schedule has not yet been determined.	A

Table 3: Calculation of Recurrence and Progression Scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2 to 7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total Score	0 - 17	0 - 23

Table 4: Probability of recurrence and progression according to total score			
Recurrence score	**Prob. recurrence 1 year**	**Prob. recurrence 5 years**	**Recurrence risk group**
0	15%	31%	Low risk
1-4	24%	46%	Intermediate risk
5-9	38%	62%	
10-17	61%	78%	High risk
Progression score	**Prob. progression 1 year**	**Prob. progression 5 years**	**Progression risk group**
0	0.2%	0.8%	Low risk
2-6	1%	6%	Intermediate risk
7-13	5%	17%	High risk
14-23	17%	45%	
Note: electronic calculators for Tables 3 and 4 are available at http://www.eortc.be/tools/bladdercalculator/			

Eur Urol 2006;49(3):466-77.

Carcinoma *in situ*

Tis 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 percent 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 Tis	GR
1. In concurrent Tis, the initial strategy (TUR, early intravesical instillation, a second TUR) is based on the features of the papillary tumour.	
2. Intravesical BCG immunotherapy including at least 1 year 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 recurrence and progression; however, the frequency and duration of cystoscopies should reflect the individual patient's degree of risk. Using the risk tables (Tables 3 and 4), the short-term and long-term risks of both recurrence and progression in individual patients can be predicted and the follow-up schedule adapted accordingly:

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.
c. The result of the first cystoscopy after TUR at 3 months is a very important prognostic factor for recurrence and for progression. The first cystoscopy should thus always be performed 3 months after TUR in all patients with non-muscle invasive bladder tumour.

The following recommendations are only based on retrospective experience.

Recommendations for follow-up cystoscopy	**GR**
Patients with tumours at low risk of recurrence and progression should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years.	C

Patients with tumours at high risk of progression should have a cystoscopy and urinary cytology at 3 months. If negative, the following cystoscopies and cytologies should be repeated every 3 months for a period of 2 years, every 4 months in the third year, every 6 months thereafter until 5 years, and yearly thereafter. A yearly exploration of the upper tract is recommended.	C
Patients with intermediate-risk of progression (about one-third of all patients) should have an in-between follow-up scheme using cystoscopy and cytology, adapted according to personal and subjective factors.	C
Patients with Tis should be followed up for life due to the high risk of recurrence and progression, both within the bladder and extravesically. Urine cytology together with cystoscopy (and bladder biopsies in cytology positive cases) is essential for monitoring of treatment efficacy. The follow-up schedule is the same as for patients with high-risk tumours.	C

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-96-0), available to all members of the European Association of Urology at their website - http://www.uroweb.org/guidelines/online-guidelines/.