GUIDELINES ON NON-MUSCLE INVASIVE BLADDER CANCER

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Introduction

The EAU Working Party on Non-muscle Invasive Bladder Cancer has published short and long versions of guidelines on non-muscle invasive bladder cancer which contain their 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 2007), with emphasis being placed on (evidence based) results from randomized clinical trials and meta-analyses. These guidelines can be used as a quick reference on the management of patients with non-muscle invasive bladder tumours.

Three levels of recommendations are used:

The principal recommendations are marked in three grades (A-C), depending on the evidence source upon which a recommendation is based. Page 3 of this publication may be consulted for reference.

The recommendations of this working party 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, 6th Edition, 2002 (Table 1).

Table 1: TNM Classification 2002

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 - Regional Lymph Nodes

N1 Single ≤ 2 cm

N2 Single > 2 to 5 cm, multiple ≤ 5 cm

N3 > 5 cm

M - Distant Metastases

M0 No

M1 Yes

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 generate 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 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. Tis can be local or diffuse and it can be concomitant with papillary tumours. Unlike a papillary tumour, Tis appears as reddened and velvety mucosa and is slightly elevated but sometimes not visible.

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 papillary non-invasive tumours, this system uses three categories:

Table 2: 2004 WHO Grading

Urothelial papilloma

- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma

The 2004 WHO grading system classifies tumours as either papillary urothelial neoplasms of low malignant potential (PUNLMP) or as urothelial carcinomas, with the latter being subdivided into only two grades: low grade and high grade (Table 2).

The intermediate group has been eliminated; this group and PUNLMP were the subject of controversy in the 1973 WHO classification. The use of the 2004 WHO classification is advocated, as this should result in a uniform diagnosis of tumours, which is better stratified according to risk potential. However, until the 2004 WHO classification has been validated by more clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications.

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.

Histological Diagnosis

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 therapy for Ta and T1 papillary bladder tumours is complete macroscopic eradication by transurethral resection (TUR) including a part of the underlying muscle. A second resection should be done in high grade tumours or if the first resection was not complete. The technique of transurethral resection is described in the EAU guidelines on Non-Muscle invasive Bladder Cancer (Eur Urol 41(2):2002;105-112).

Tis cannot be eradicated by transurethral resection. The diagnosis of Tis is made by multiple biopsies from the bladder wall in conjunction with urine cytology. Fluorescence cystoscopy improves the detection rate of Tis.

Prognostic Factors and Adjuvant Treatment

Since there is considerable risk for recurrence and/or progression of tumours after transurethral resection, adjuvant intravesical therapy is recommended for all stages (Ta, T1 and Tis). All patients should receive one immediate post operative instillation of chemotherapy within 6 hours after TUR. The 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 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 recurrences but not progression and is 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. However, intravesical BCG is more toxic.

Recommendations for Low Risk Tumours

Patients with a single, small, low grade Ta tumour without CIS are at low risk for both recurrence and progression. They should receive:

1. A complete TUR (Grade of recommendation: A).
2. An immediate single post operative instillation with a chemotherapeutic drug (drug optional) (Grade of recommendation: A).
3. No further treatment is recommended prior to recurrence.

Recommendations for High Risk Tumours

Patients with TaT1 high grade tumours with or without carcinoma *in situ* and those with carcinoma *in situ* alone are at high risk of progression. Treatment should consist of:

1. Complete TUR of papillary tumours followed by an imme-

diate single post-operative instillation with a chemotherapeutic drug (drug optional) (Grade of recommendation: A).

2. re-TUR after 4 - 6 weeks (recommended).

3A Adjuvant intravesical immunotherapy with BCG (full dose or reduced dose in case of side-effects). Maintenance therapy is necessary although the optimal maintenance scheme has not been determined yet.

Maintenance: at least 1 year of BCG, optionally up to 3 years.

Or

3B Radical cystectomy plus urinary diversion up front (optional) or if no response to BCG therapy is achieved (Grade of recommendation: A).

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 optimal scheme.

The major issue in intermediate risk tumours is to prevent recurrence and progression, of which recurrence is clinically the most frequent. Treatment should include:

1. Complete TUR followed by an immediate single post-operative instillation with a chemotherapeutic drug (drug optional) (Grade of recommendation: A).
2. Standard re-TUR if a complete resection is not achieved

3A Adjuvant intravesical chemotherapy (drug optional), schedule: optional although the duration of treatment should not exceed 1 year.

Or

3B Adjuvant intravesical immunotherapy: drug BCG (full dose

or reduced dose in case of side effects).
Schedule: maintenance for at least 1 year, optionally up to 3 years.

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/

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Follow-up for non-muscle invasive bladder tumours

Because of the risk of recurrence and progression, patients with non-muscle invasive bladder tumours need to be followed; however, the frequency and duration of cystoscopies should reflect the individual patient's degree of risk. Using risk tables (see Tables 3 and 4), we are able to predict the short-term and long-term risks of both recurrence and progression

in individual patients and can adapt the follow-up schedule 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 based only on retrospective experience.

Recommendations for follow-up cystoscopy

- 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. (Grade of recommendation: B)
- Patients with tumours at high risk of progression should have a cystoscopy at 3 months. If negative, the following cystoscopies 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. (Grade of recommendation: B)
- Patients with intermediate-risk of progression (about one-third of all patients) should have an in-between follow-up scheme, adapted according to personal and subjective factors. (Grade of recommendation: B)

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-70244-91-0), available to all members of the European Association of Urology at their website - http://www.uroweb.org.