NON-MUSCLE INVASIVE BLADDER CANCER

Recommendations from the EAU Working Party on Superficial Bladder Cancer

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Introduction

The EAU Working Party on Superficial Bladder Cancer has published guidelines on bladder cancer (a long and short version) comprising the background, classification, risk factors, diagnosis and treatment of superficial bladder tumours.

The current recommendations are ultra short and are limited to the treatment of non-muscle invasive bladder cancer. They are based on the current literature (until 2003) as well as on (evidence based) results from meta-analyses and randomized clinical trials and can be used as a quick reference work on how to manage patients with superficial bladder tumours.

Three levels of recommendations are used:

Standard: Health and economic outcomes are sufficiently known and within Europe there is virtual unanimity about the mode of intervention

Guidelines: The recommendations are less strong and there is no unanimity regarding intervention

Option: The recommendation comprises different procedures as the outcome, the interventions and the preferences of patients and doctors are not sufficiently well known.

The recommendations of the working party apply to patients with papillary tumours stages Ta and T1, as well as to carcinoma in situ (CIS), a flat neoplasm. The classification of non-muscle invasive tumors (Ta, T1 and CIS) is according to the TNM classification 2002, table 1.

Table 1: TNM classification 2002

Urinary Bladder	
Ta	Noninvasive papillary
Tis	In situ: “flat tumour”
T1	Subepithelial connective tissue
T2	Muscularis
	T2a Inner half
	T2b Outer half
T3	Beyond muscularis
	T3a Microscopically
	T3b Extravesical mass
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a Prostate, uterus, vagina
	T4b Pelvic wall, abdominal wall
N1	Single ≤ 2 cm
N2	Single > 2 to 5 cm, multiple ≤ 5 cm
N3	> 5 cm

Characteristics of Stages Ta, T1 and CIS

Stage Ta tumours are confined to the urothelium, have a papil-

lary configuration of their exophytic part and do not penetrate the urothelium towards 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 (CIS) is a high-grade (anaplastic) carcinoma confined to the urothelium, but with flat non-papillary configurations. CIS can be local or diffuse and it can be concomitant with papillary tumours. Unlike a papillary tumour, CIS appears as reddened, velvety mucosa is slightly elevated but sometimes not visible at all.

Characteristics of grade (WHO classification)

Apart from the architecture the individual cells show different degrees of anaplasia:

Grade 1: well differentiated tumour
Grade 2: moderately differentiated tumour
Grade 3: poorly differentiated tumour

The prognosis of patients is correlated with stage and grade being excellent for TaG1 and less favourable for T1G3 or CIS.

Therapy and Histological diagnosis

The standard therapy for Ta and T1 papillary bladder tumours is complete macroscopic eradication by transurethral resection (TUR) including the underlying muscle. The technique of transurethral resection is described in the EAU guidelines on Superficial Bladder Cancer.

CIS cannot be eradicated by transurethral resection. The diagnosis of CIS is made by multiple biopsies from the bladder wall, in conjunction with urine cytology. Since there is considerable risk for recurrences and/or progression of tumours after transurethral resection, adjuvant intravesical therapy for all stages (Ta, T1 and CIS) is recommended.

The choice of intravesical adjuvant therapy depends on the risk of recurrence and/or progression. Patients with non-muscle invasive bladder cancer can be divided into 3 risk groups: low, intermediate and high risk.

Prognostic Factors

Low risk tumours: single, TaG1, ≤ 3 cm diameter.
High risk tumours: T1G3, multifocal or highly recurrent, CIS.
Intermediate risk: all other tumours, Ta-1, G1-2, multifocal, > 3 cm diameter.

- The optimal treatment for low risk, solitary TaG1 lesions is complete TUR (standard) plus one instillation of a chemotherapeutic drug (mitomycin C, epirubicin or doxorubicine) within 6 hours after transurethral resection. The immediate instillation is considered as standard, the choice of therapeutic drug is optional.
- The treatment for intermediate Ta-T1, G1-2, multifocal tumours consists of complete TUR (standard) followed by a second TUR after 4 - 6 week(s), if there is any doubt regarding the completeness of the initial TUR (optional).
- Adjuvant intravesical therapy is necessary but no consensus exists regarding the optimal drug and the optimal

scheme for intermediate risk tumours. The major issue in intermediate risk tumours is to prevent recurrence and progression, of which recurrence is clinically the most relevant. Intravesical chemotherapy will reduce recurrences but not progression and is associated with minor side effects.

- Intravesical immunotherapy with BCG is superior to intravesical chemotherapy in reducing recurrences and is able to prevent or delay progression to muscle-invasive BC in some, but not all, cases. However, intravesical BCG is more toxic.
- BCG is the recommended drug for high-risk tumours.
- Maintenance therapy is necessary although the optimal maintenance scheme has not been determined yet.

Recommendations for Low risk tumours

1. Complete TUR (standard)
2. An immediate single instillation with a chemotherapeutic drug (standard, drug optional)

Recommendations for Intermediate risk tumours

1. Complete TUR (standard)
2. re-TUR if complete resection is not achieved (optional)

3A Adjuvant intravesical chemotherapy (drug - optional), schedule - optional although the schedule used should not exceed 1 year.
Or

3B Adjuvant intravesical immunotherapy: drug BCG (full dose or reduced dose in case of side effects).
Schedule: maintenance: at least 1 year, optionally up to 3 years.

Recommendations for High risk tumours

The treatment for high risk Ta-T1, G3 with or without carcinoma in situ or for carcinoma in situ (alone) consists of:

1. Complete TUR of papillary tumours (standard)
2. re-TUR after 4 - 6 weeks (recommended)

3A Adjuvant intravesical immunotherapy
drug: BCG (full dose or reduced dose in case of side-effects).
Maintenance schedule: at least 1 year - optionally up to 3 years
Or

3B Radical cystectomy plus urinary diversion up front (optional) or if no response to BCG therapy is achieved (standard)

Diagnostic procedures and follow-up are described in the short and long versions of the EAU guidelines on Superficial Bladder Cancer.

This short booklet is based on the more comprehensive EAU guidelines (ISBN 90-806179-8-9), available to all members of the European Association of Urology at their website - www.uroweb.org