

The role of histological examination for prognostic evaluation and therapeutic algorithm in urinary bladder tumors

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Abstract

Pathological examination plays a major role in order to determine the prognostic and therapy of patients with urinary bladder tumors after a prior transurethral resection (TUR). The prognostic factors are studied to identify the risk of recurrence and tumoral progression of patients with superficial urothelial tumors and for appreciate the metastatic potential and response to therapy for patients with invasive carcinoma.

Keywords: urinary bladder tumors, prognostic, therapy.

Introduction

Nearly 95% from malignant tumors arising from urinary bladder are epithelial origin, and from these, majorities (90%) are urothelial carcinoma [1].

The prognostic of patients with urothelial carcinoma and therapeutic possibility depend by clinical stage and evaluation of morphological grading.

Material and methods

We performed a study on 118 patients with bladder tumors hospitalized on Urology Department of Turnu-Severin District Hospital during year 2004. Surgical pieces removed were histological and immuno-histochemical studied.

In superficial tumors we studied the following anatomic and clinical prognostic factors: tumor grade, numbers and dimension of tumors, the level of invasion (Ta versus T1), recurrence (short time until first recurrence and high rate of recurrence per year), Tis modification in urothelial mucosae near tumor, sex, and localization on urinary bladder wall.

In invasive tumors we followed: stage (level of invasion), extension to pelvic lymph nodes and number of invaded lymph nodes, age, sex, perineural and haemato-lymphatic invasion. The tumor grade has less significance in invasive disease because the majorities are high grade tumors (G2 or G3).

1. *Tumor grade* must be established accurate is possible because there is correlation with tumor stage and with biological behavior. Unfortunately, tumor grade like all histologic grade are subjective and must be more reproducible in future for compare correct some studies and therapy and for management of therapy [2–4].

Tumor grade is correlated with the possibility of invasion and metastasis as well as with survival rate.

Majority tumors in pTa stage (60 cases) are grade 1 and almost all cancers in stage pT1 (40 cases) are 2 or 3 grade. 62% (62 cases) from non invasive tumors are local recurrence and potential of progression.

30% from urothelial carcinoma grade 1 (18 cases) are local recurrent and progression to invasion.

From all cases with recurrent or progressed disease (32 cases), 75% (24 cases) present a higher tumor grade than initial biopsy. 3% (two cases) from grade 1 cancers progressed to grade 3. 61% (37 cases) from patients with papillary urothelial no invasive grade one tumor have other papillary tumors. 10% (six cases) have progression to invasive carcinoma.

2. *Tumor stage.* Clinically, urinary bladder superficial tumors (pTa, pTis, pT1 stages) have an 85% frequency (100 cases) from all neoplasias, 15% (18 cases) being invasive (pT2, pT3, pT4) or metastasis disease. WHO standardize very clear the tumor stages (Figure 1, Table 1).

Table 1 – WHO tumor stage

Tumor stage	Tumoral progression through bladder wall
Tis	Neoplastic changes in urotelium
Ta	Invasion in urothelial mucosae
T1	Invasion in lamina propria
T2a	Invasion in muscularis propria, internal half
T2b	Invasion in muscularis propria, external half, without serosa involvement
T3a	Invasion in muscularis propria profund, with serosa involvement
T3b	Extension of tumor in perivesical adipose tissue
T4a	Extension of tumor in local organs (prostate, uterus, vagina)
T4b	Extension of tumor to pelvin or abdominal wall

Under stage of pT1 is not recommended WHO for usual report but is very important in daily practice, special for the fragment obtained by transurethral resection (TUR) that not contain muscle fibers from muscularis propria.

Recognition of muscularis mucosae like histological element present in urinary bladder wall structure permitted under level of pT1: pT1a invasion in conjunctive tissue upper muscularis mucosae, pT1b invasion in muscularis mucosae, pT1c invasion lower muscularis mucosae, but without touching muscularis propria.

Identification muscularis mucosae level and understaging pT1 establish two categories of patients with different prognostic.

The prognostic of patients with invasion in deep muscularis mucosae has the same signification like pT2 stage.

Histological, the muscle fibers from muscularis mucosae are thin, with parallel arrangement with discontinuous character in majority, in a dispersed manner. Very rare there are no muscle fibers in lamina propria [3–6].

Presence of continuous or discontinuous blood vessels with thick wall at the same level with muscularis mucosae help to correctly precise invasion level even in the absence of muscle fibers from lamina propria.

Marshall staging is another classification for invasion level (Table 2). This one integrates the level of invasion in bladder wall with invasion of pelvin lymph nodes (N) and with metastasis (M).

Table 2 – Marshall stage

Marshall stage	Tumor (T)	Lymph node (N)	Metastasis (M)
O	Ta, Tis	–	–
A1	T1	–	–
B1	T2a	–	–
B2	T2b – T3a	–	–
C	T3b	–	–
D1	any T (Tx)	+N1	–
D2	any T (Tx)	+N2	+

O–A1, superficial urothelial tumor; **B1–C**, profound urothelial tumor; **D1–D2**, metastasis

Histological evaluation for correctly appreciation of tumor stage is sometimes very difficult and has a capital value not only for prognostic but most important for therapeutic management of patients with urinary tumor transurethral resection (TUR) operated.

Tumors that invade muscularis propria are treated by partial or total cystectomy and for superficial carcinoma is not necessary any radical procedure. Urologist plays an important role to perform TUR with muscle fibers from muscularis propria and pathologist must appreciate correctly invasion in bladder wall. In cases with absence of muscularis propria on fragments removed and sent to pathological examination is very important to establish the invasion of muscularis mucosae.

For correctly staging special for TUR fragments is necessary to keep in mind the following:

- the possibility of intravesical adipose tissue in lamina propria or and in muscularis propria, avoid the confusion between muscle fibers of muscularis propria (thick and continuous) and muscle fibers of muscularis mucosae (thin and discontinuous) [7],

- the histological criteria for invasion to lamina propria (growth pattern, the aspect of basal membrane, stromal reaction, artefactual periinsular reaction of tumoral island, paradox differentiation).

3. *Tumor configuration*. Papillary tumors (Figure 2) are lower stage and grade. Tumors with nodular configuration (Figure 3) are more aggressive and are observed in higher stage. Mix tumors are medium aggressively.

4. Invasion in small vessels is difficult to evaluate with usual histopathological methods. For certainly prove

are necessary immunohistochemical tests in order to identify endothelial cells. We determined in our study invasion in small vessels of lamina propria have high risk of tumor progression. On invasive tumors that present invasion in vessels of lamina propria we found lymph nodes involvement more frequent.

5. Multiple tumors. We found more frequency recurrence and progression tumor at patients with multiple tumors (20 cases).

6. The localization of tumors at vesical cervix and posterior wall has a bad prognostic than other localization.

7. Dimension of tumor has no prognostic significance. A bad prognostic have the tumor with more than 5 cm diameter (11 cases).

8. CIS modification in peritumoral urothelium is frequent associated with deep tumoral invasion (14 cases).

9. Histological type is very important for vesical carcinoma prognostic. Urothelial carcinoma has a better prognostic [2, 8–11].

10. Inflammatory infiltrate. Urothelial carcinoma without inflammation is more aggressively.

11. Pattern of invasion. Tentacle pattern has a bad predictive value.

12. Moderns prognostic markers: suppressor tumoral genes (p53, pRb, NF1), oncogenes production (c-erbB2, Hras), cromosomal anomalies (Cr9, MMR, CDKN1B, protein mdm2, cycline D1), markers for appreciation of basal membrane integrity, extracellular matrix and adhesion cells molecules, growth factors receptors (EGFR, FGFR), angiogenesis, etc. [12, 13].

✉ Discussions

We studied evolution of patients with urinary bladder tumors following the histological factors: tumor grade, tumoral stage, histological stage, growth configuration, multifocality, localization and dimension of tumors, *in situ* carcinoma (ISC) modification in peritumoral urothelial mucosae, invasion in small vessels of lamina propria.

Clinical and pathological observations

The risk of recurrence and tumor progression was associated with high tumor stage and grade. Invasion in lamina propria of muscularis mucosa establish a patient prognostic similar with invasion in muscularis propria superficial.

We prefer partial cystectomy at patients with pT1b and pT1c.

Urothelial carcinoma has a better prognostic than other histological types of tumors (adenocarcinoma, urothelial micro-papillary carcinoma, nested variant, scuamos carcinoma etc.).

Papillary configuration of urothelial tumors is identifying at lower tumor grade. *In situ* carcinoma (ISC) modification in urothelium near tumor announces a bad prognostic. Invasion of small vessels of lamina propria is associated with high risk of tumor progression. Multifocality and short time until first recurrence raise the recurrence risk.

Figure 1 – Tumoral progression through bladder wall
(1. Urothelial mucosae; 2. Lamina propria;
3. Muscularis propria; 4. Serosa)

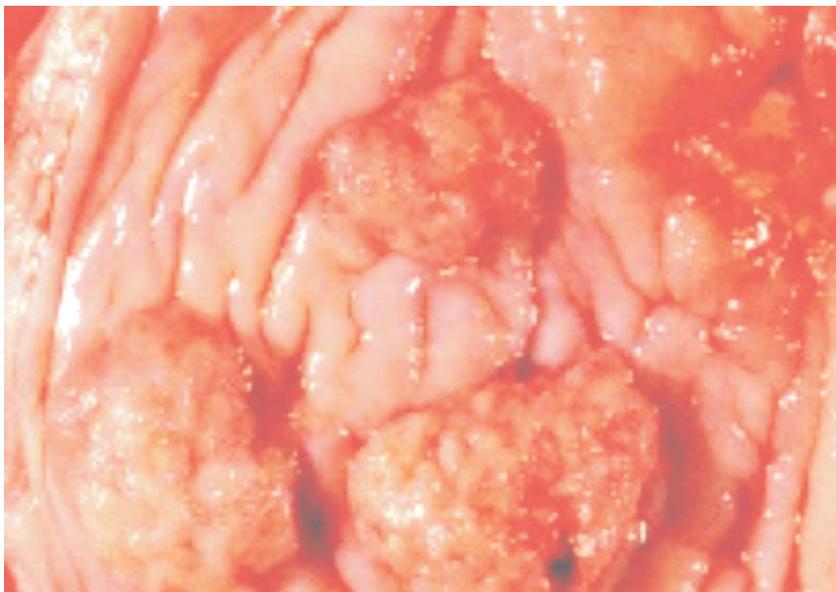
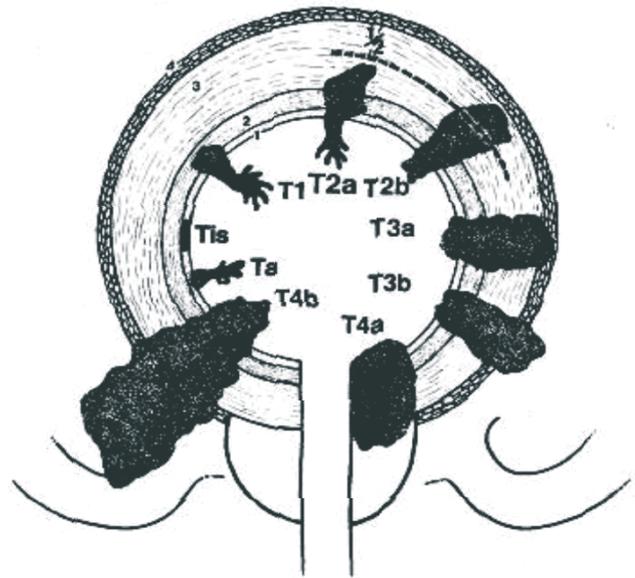


Figure 2 – Exofitic papillary vesical tumor. Surgical pieces

Figure 3 – Nodular vesical tumor. Surgical pieces



☐ Conclusions

Pathological examination of surgical pieces together with clinic and paraclinic examination permitted to appreciate the tumor stage.

Initially, in all cases of urinary bladder tumors we performed transurethral resection transvesical (TUR TV) followed by histological and prognostic evaluation.

Therapeutic algorithm is represent by TUR TV, partial cystectomy with urethral cistoneostomy (UCN) and total cystectomy.

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