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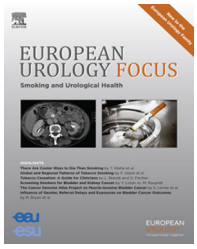

Bladder Cancer

Feasibility and Clinical Roles of Different Substaging Systems at First and Second Transurethral Resection in Patients with T1 High-Grade Bladder Cancer

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Abstract

Background: Decision making in T1 high-grade bladder cancer patients remains a challenging issue in urologic practice.
Objective: To assess the feasibility and potential prognostic role of three different substaging systems in specimens from both primary and second transurethral resection (TUR) of the bladder in T1 high-grade bladder cancer patients.
Design, setting, and participants: A total of 250 consecutive, confirmed pure transitional T1 high-grade bladder tumors submitted to second TUR entered the retrospective study.
Outcome measurements and statistical analysis: Feasibility of two already clinically tested microstaging systems (anatomy-based T1a/T1b/T1c and micrometric T1m/T1e with 0.5-mm thresholds of invasion) and that of a micrometric substage designed by the authors and based on a 1-mm threshold of invasion (Rete Oncologica Lombarda [ROL] system) was assessed by five independent uropathologists on both first and second TUR specimens. Univariable Cox proportional hazards models were attempted to identify significant independent predictors of recurrence and progression after TUR. Kaplan-Meier curves were plotted to compare different substaging methods analyzing recurrence and progression.
Results and limitations: The ROL system proved to be feasible in nearly all cases at both first and second TUR. Median follow-up was 60 mo. The univariate Cox regression analysis documented the ROL substage (ROL2 vs ROL1) to be the only statistically significant predictor of progression (hazard ratio: 2.01; 95% CI, 1.03–3.79; $p < 0.03$). For the first time to our knowledge, the substage was investigated and used to assess T1 tumors found at second TUR, registering a high rate of feasibility.
Conclusions: T1 microstaging using different procedures is feasible on both primary- and second-TUR specimens. A high rate of feasibility may be expected for T1m/T1e and ROL systems. The clinical role of microstaging on second TUR remains to be defined.
Patient summary: The Rete Oncologica Lombarda system showed feasible results in T1 high-grade bladder tumors. Our substratification was predictive of progression of disease.

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1. Introduction

Patients with non–muscle-invasive bladder carcinoma (NMIBC) represent approximately 75% of overall bladder cancers (BCa) at first observation. Among them, patients with T1 high-grade (HG) BCa face a worrying long-term rate of cancer-specific mortality. Deciding when T1 HG BCa patients should undergo radical cystectomy [1] remains a critical issue in urological practice. Many clinical and pathological factors [2–10] were documented to be reliable predictors of oncologic outcomes in this subset of patients. Until now, the pathological T1 substaging was neither recommended by the World Health Organization (WHO)/International Society of Urologic Pathology nor included in the TNM Classification of Malignant Tumors, seventh edition, but some form of estimate of lamina propria invasion in pT1 tumors, as recently stated by Amin et al [11], is strongly advocated by clinicians. Accordingly, different pT1 substaging systems have been proposed during the last decade [12–18]. Many factors, including thermal damages, inadequate orientation of specimens from transurethral resection (TUR), and reduced inter- and intraobserver agreement [19–21], limited the adoption of T1 substaging as a standard prognostic tool in routine practice. The fact that the muscularis mucosa–vascular plexus (MM-VP) cannot be visualized in a consistent number of patients has further strongly reduced the use of anatomic substaging procedures [13]. All clinical investigations on the role of T1 microstaging were completed on heterogeneous series of patients, including those who received a second TUR and those who did not. Taking into consideration the critical effects of second TUR on oncologic outcomes [22,23], investigating the feasibility and clinical role of microstaging on selected consecutive patients submitted to second TUR is strongly suggested. In this direction, this multicenter study was aimed to investigate both the feasibility and prognostic role of different substaging systems assessed on both first and second TUR specimens in a large, homogeneous series of patients with pT1 HG bladder cancer submitted to second TUR.

2. Materials and methods

In a multi-institutional review board–approved study, the institutional registry was queried for all consecutive patients between January 2007 and December 2011 diagnosed with pT1 HG bladder tumors at first TUR. Among them, only patients who had completed initial TUR and were submitted to second TUR within 1–3 mo from primary resection were considered for this study. Five experienced uropathologists from four different high-volume urologic centers independently reviewed multiple slides of specimens from primary TUR of this population. Patients diagnosed with incorrect grading or a histotype other than transitional (focal variant<5% was accepted) at this revision as well as patients with pT2 tumors at second TUR were excluded from the study. Of the remaining patients, only those who started bacillus Calmette-Guérin (BCG) treatment (according to the SWOG schedule of administration) after the second TUR and completed at least the 6-wk inductive cycle were included and analyzed for the end points of the study.

2.1. End points

The primary end point was to assess the feasibility of three microstaging systems (T1a/T1b/T1c; T1m/T1e; Rete Oncologica Lombarda [ROL]) on both first and second TUR. The secondary end point was to compare the prognostic value of the different microstaging procedures in terms of both recurrence and progression rate after TUR. Recurrence was defined as pT1 or lower grade tumor relapse; progression was defined as a recurrent tumor of higher stage or the presence of clinical metastasis.

2.2. Pathological aspects

For ROL substaging, as designed by the authors of this study, the threshold of 1 mm for lamina propria (LP) tumor invasion was adopted. In detail, ROL was stratified as the following: ROL1 indicated less than one high-power field (HPF; objective 20×, ocular 10×/field 22, diameter of 1 × 1 mm) invasion, corresponding approximately to ≤1-mm-thick invasion of LP; ROL2 indicated more than one HPF (objective 20×), corresponding approximately to >1-mm-thick invasion of the LP or multifocality of invasion totaling >1-mm-thick invasion of the LP (ie, the sizes of individual foci were summed). For this purpose, the major diameter of invasion, that is, the extent of invasion in any direction, was measured. The assessment of T1a/T1b/T1c (above or under the muscularis mucosae) and T1m/T1e (microinfiltration and extended infiltration of LP) microstaging was rigorously completed according to the authors' indications [14,15].

All pathologists participated in classifying all tumors according to these three substaging systems. For the definition of pathologic concordance of substage attribution, a set including the first 50 consecutive T1 HG cases of the series was blindly reviewed by the five pathologists. The cases with divergent opinion were collectively discussed to achieve a consensus. In addition, all cases confirmed as pT1 at second TUR were separately reviewed by the same pathologists blinded to the diagnosis of the other pathologists and to the oncologic outcome, with the intent to assess and compare the feasibility and reliability of different substaging systems on the same basis adopted for the first TUR.

2.3. Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges (IQRs) were reported for continuously coded variables. Univariable Cox proportional hazards models were constructed and Kaplan-Meier analyses were plotted to compare different substaging methods for the prediction of both recurrence and progression. All statistical tests were two tailed and significance was defined as $p < 0.05$. All analyses were performed using SPSS v.20.0 (IBM Corp, Armonk, NY, USA). The construction of a multivariate analysis including sex, tumor focality, recurrence status, carcinoma in situ (CIS), and lymphovascular invasion (LVI) as covariates was also included in the design of the study.

3. Results

Data from a total of 502 consecutive pT1 HG patients who underwent a primary TUR between January 2007 and December 2011 were retrospectively collected. Of these patients, 64 who did not undergo second TUR as well as 52 staged pT2 or higher at second TUR were preliminarily excluded. Of the remaining patients, 136 were also excluded for additional reasons: incorrect grading, such as ambiguous pattern or deceptive pattern of infiltration reclassified as pTa (n = 42 [32.3%]); histotype other than

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