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Original article

Metric substage according to micro and extensive lamina propria invasion improves prognostics in T1 bladder cancer

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Abstract

Background: Reliable prognosticators for T1 bladder cancer (T1BC) are urgently needed. *Objective:* To compare the prognostic value of 2 substage systems for T1BC in patients treated by transurethral resection (TUR) and adjuvant bacillus Calmette-Guérin therapy.

Design, setting, and participants: The slides of 601 primary T1BCs from four institutes were reviewed by 2 uropathologists and substaged according to 2 classifications: metric substage according to T1 microinvasive (T1m—lamina propria invasion < 0.5 mm) and T1 extensive invasive (pT1e—invasion ≥ 0.5 mm), and according to invasion of the muscularis mucosae (MM) (T1a—invasion above or into MM/T1b).

Outcome measurements and statistical analysis: Multivariable analyses for progression-free (PFS) and cancer-specific survival (CSS) were performed including substage, size, multiplicity, carcinoma in situ, sex, age, WHO-grade 1973, and WHO-grade 2004 as variables.

Results: Median follow-up was 5.9 years (interquartile range: 3.3–9.0). Progression to T2BC was observed in 148 (25%) patients and 94 (16%) died of BC. The MM was not present at the invasion front in 135 (22%) of tumors. Slides were substaged as follows: 213 T1m and 388 T1e and 281 T1a and 320 T1b. On multivariable analysis, T1m/e substage and WHO 1973 grade were the strongest prognosticators for PFS (hazard ratio [HR] $= 3.8$ and HR $= 1.8$) and CSS (HR $= 2.7$ and HR $= 2.6$), respectively. Other prognostic factors for CSS were age (HR $= 1.03$), and tumor size (HR $= 1.8$). Substage according to MM-invasion was not significant. Our study was limited by its retrospective design and that standard re-TUR was not performed if TUR was macroscopically complete and muscularis propria was present in resected specimens.

Conflict of interest: none.

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Conclusions: Metric substaging of T1BC was possible in all cases of 601 T1BC patients and it was a strong independent prognosticator of both PFS and CSS.

Keywords: Bladder cancer; Stage; T1; Grade; WHO; Prognosis; Urothelial, Substage

1. Introduction

In the western world, up to 80% of bladder cancers (BCs) are nonmuscle-invasive at initial diagnosis [1]. Although the majority of nonmuscle-invasive BCs (NMIBCs) have an excellent prognosis, results of conservative management are influenced by several risk factors [2,3]. Known risk factors for progression are stage, presence of carcinoma in situ (CIS), and grade [4,5]. Most importantly, stage T1, defined as invasion of the lamina propria, increases the risk of progression and mortality. T1BC progresses to muscle-invasive BC in up to 50% of cases and approximately one-third metastasizes [6]. Aggressive treatment by means of early radical cystectomy (RC) is recommended by many experts [7]. However, for those T1BCs destined to be nonprogressive, RC is overtreatment. Decision models for RC timing in T1BC are currently lacking [8,9].

T1 substage is a promising tool for predicting progression and mortality. Over the years, 2 substaging classifications have been developed. The first classification is based on presence of muscularis mucosae (MM) invasion. The MM is a small layer of smooth muscle fibers approximately midway in the lamina propria. Stage T1a is defined as invasion above the MM, and T1b as invasion beyond the MM [10]. The second classification, called metric substage, is based on invasion diameter. T1 microinvasive (T1m) has been defined as a single spot < 0.5 mm invasion (within one high-power field, ×400), and T1 extensive invasive (T1e) as ≥ 0.5 mm [11]. Both classifications have been investigated in several noncomparative studies and both have a strong prognostic value [12–14]. Therefore, their use is recommended by the 2016 World Health Organization (WHO) classification [15]. However, the optimal system to substage T1 still remains to be defined [2,15]. In this multicenter study, we compared the prognostic value of the 2 T1BC substaging systems.

2. Material and methods

2.1. Patients

Primary transurethral resection (TUR) slides were collected from 601 T1BC patients at initial diagnosis that had been treated at 1 of 4 university hospitals between 1982 and 2010. Treatment had initially been bladder sparing for all patients and included at least 6 intravesical BCG instillations. The patients received a re-TUR if the initial resection was incomplete or if muscularis propria was absent in the resected tissue. Follow-up was according to NMIBC guidelines and included cystoscopy and urinary cytology every 3 to 4 months for 2 years, followed by every 6 to 12 months if disease did not recur. The study was approved by ethic review boards at each participating site.

2.2. Pathology review

TUR-slides were reviewed and confirmed to be T1 urothelial carcinoma by 6 pathologists (A.H., Tvd.K., E. C., S.B., R.S., and Gv.L.). Next, 2-center pathology review for grade and substage assessment was performed by Tvd. K. (Toronto, $n = 93$; Paris, $n = 133$; and Rotterdam, $n = 66$ cohorts) and A.H. (Regensburg cohort, $n = 309$). Slides were graded according to both WHO 1973 and 2004 classification systems and tumors were substaged according to 2 classification systems in 2 different rounds.

Metric substage was defined as T1m or T1e according to <0.5 mm or ≥ 0.5 mm lamina propria invasion, respectively. Secondly, tumors were staged T1a or T1b defined as absence or presence of muscularis mucosae (MM) invasion, respectively. If MM was not identified, T1a/b substage was estimated according to invasion of the MM-associated vascular plexus or the depth of the MM identified not at the invasion front. Pathologists were blinded for clinical data, apart from initial T1BC diagnosis.

2.3. Statistics

T1 substage classifications were correlated with patient age using the Mann-Whitney U test. The association with other baseline characteristics was tested using Pearson chi-square tests. The primary endpoint was progression-free survival (PFS), defined as time from initial TUR to the moment of diagnosis of invasion of the muscularis propria (≥T2) or lymph node metastases or visceral metastases in follow-up. The secondary endpoint was cancer-specific survival (CSS) defined as time from initial TUR to death of disease or last follow-up. Both were estimated using the Kaplan-Meier method. $P < 0.05$ was considered significant on 2-sided analysis. We determined the prognostic value for metric T1 substage and T1a/b substage on multivariable Cox-regression analyses. The following variables were included in the step-wise backward regression models comparison using likelihood-ratio tests and $P > 0.10$ as covariate exclusion criterion: tumor size (>3 cm vs. ≤ 3 cm), multiplicity, CIS, sex, age, WHO 1973 classification, and WHO 2004 classification. We used SPSS