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Original article

Impact of bladder neck involvement on progression in patients with primary non–muscle invasive bladder cancer: A prospective validation study

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Abstract

Purpose: Our previous retrospective study reported that bladder neck involvement (BNI), as well as tumor grade and stage, was a significant risk factor for progression in primary non–muscle invasive bladder cancer (NMIBC). We prospectively validated BNI as a significant predictor for progression using a new cohort of patients with primary NMIBC.

Patients and methods: A total of 297 new Japanese patients who underwent transurethral resection and were pathologically diagnosed with Ta or T1 urothelial carcinoma were enrolled in this prospective study. Clinicopathologic data were collected at study entry. Multivariate Cox proportional hazards regression models were performed to identify the independent predictors for progression. A predictive scoring model for progression was developed using the regression coefficients (RCs) from the final multivariate model. The predictive ability of the model was assessed using Harrell's c-index.

Results: With a median follow-up of 37 months, 16 patients (5.4%) progressed. Progression probability at 1 and 5 years were 1.5% and 8.0%, respectively. Multivariate analysis revealed that histologic grade 3 (hazard ratio [HR] 9.45, $P = 0.0004$, RC 2.25), pathologic T1 stage (HR 6.91, $P = 0.0014$, RC 1.93), and BNI (HR 11.75, $P = 0.0009$, RC 2.46) were all independent predictors of progression. When all 3 variables were scored as 1 point and the patients were divided into 3 groups, progression rates were clearly discriminated ($P < 0.0001$). The c-index was 0.80.

Conclusions: This prospective validation study has shown that BNI is a significant prognostic factor for progression in primary NMIBC. The scoring model including BNI enables the physician to classify patients with primary NMIBC into 3 groups with clearly different progression rates.

Keywords: Urinary bladder; Urinary bladder neoplasms; Carcinoma; Progression; Bladder neck

1. Introduction

Urinary bladder cancer is one of the most common genitourinary malignancies. Approximately 70% of new urothelial bladder cancer cases are classified as non–muscle invasive bladder cancers (NMIBC: pTa, pT1, and pTis) [1,2]. Despite a high recurrence rate of 40% to 80%, the prognosis of NMIBC is generally favorable because progression to muscle invasive or metastatic disease or both occurs in only approximately 15% of patients. However, once patients develop progression, their prognoses are generally unfavorable [3]. Thus, an accurate prediction of progression is critically important in patients with NMIBC.

Although there are multiple different definitions and formulas to determine high-risk patients, numerous studies have shown that tumor grade and stage are the most important prognostic variables commonly available to the physician to identify the patients at greatest risk of developing MIBC [4,5]. In addition, previous studies have reported that the presence of carcinoma in situ (CIS), prior

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recurrence rate, multiplicity, urine cytology, and response to bacillus Calmette-Guérin (BCG) are also associated with increased risk of progression [6-9].

Some previous studies, including one we performed, have reported that the location of tumors, in particular bladder neck involvement (BNI), is also a predictor of tumor progression [4,10,11]. In our retrospective study [4] of 277 patients with primary NMIBC, progression occurred in 28 (10.1%) of the patients during a median follow-up period of 7.7 years, and multivariate analysis showed that BNI (hazard ratio [HR] 4.85, $P < 0.001$), tumor grade (grade 3 vs. 1–2, HR 2.80, $P = 0.016$), and stage (T1 vs. Ta, HR 2.07, $P = 0.003$) were all independent factors for progression [4]. When the patients were divided into 3 groups according to the number of the 3 independent factors they had, their progression rates were clearly discriminated. Groups having none, 1, or 2 or 3 factors showed 5-year progression rates of 0.8%, 4.6%, and 27.5%, respectively. Kurth et al. reported that BNI was one of the significant factors for progression in their univariate analysis [11].

In this study, we prospectively validated BNI as a significant predictor for progression using a new cohort of patients with primary NMIBC. A prediction model for progression was developed using the regression coefficients (RCs) from the final multivariate Cox proportional hazard model.

2. Materials and methods

Between January 2000 and June 2010, a total of 311 new Japanese patients underwent transurethral resection (TUR) and were pathologically diagnosed with Ta or T1 (N0M0) urothelial carcinoma of the bladder based on the 2009 tumor-node-metastasis classifications at Tokyo Medical and Dental University Hospital. Patients with primary CIS and tumors located definitely in the prostatic urethra were excluded from this study. Of the 311 patients, 14 patients who received chemoradiotherapy or cystectomy after TUR without histologically confirmed muscle invasion were excluded. Thus, 297 patients (245 men and 52 women) were enrolled in this prospective study. Clinicopathologic data were collected at study entry and are listed in Table 1. These included age, gender, tumor number, tumor size, histologic stage, grade, concomitant CIS, presence of intravesical treatment, and tumor location. In this study, tumor location was determined by urologists who performed TUR. Tumors located adjacent to the bladder neck, within approximately 1 cm from the internal urethral orifice, but not in the prostatic urethra were defined as bladder neck tumors. Tumors were histologically graded according to the 1973 World Health Organization grading system. The mean age of the patient population was 67 years. The institutional review board approved this study, and informed consent was obtained from each participant.

In general, all the patients received single-dose intravesical chemotherapy using adriamycin or mitomycin in the immediate postoperative period. A second TUR was recommended if tumors were pathologically diagnosed as T1 at the initial TUR. The 297 patients underwent TUR a total of 528 times (297 times for primary tumors and 231 times for recurrent tumors) during the study period. There were 108 cases of pathologically diagnosed pT1 tumors, and of these, 56 (52%) were treated with a second TUR. In these patients, no MIBCs were found at the second TUR.

The patients underwent urinary cytology and cystoscopy every 3 months after TUR for the first 2 years, and then every 6 months for the next 3 years. After the TUR for primary tumors, BCG therapy was recommended if tumors were pathologically diagnosed as grade 3 and T1. Intravesical

Table 1
Patient and tumor characteristics

Variables	No. pts (%)
Age, y	
>70	118 (39.7)
≤70	179 (60.3)
Gender	
Male	245 (82.5)
Female	52 (17.5)
Number of tumors	
Single	164 (55.2)
2–7	115 (38.7)
≥8	18 (6.1)
Tumor size	
<3 cm	261 (87.9)
≥3 cm	36 (12.1)
Pathologic stage	
Ta	213 (71.7)
T1	84 (28.3)
Concomitant CIS	
No	268 (90.2)
Yes	29 (9.8)
Histologic grade	
G1	29 (9.8)
G2	223 (75.1)
G3	45 (15.2)
Tumor location	
Anterior wall	17 (5.7)
Bladder neck	30 (10.1)
Dome	18 (6.1)
Left lateral wall	62 (20.9)
Right lateral wall	85 (28.6)
Posterior wall	101 (34.0)
Trigone	83 (27.9)
T1G3	
No	263 (88.6)
Yes	34 (11.4)
Intravesical treatment	
No	69 (23.2)
MMC or ADM	203 (68.4)
BCG	19 (6.4)
Unknown	6 (2.0)

MMC = mitomycin; ADM = adriamycin.