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Risk Factors Predictive of Recurrence and Progression for Patients Who Suffered Initial Recurrence After Transurethral Resection of Stage pT1 Bladder Tumor in Chinese Population: A Retrospective Study

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Abstract: Bladder cancer is one of the most common malignancies worldwide and the stage pT1nonmuscle invasive bladder cancer (NMIBC) has a high probability of recurrence after initial diagnosis and treatment. However, risk factors predictive of repeated recurrence and progression of pT1 bladder tumors after primary relapse have not been uncovered. Thus, we conducted the retrospective study.

A total of 418 patients who suffered initial recurrence after transurethral resection (TUR) of pT1 bladder tumor were selected for the analyses. Clinic information of the patients was retrieved from their medical records. Recurrence-free survival (RFS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model. The probability of recurrence and progression by multivariate analyses was used as a surrogate marker to construct receiver operating curve (ROC).

Results showed that variables including time to prior recurrence time, prior treatment, number of tumor, tumor size, tumor grade, and time of instillation after surgery were associated with the repeated recurrence of pT1 bladder tumor ($P < 0.05$). The variables including time to prior recurrence time, tumor size, tumor grade, carcinoma in situ (CIS), and time of instillation after surgery were associated with progression of pT1 bladder tumor ($P < 0.05$). In the present study, the multivariate model showed an area under ROC (AUC) value of 0.754 and 0.798 for tumor recurrence and progression, respectively, which was more effective in prediction than a single risk factor.

In conclusion, we have identified several risk factors relevant to RFS and PFS for patients who have had a history of recurrence of pT1 bladder tumor after TUR. These predictive factors may help urologists to stratify patients into distinct risk groups of recurrence and progression, which probably contributes to the individualized treatment for patients.

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Abbreviations: AUC = area under receiver operating curve, CI = confidence interval, CIS = carcinoma in situ, HR = hazard ratio, MIBC = muscle invasive bladder cancer, NMIBC = nonmuscle invasive bladder cancer, PFS = progression-free survival, Ref = reference, RFS = recurrence-free survival, ROC = receiver operating curve, TUR = transurethral resection, TURBT = transurethral resection of bladder tumor.

INTRODUCTION

Bladder cancer is one of the major causes for new cancer cases and cancer-related mortality for men worldwide. It is estimated that 429,800 new cases and 165,100 deaths of bladder cancer occurred in 2012 worldwide.[1] Approximately 75% of patients with bladder cancer belong to nonmuscle invasive bladder cancer (NMIBC).[2,3] The tumors of NMIBC are routinely treated by transurethral resection (TUR) and/or intravesical instillation. However, the prognosis of NMIBC is not satisfying, as the 5-year recurrence rate for NMIBC was reported ranging from 31% to 78% and the progression rate from NMIBC to muscle invasive bladder cancer (MIBC) ranged from 0.8% to 45%.[4]

In EAU guidelines, patients with stage pT1 bladder tumor are considered at a high risk for recurrence, whereas patients with stage pTa tumor are classified into the group of low risk for recurrence (Guidelines on Nonmuscle-invasive Bladder Cancer (Ta, T1, and CIS), http://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/, July 21, 2015). Accordingly, strict tumor surveillance for patients with stage pT1 bladder cancer and a recurrent history are highly suggested, which probably makes use of prognostic factors with a high efficacy in prediction of recurrence and progression. Over the past decades, although a number of studies aiming to determine the prognostic factors for patients with superficial bladder cancer have been published,[5–9] most of them focused on the initial recurrence and progression of the tumor. With respect to patients who were initially diagnosed with pT1 bladder tumor and have suffered primary recurrence after TUR, the risk factors for repeated recurrence and progression have not been revealed.

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The aim of this study is to evaluate the risk factors predictive of repeated recurrence and progression for patients with pT1 bladder tumor in Chinese population based on a set of routinely assessed clinical and pathological factors.

PATIENTS AND METHODS

Study Population

The present study was conducted with approval of the institutional review board of Second Hospital of Tianjin Medical University. A total of 1549 patients with NMIBC who underwent TUR form June 2005 to June 2011 at the hospital were screened and eventually a total of 418 cases fulfilled the predefined inclusion criteria. Clinical and pathological information was retrospectively obtained from patient charts and electronic medical records. The inclusion criteria were as follows. First, cystoscopy and cytology were performed before TUR. All exophytic lesions underwent a complete resection including deep resection of the tumor base. Three to six weeks later, the secondary transurethral resection was conducted and patients with MIBC were confirmed by radical cystectomy. Second, all patients must have a history of primary recurrence and the tumor was initially diagnosed as NMIBC. Third, tumor was pathologically diagnosed as stage pT1 bladder tumor. Fourth, the detailed assessment of primary tumor histology was available. Fifth, adjuvant intravesical chemotherapy was adopted after TUR. The chemotherapy drug was the Epirubicin or Pirarubicin. None of the patients received adjuvant immunotherapy due to the inaccessibility of BCG in China. Exclusion criteria included presence of urethral or upper tract primaries, or distant metastasis at diagnosis, absence of re-TUR, or patients with MIBC were not confirmed by radical cystectomy, and patients failed to receive further treatment.

All patients were treated with TUR, which was carried out according to a standardized procedure. All visible tumors or suspicious mucosal lesions were resected with a monopolar loop electrode. The resection was extended to the deep muscle layer of the bladder at the base of the tumor, reaching perivesical fat.

The clinicopathological variables involved in the present study included patient age, gender, smoking history, diabetes, prior recurrence time, prior treatment, location, number of tumors, tumor size, pathological stage, pathological grade, chemotherapeutic agents, and immediate instillation or not. Tumor size was defined as the largest diameter of the surgical specimen on macroscopic analysis. Pathological stage was reassigned by a single genitourinary pathologist (JCC) according to the TNM classification (2002) staging system (TNM Classification of Malignant Tumors, 6th edition, http://www.uicc.org/tnm-classification-malignant-tumours-6th-edition, July 21, 2015), and tumor grading was done according to the 2004 WHO grading system.[10] Postoperative follow-up proceeded with cystoscopy at 3-month interval for the first 2 years followed by 6-month interval until the fifth year and annually thereafter according to the US and European guidelines.[11] The end points of this study were recurrence-free survival (RFS): time from randomization to the date of the first bladder recurrence. Patients who still alive and without recurrence were censored at the date of the last available follow-up cystoscopy. Time to progression to muscle invasive disease (progression-free survival, PFS): time from randomization to the date of first increase to stage T2 or higher disease in the bladder. Patients who still alive and without muscle invasion were censored at the date of the last available follow-up cystoscopy.[4,12]

Statistical Analysis

Descriptive statistical analysis was conducted for the variables. Continuous variables were analyzed using independent-sample t test, and categorical variables were analyzed using Chi-square test. Univariate Cox proportional hazard analysis was performed to verify independent parameters predictive of recurrence and progression. Selected variables that showed significant differences in univariate analysis were included in a multivariate Cox proportional hazard analysis to further identify parameters predictive of recurrence and progression. The probability of recurrence and progression resulting from multivariate Cox proportional hazard model was used as a surrogate marker to construct receiver operating characteristic (ROC) curve. Area under curve (AUC) of ROC was used to evaluate the performance of factors predictive of recurrence and progression. Z-test was performed to evaluate the difference between AUCs of factors in the model.[15] RFS and PFS curves were calculated by the Kaplan–Meier method and the differences between curves were analyzed by the log-rank test. All statistical analyses were performed using statistical software (version 20.0, SPSS, IBM company, Armonk, New York). All statistical tests were 2-sided and considered to be significant if the P value was <0.05.

RESULTS

The main characteristics of the patients are given in Table 1. There were 348 males (83.3%) and 70 females (16.7%) enrolled in our study. Mean age at surgery was 65.1 years (range 27–91 years). The median follow-up duration was 53.5 months (range 2–120 months). Of these patients, 197 (47.1%) suffered recurrence and 63 (15.1%) suffered progression.

Results from univariate (Tables 2 and 3) and multivariate (Table 4) Cox proportional hazard analysis showed that the variables, including prior recurrence time, previous treatment, number of tumors, tumor size, tumor grade, time of instillation, were associated with repeated recurrence. The variables including prior recurrence time, tumor size, tumor grade, CIS, and time of instillation were found to be associated with tumor progression in the cohort of this study.

For high-grade pT1 bladder tumor, the factors including prior recurrence time, previous treatment, number of tumor, and time of instillation were in relation to repeated recurrence. The progression of high-grade pT1 bladder tumor was influenced by prior recurrence time, tumor size, CIS, and time of instillation after surgery (Table 5).

To evaluate the performance of the risk factors on prediction of recurrence, ROC analysis was performed (Table 6, Figure 1). The AUCs regarding prior recurrence time, previous treatment, number of tumor, tumor size, tumor grade, time of instillation were 0.652, 0.568, 0.501, 0.638, 0.645, and 0.596, respectively. The AUC for multivariate model on prediction was 0.754, showing a higher efficacy than a single factor. With respect to progression prediction, the AUCs for prior recurrence time, tumor size, tumor grade, CIS, and timing of instillation were 0.646, 0.643, 0.647, 0.553, and 0.591, respectively. The AUC of multivariate prediction model for progression was 0.798, suggesting that a group of risk factors were more effective on prediction than a single factor (Table 6, Figure 2).

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TABLE 1. Demographic and Clinical Characteristics of Patients

Variable	No. of Patients (%)
Age (yrs)	
≤65	198 (47.4)
>65	220 (52.6)
Gender	
Male	348 (83.3)
Female	70 (16.7)
Smoking history	
Never smoker	251 (60)
Former or current smoker	167 (40)
Diabetes	
Yes	68 (16.3)
No	350 (83.5)
PRT	
Recurrent ≤1 yr	114 (23.7)
Recurrent >1 yr	304 (72.7)
Prior treatment	
Yes	276 (66.0)
No	142 (34.0)
Location	
With trigone	42 (10.0%)
With neck	72 (17.2%)
With trigone and neck	13 (3.1%)
Without trigone or neck	279 (66.7%)
Unknown	12 (2.9%)
Number of tumors	
1	173 (41.4)
2–3	113 (27.0)
>3	122 (29.2)
Unknown	10 (2.4)
Tumor size (cm)	
<3	307 (73.4)
≥3	91 (21.8)
Unknown	20 (4.8)
Pathology grade	
Low	204 (48.8)
High	207 (49.5)
Unknown	7 (1.7)
Pathology	
Urothelial carcinoma	370 (88.5)
CIS	10 (2.4)
Others	37 (8.9)
Unknown	1 (0.2)
Chemotherapeutic agents	
Epirubicin	227 (54.3)
Pirarubicin	174 (41.6)
Unknown	16 (3.8)
Immediate instillation	
≤24 hr	166 (39.7)
>24 hr	236 (56.5)
Unknown	16 (3.8)
Recurrence	
Yes	197 (47.1)
No	221 (52.9)
Progression	
Yes	63 (15.1)
No	355 (84.9)

CIS = carcinoma in situ, PRT = prior recurrence time, tumor size = the diameter of the largest lesion.

Mean follow-up duration was 72.6 and 58.9 months for patients with low-grade pT1 tumor and high-grade pT1 tumor, respectively. Eighty-three out of the 204 (40.7%) patients with low-grade tumor and 111 out of the 207 (53.6%) patients with high-grade pT1 tumor suffered repeated recurrence. Analysis showed that 18 of the 204 (8.8%) patients with low-grade pT1 tumor and 45 of the 207 (21.7%) patients with high-grade tumor suffered progression of the tumor. There was significant difference in rate of recurrence between the low-grade group and the high-grade group ($P = 0.01$), as well as in rate of progression between the 2 groups ($P < 0.001$) (Table 7). The patients with high-grade pT1 tumor had shorter mean RFS ($P = 0.006$) and PFS ($P < 0.001$) than those with low-grade pT1 tumor (Figures 3 and 4).

DISCUSSION

Patients who were diagnosed with stage pT1 bladder cancer and treated with TUR have a high probability of recurrence and progression of the tumor. Thus, it is important to find out the risk factors predictive of recurrence and progression, so that postoperative follow-up or radical cystectomy might be adopted in time for better treatment. With respect to the stage pT1 bladder cancer, previous studies focused on the risk factors in relation to the primary recurrence of pT1 bladder tumor and its progression to MIBC. For instance, Takaoka et al[13] retrospectively analyzed 73 patients with high-grade pT1 bladder cancer, focusing on the initial TUR, RFS, and PFS, as well as risk factors related to the presence of residual tumors in the second TURBT. To evaluate the prognostic value of the depth of lamina propria invasion in patients with pT1 bladder cancer, Soukup et al[14] made a retrospective analysis, which led to the finding that deep invasion of the lamina propria is a significant adverse prognostic factor for tumor progression, disease-specific survival, and overall survival. Similarly, another study[9] showed that the aggregate length of invasion might be a prognostic variable for high-risk NMIBC. Taken together, the aforementioned studies all focused on pT1 bladder cancer and are featured by the investigation of a single factor associated with recurrence and progression. Although Liu et al[15] have identified several risk factors relevant with recurrence through reviewing 698 patients who received TURBT in a single center and proposed a new model on the basis of multivariate logistic result, their model is applicable for the initial recurrence prediction, not for repeated recurrence.

In the present study, we propose a prediction model via multivariate logistic regression incorporating the impacts of a set of clinicopathologic variables, to evaluate the prognosis of patients who had pT1 bladder cancer and had suffered initial recurrence after TUR treatment. The multivariate model showed an AUC value of 0.754 and 0.758 for repeated recurrence and progression, respectively, in the cohort including 418 patients. Our model makes use of the clinicopathologic parameters that can be readily collected, as well as enables an early prognosis prediction for the patients. Therefore, it might be of significance to the patient population who meet the inclusion criteria in this study.

The poor prognosis of T1G3 patients has been the subject of a number of recent publications.[16–18] We also observed that high-grade pT1 bladder tumor had shorter mean RFS and PFS than low-grade pT1 bladder tumor in the cohort. It has been reported that patients with high-risk NMIBC have poor prognosis due to the tumor progression and approximately 5% of pT1 bladder tumors have regional nodal metastasis at

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TABLE 2. Univariate Analysis Predictive of Prognostic Factors for Recurrence-free Survival and Progression-free Survival

	Recurrence		Progression	
Factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age: ≤65 yrs, >65 yrs	1.203 (0.910–1.592)	0.194	1.832 (1.091–3.076)	0.022
Gender: male, female	1.005 (0.694–1.455)	0.979	1.459 (0.695–3.066)	0.318
Smoking history: yes, no	1.054 (0.794–1.399)	0.717	1.525 (0.930–2.501)	0.094
Diabetes: yes, no	1.095 (0.750–1.599)	0.639	1.137 (0.561–2.303)	0.721
Prior recurrence time: ≤1 yr, >1 yr	2.476 (1.864–3.289)	0.000	2.702 (1.649–4.430)	0.000
Prior treatment: yes, no	2.611 (1.970–3.459)	0.000	1.658 (1.009–2.726)	0.046
Location: Without trigone or neck	1.000 (Ref)	Ref	1.000 (Ref)	Ref
With trigone	1.213 (0.765–1.924)	0.412	1.842 (0.918–3–698)	0.086
With neck	0.815 (0.545–1.219)	0.320	1.012 (0.504–2.032)	0.972
With trigone and neck	1.646 (0.837–3.235)	0.149	1.052 (0.254–4.360)	0.945
Number of tumors: 1	1.000 (Ref)	Ref	1.000 (Ref)	Ref
2–3	1.282 (0.894–1.838)	0.177	1.116 (0.609–2.046)	0.723
>3	1.756 (1.257–2.453)	0.001	1.020 (0.560–1.855)	0.949
Tumor size: <3 cm, ≥3 cm	1.674 (1.224–2.291)	0.001	3.139 (1.779–5.538)	0.000
Pathology grade: Low, High	1.487 (1.118–1.977)	0.006	2.713 (1.570–4.688)	0.000
Pathology: Urothelial carcinoma	1.000 (Ref)	Ref	1.000 (Ref)	Ref
CIS	2.452 (1.252–4.801)	0.008	6.944 (3.137–15.368)	0.000
Others	0.937 (0.576–1.524)	0.937	1.640 (0.776–3.466)	0.195
Chemotherapeutic agents: Epirubicin, Pirarubicin	1.004 (0.753–1.339)	0.976	1.451 (0.870–2.419)	0.153
Immediate instillation: ≤24 hr, >24 hr	1.807 (1.325–2.463)	0.000	2.385 (1.309–4.346)	0.005

CI = confidence interval, HR = hazard ratio, Ref = reference.

TABLE 3. Univariate Analysis Predict the Prognostic Factors for Recurrence-free Survival and Progression-free Survival of pT1 High Grade

	Recurrence		Progression	
Factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age: ≤65 yrs, >65 yrs	1.354 (0.933–1.967)	0.111	1.519 (0.817–2.823)	0.187
Gender: male, female	1.036 (0.591–1.815)	0.903	1.120 (0.442–2.838)	0.811
Smoking history: yes, no	1.068 (0.734–1.554)	0.731	1.398 (0.779–2.509)	0.261
Diabetes: yes, no	1.114 (0.673–1.847)	0.674	1.181 (0.527–2.644)	0.687
PRT: ≤1 yr, >1 yr	2.689 (1.851–3.907)	0.000	3.138 (1.728–5.699)	0.000
Prior treatment: yes, no	2.058 (1.410–3.004)	0.000	1.544 (0.850–2.804)	0.153
Location: Without trigone or neck	1.000 (Ref)	Ref	1.000 (Ref)	Ref
With trigone	1.341 (0.769–2.341)	0.301	1.650 (0.749–3.632)	0.214
With neck	0.674 (0.392–1.159)	0.154	0.736 (0.304–1.782)	0.496
With trigone and neck	1.918 (0.603–6.103)	0.270	1.336 (0.181–9.833)	0.776
Number of tumors: 1	1.000 (Ref)	Ref	1.000 (Ref)	Ref
2–3	1.456 (0.921–2.301)	0.108	1.707 (0.870–3.349)	0.120
>3	1.801 (1.137–2.851)	0.012	1.069 (0.494–2.317)	0.865
Tumor size: <3 cm, ≥3 cm	1.151 (0.761–1.742)	0.506	2.624 (1.439–4.784)	0.002
Pathology: urothelial carcinoma	1.000 (Ref)	Ref	1.000 (Ref)	Ref
CIS	2.209 (1.022–4.774)	0.044	5.348 (2.231–12.816)	0.000
Others	0.864 (0.483–1.574)	0.624	1.494 (0.659–3.386)	0.336
Chemotherapeutic agents: epirubicin, pirarubicin	1.109 (0.754–1.632)	0.600	1.477 (0.812–2.686)	0.201
Immediate instillation: ≤24 hr, >24 hr	2.018 (1.330–3.063)	0.000	2.798 (1.378–5.679)	0.004

CI = confidence interval, CIS = carcinoma in situ, HR = hazard ratio, PRT = prior recurrence time, Ref = reference.

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TABLE 4. Multivariate Analysis Predictive of Prognostic Factors for RFS and PFS

	Recurrence		Progression	
Factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age: ≤65 yrs, >65 yrs	—	0.158	1.709 (0.963–3.034)	0.067
PRT: ≤1 yr, >1 yr	2.465 (1.796–3.382)	0.000	2.801 (1.608–4.880)	0.000
Prior treatment: yes, no	2.135 (1.565–2.914)	0.000	1.258 (0.717–2.209)	0.424
Number of tumors:1	1.000 (Ref)	Ref	—	—
2–3	1.310 (0.894–1.920)	0.166	—	—
>3	2.082 (1.447–2.995)	0.000	—	—
Tumor size: <3 cm, ≥3 cm	1.402 (0.997–2.004)	0.042	2.864 (1.655–4.956)	0.000
Pathology grade: low, high	1.524 (1.107–2.097)	0.010	2.356 (1.249–4.445)	0.008
Pathology: urothelial carcinoma	1.000 (Ref)	Ref	1.000 (Ref)	Ref
CIS	1.131 (0.485–2.640)	0.775	3.407 (1.300–8.929)	0.013
Others	1.130 (0.655–1.948)	0.660	1.176 (0.491–2.820)	0.716
Immediate instillation: ≤24 hr, >24 hr	1.828 (1.303–2.566)	0.000	2.098 (1.124–3.917)	0.020

CI = confidence interval, HR = hazard ratio, Ref = reference.

TABLE 5. Multivariate Analysis Predict the Prognostic Factors for Recurrence-free Survival and Progression-free Survival of pT1 High Grade

	Recurrence		Progression	
Factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
PRT: ≤1 yr, >1 yr	3.104 (2.064–4.668)	0.000	3.401 (1.784–6.483)	0.000
Prior treatment: yes, no	1.580 (1.048–2.380)	0.029	—	—
Number of tumors:1	1.000 (Ref)	Ref	—	—
2–3	1.756 (1.079–2.858)	0.023	—	—
>3	2.182 (1.346–3.539)	0.002	—	—
Tumor size: <3 cm, ≥3 cm	—	—	2.422 (1.294–5.533)	0.006
Pathology: urothelial carcinoma	1.000 (Ref)	Ref	1.000 (Ref)	Ref
CIS	1.321 (0.598–2.921)	0.491	2.870 (1.092–7.544)	0.032
Others	1.262 (0.638–2.494)	0.503	1.241 (0.476–3.234)	0.658
Immediate instillation: ≤24 hr, >24 h	2.390 (1.520–3.759)	0.000	2.467 (1.185–5.135)	0.016

CI = confidence interval, CIS = carcinoma in situ, HR = hazard ratio, PRT = prior recurrence time, Ref = reference.

TABLE 6. Area Under Receiver Operating Curve

	Recurrence		Progression	
Variables	**Area Under Curve**	***P*** *	**Area Under Curve**	***P*** *
PRT: ≤1 yr, >1 yr	0.652	0.063	0.646	0.004
Prior treatment: yes, no	0.568	<0.001	—	—
Number of tumors:1, 2–3, >3	0.501	<0.001	—	—
Tumor size: <3 cm, ≥3 cm	0.638	0.040	0.643	0.004
Pathology grade: low, high	0.645	0.030	0.647	0.002
Pathology: urothelial carcinoma, CIS, others	—	—	0.553	<0.001
Immediate instillation: ≤24 hr, >24 hr	0.596	0.003	0.591	<0.001
Multivariate model†	0.754		—	—
Multivariate model‡	—	—	0.798	—

CIS = carcinoma in situ, PRT = prior recurrence time.

* *P* values presented the differences between multivariate model and other variables.

† The multivariate model was built based on the variables of PRT, prior treatment, number of tumors, tumor size, pathology grade, and immediate instillation.

‡ The multivariate model was built based on the variables of PRT, tumor size, pathology type, pathology grade, and immediate instillation.

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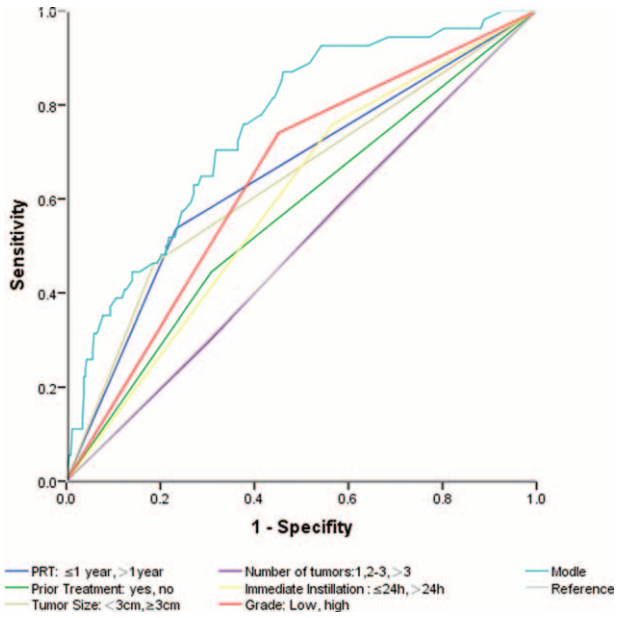

FIGURE 1. Receiver operating curve of recurrence.

presentation.[19] Currently, T1G3 bladder cancer is treated with early radical cystectomy or TURBT followed by adjuvant intravesical therapy with BCG, but the prognosis was not satisfying. More effective therapeutic methods are anticipated to treat T1G3 bladder cancer.

Chemotherapy instillation following TUR of bladder tumor was the only option for patients in China before the approval of BCG in 2014, although BCG instillation is considered as the best choice for adjuvant therapy after TUR.[11] A randomized study conducted by Okamura et al[20] showed that

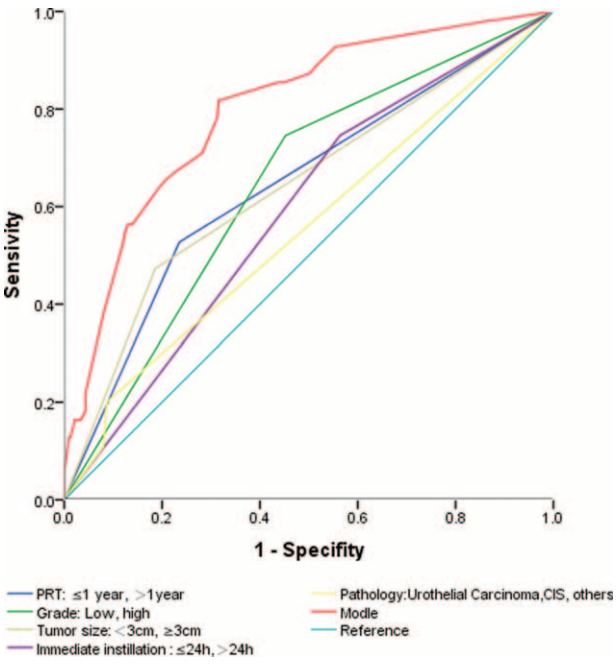

FIGURE 2. Receiver operating curve of progression.

TABLE 7. Recurrence and Progression Outcomes of Different Pathology Grade Treatments After TUR for pT1 Bladder Cancer With a History of TUR

	pT1 Low Grade	pT1 High Grade	*P*
Recurrence, no. (%)			
Yes	83 (40.7)	111 (53.6)	0.006
No	121 (59.3)	96 (46.4)	
Mean RFS, mnths (range)	72.6 (3–117)	58.9 (2–117)	0.006
Progression, no. (%)			
Yes	18 (8.8)	45 (21.7)	<0.001
No	186 (91.2)	162 (78.3)	
Mean PFS, mnths (range)	67.9 (4–120)	74.3 (3–120)	<0.001

PFS = progression-free survival, RFS = recurrence-free survival.

immediate pirarubicin instillation after TUR reduced recurrence of superficial bladder carcinoma. Perlis et al[21] found that epirubicin reduced recurrence of NMIBC after a pooled analysis of 2548 patients. For Chinese patients, Liu et al[15] found that anthracycline antibiotics (eg, epirubicin and pirarubicin) outweighed other agents (eg, mitoxantrone, mitomycin C, and hydroxycamptothecine) in preventing short-term recurrence. In this study, we find that epirubicin and pirarubicin have the same effects on prognosis of pT1 bladder cancer after TUR. We also observed that immediate instillation (≤24 hours) hours) after TUR is an independent prognostic factor for patients with pT1 bladder cancer. As immediate instillation may destruct circulating tumor cells resulting from TURBT[20] and ablate residual tumor cells at resection sites and small overlooked tumors,[22–24] it is expected that to some extent timing of instillation after TUR is associated with prognosis of the patients.

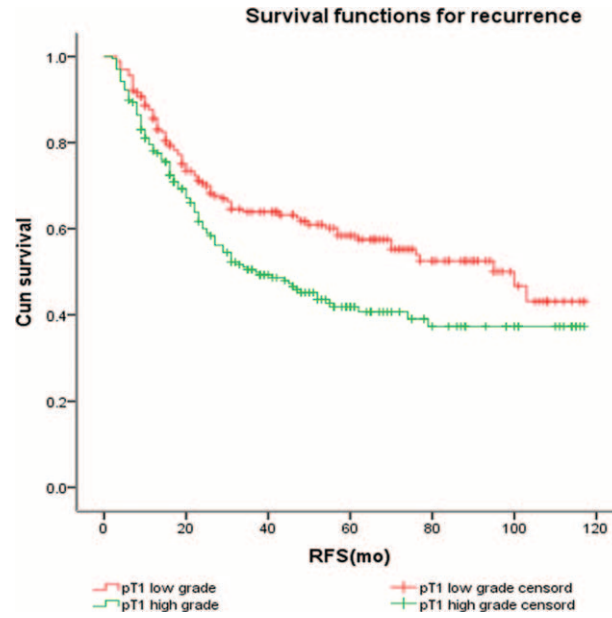

FIGURE 3. Kaplan–Meier curves of the recurrence-free survival rates for the 2 groups (log-rank test result: 0.006). Cum = cumula-cumulative; RFS = recurrence-free survival.

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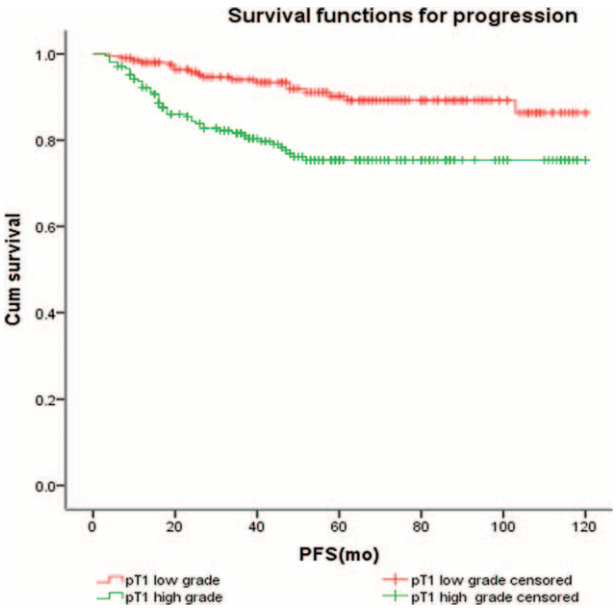

FIGURE 4. Kaplan–Meier curves of the progression-free survival rates for the 2 groups (log-rank test result: <0.001). Cum = cumulative; PFS = progression-free survival.

Lammers et al[25] found that the recurrent history, multiplicity, and smoking status were predictive factors for RFS of NMIBC. Later, Rink et al[26] showed that accumulative smoking exposure was associated with bladder cancer recurrence, progression, and overall survival. In contrast, Grotenhuis et al[27] showed that smoking status, smoking intensity, or timing of cessation before diagnosis did not seem to alter the risk of recurrence and progression for patients with NMIBC. In the present study, our analysis generally support that smoking status has no impact on recurrence and progression of patients who had suffered initial recurrence after TUR of stage pT1 bladder tumor and immediate instillation chemotherapy. As cigarette smoking is an environmental stress that acts via interplaying with genetic factors, the difference in conclusion regarding smoking status and bladder cancer incidence in the studies referenced above may be attributed to genetic heterogeneity of the cohorts. In this study, we were unable to determine the associations of smoking intensity and timing of cessation with prognosis of patients in this study due to lack of information of patients on the 2 variables.

Hwang et al[28] showed that diabetes was an independent predictive factor of RFS and PFS in NMIBC patients. In the study by Hwang et al,[28] 92 of the 251 (37%) patients who underwent TUR for NMIBC from January 2000 to June 2010 had diabetes. In the present study, we observed that diabetes was not associated with the risks of recurrence ($P = 0.639$) and progression ($P = 0.721$) in the cohort. The proportion of diabetes in our cohort was 16.3% (n = 68), which is much smaller than that in the study by Hwang et al.[28] To be noticed, patients in our cohort were initially diagnosed with pT1 bladder cancer and had suffered recurrence after TUR. Considering the differences in proportion of diabetes and clinic status of patients between the 2 studies, the discrepancy in conclusions regarding the impact of diabetes on outcomes between the 2 populations might be reasonable. Further prospective studies are anticipated to establish the prognostic significance of postoperative glycemic control for patients with stage pT1 NMIBC.

In conclusion, our study identifies several predictive factors for RFS and PFS of patients who initially had stage pT1 bladder cancer and suffered initial recurrence after TUR. These predictors allow the urologists to stratify patients into groups according to the risk of recurrence and progression for an individualized treatment and follow-up plan. We realize the limitations in the study that are inherent to its retrospective, nonrandomized, and its single-institution nature, which might cause selection bias. Thus, a prospective and randomized study should be conducted to validate our findings.

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