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 pT1 nonmuscle 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 analysis 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.

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,2–9 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.
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 clinico-pathological variables involved in the present study included patient age, gender, smoking history, diabetes, prior recurrence time, prior treatment, 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 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 resection was extended to the deep muscle layer of the bladder at the base of the tumor, reaching perivesical fat.

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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 time 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).
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 \((P = 0.006)\) 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, Soukop 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 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. Eighty-three out of the 204 (40.7%) 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).

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

| Factors | Recurrence | | | Progression | |
| --- | --- | --- | --- | --- | --- |
| | 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 (1.090–2.726) | 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: | 1.000 (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 | 2.452 (1.252–4.801) | 0.008 | 6.944 (3.137–15.368) | 0.000 |
| CIS | 1.000 (Ref) | Ref | 1.000 (Ref) | Ref |
| 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

| Factors | Recurrence | | | Progression | |
| --- | --- | --- | --- | --- | --- |
| | 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 (1.410–3.040) | 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: | 1.000 (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 | 2.209 (1.022–4.774) | 0.044 | 5.348 (2.231–12.816) | 0.000 |
| CIS | 1.000 (Ref) | Ref | 1.000 (Ref) | Ref |
| 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.
### TABLE 4. Multivariate Analysis Predictive of Prognostic Factors for RFS and PFS

| 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)          | —   | —                    | —   |
| 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)          | —   | 1.000 (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

| 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)          | —   | —                    | —   |
| 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)          | —   | 1.000 (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 hr | 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

| Variables                        | Recurrence Area Under Curve | P * | Progression 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                      | —   | 0.798                          | —   |
| Multivariate model†               | —                          | —   | —                              | —   |

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.
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. A randomized study conducted by Okamura et al showed that immediate pirarubicin instillation after TUR reduced recurrence of superficial bladder carcinoma. Perlis et al found that epirubicin reduced recurrence of NMIBC after a pooled analysis of 2548 patients. For Chinese patients, Liu et al 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) after TUR is an independent prognostic factor for patients with pT1 bladder cancer. As immediate instillation may destruct circulating tumor cells resulting from TURBT and ablate residual tumor cells at resection sites and small overlooked tumors, it is expected that to some extent timing of instillation after TUR is associated with prognosis of the patients.

### 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, mthns (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, mthns (range) | 67.9 (4–120) | 74.3 (3–120)   | <0.001 |

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

### FIGURE 1. Receiver operating curve of recurrence.

### FIGURE 2. Receiver operating curve of progression.

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