

Important Therapeutic Considerations in T1b Penile Cancer: Prognostic Significance and Adherence to Treatment Guidelines

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ABSTRACT

Background. The clinical implications and contemporary management of T1b penile cancer are unknown. National treatment guidelines advocate surgical lymph node examination (SLNE) for T1b disease.

Objective. The aim of this study was to evaluate the prognosis of T1b disease and adherence to corresponding treatment guidelines.

Methods. We analyzed 296 patients from two academic centers, and 1263 patients from the Surveillance, Epidemiology, and End Results (SEER) registry (median follow-up 48.3 and 21 months, respectively). Multivariate Cox and Fine–Gray regressions were applied for penile cancer-specific survival (PCSS) analyses.

Results. In the academic center cohort, 28.3% of T1 patients had T1b disease, all of whom underwent SLNE. Nodal metastases were detected in 86.7% of T1b patients and 13.2% of T1a patients ($p < 0.001$). Using T1a as a reference, PCSS was significantly poorer in the T1b patients, with an adjusted hazard ratio (aHR) of 4.10 ($p = 0.03$). In the SEER cohort, 16.8% of T1 patients were

classified as T1b. SLNE was performed in 21.7% of the T1b patients versus 38.2% of the T2 patients ($p = 0.002$). The probability of nodal metastases was 2.23-fold higher in T1b patients than in T1a patients ($p < 0.001$). In clinical NOM0 patients without SLNE, compared with T1a disease, T1b was associated with an aHR of 4.40 and a subdistribution HR of 4.53 for PCSS (both $p = 0.003$).

Conclusions. T1b penile cancer is strongly associated with nodal metastases and adverse PCSS, and is poorly managed according to guidelines recommended in the nationwide registry.

Penile cancer is a rare malignant disease with an annual incidence of 0.8–1.7 per 100,000 men in North America and Europe; however, a higher incidence has been noted in Asia, Africa and South America (6.8 per 100,000).¹ According to cancer statistics in the UK, an increased incidence of 21% has been observed over the last decade.² Most penile cancer cases in Western countries are considered T1 disease, accounting for 54.1% of all cases in our previous analyses of Surveillance, Epidemiology, and End Results (SEER) registry data.³ For T1 disease, the aim of management is to maximize curative treatment via surgery while minimizing complications. Therefore, the main focus of treatment is appropriate patient selection for conservative penile surgery and invasive lymph node (LN) evaluation.

The TNM staging system is a widely used platform for prognostic stratification. Better staging systems reflect the biology of disease and stratify patients according to their risk, to determine appropriate treatment selection. In 2010, the 7th TNM staging system of penile cancer introduced lymphovascular invasion (LVI) and high-grade (HG) primary tumor as stratification criteria for T1 disease.⁴ From

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the first edition in 2012 to the most recent edition in 2018, the National Comprehensive Cancer Network (NCCN) penile cancer guidelines have consistently recommended inguinal LN dissection or dynamic sentinel LN biopsy for T1b disease.^{5,6} Although LVI and HG were previously shown to be associated with LN metastases (LNM),^{7–10} several limitations should be addressed, i.e. no study has focused on analyzing T1 disease, most results were obtained from small sample sizes in individual centers, and the prognostic value of observed long-term outcomes has rarely been reported. Therefore, the aim of the current study was to evaluate the prognostic impact of T1a/b stratification in both academic centers and a contemporary population-based database. Adherence to NCCN guidelines in a North American population was also evaluated.

PATIENTS AND METHODS

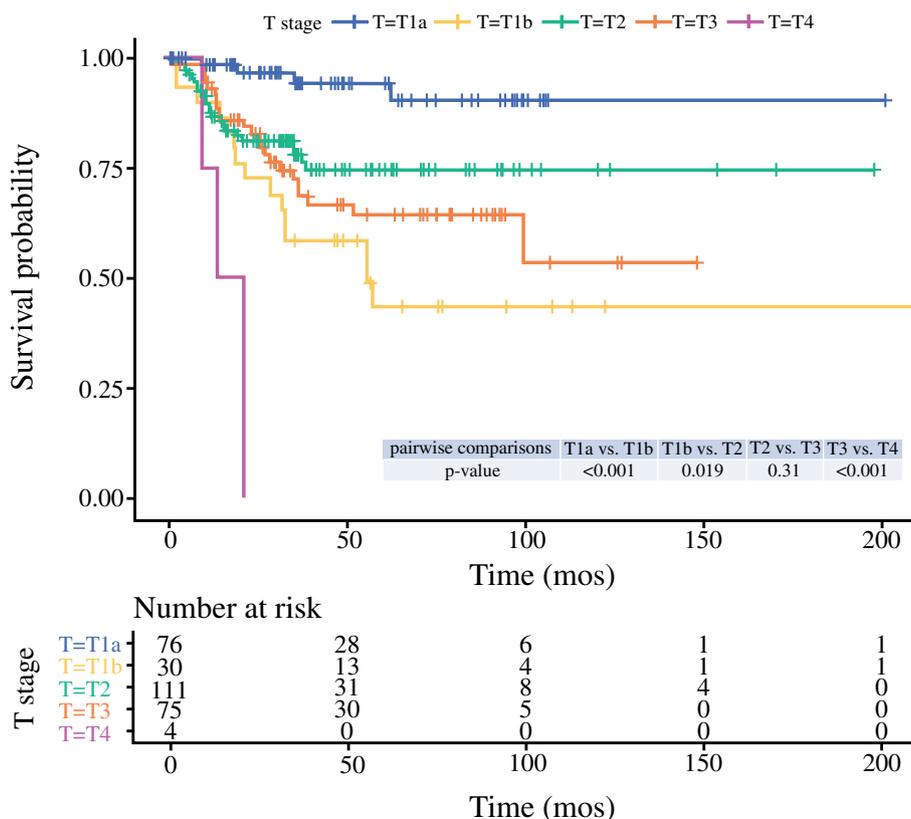
Study Design

This study was performed using two contemporary cohorts. The first cohort included consecutive patients treated at Fudan University Shanghai Cancer Center (FUSCC) in Shanghai, China (period 2006–2016, $n = 214$) and Moffitt Cancer Center (MCC) in Florida, USA (period 1998–2015, $n = 87$), and the second cohort included

patients whose data were retrieved from the SEER registry (period 2010–2014, $n = 1499$). The flowchart for case selection is shown in electronic supplementary Fig. 1. Missing information was found in 4.4% of cases in the SEER database and 1.7% of cases in the academic center database. Finally, we included 1263 eligible cases from the SEER cohort and 296 men from the academic center cohort. Clinicopathological characteristics and outcomes were obtained from both databases. The treatment algorithm for penile cancer in the academic center cohort has been previously published in a series of studies.^{11–13} Case review revealed 83.4% of patients were treated according to the NCCN guidelines.⁶

All patients were staged according to the 7th American Joint Committee on Cancer's TNM system. In the SEER database, surgical LN evaluation (SLNE) was defined as reports of LN removal, biopsy or aspiration of LNs, as well as sentinel LN biopsy. N stage with SLNE was defined as pathological N stage, but, on the other hand, those without SLNE were defined as clinical N stage. In the academic center cohort, patients with clinical node-positive disease underwent LN dissection. Those patients with clinically negative disease were recommended to surveillance or prophylaxis SLNE. Clinical nodal status was retrieved from medical records and was determined by physical examination and cross-sectional imaging. The clinical

FIG. 1 Kaplan–Meier curves of penile cancer-specific survival according to T stage, in the academic center cohort. Pairwise log-rank comparisons between different T stages are provided in the table



endpoint was penile cancer-specific survival (PCSS), which was defined as the time between the date of a histologically confirmed penile cancer diagnosis and the date of death from penile cancer.

Approval for this retrospective study was obtained from the Institutional Review Board at both institutions.

Statistical Methods

Differences in categorical variables were assessed using Pearson's Chi square test or Fisher's exact test. PCSS was calculated using the Kaplan–Meier method and was compared using the log-rank test, while Cox proportional hazards regression was used to calculate the hazard ratios (HRs) and confidence intervals (CIs) of covariates. Competing risk analysis was performed when the absolute percentages of competing events were $> 10\%$.¹⁴ Cumulative incidence functions were used to estimate the incidence of competing events, and the Fine–Gray subdistribution hazard model was used to analyze the prognosis associated with covariates. Significance was defined as a p value ≤ 0.05 . All analyses were performed using R software.¹⁵

RESULTS

The academic center cohort from FUSCC and MCC included 296 patients, while in the SEER cohort, a total of 1263 patients were eligible for inclusion in the statistical analyses. The demographic data of the two cohorts are shown in Table 1. Patients from the academic centers were generally young and had more advanced disease (\geq T2 or N+). Of the T1 cases, 16.8% and 28.3% were classified as T1b in the SEER cohort and academic center cohort, respectively.

We then evaluated the rate of SLNE, as well as the percentage of metastases in the corresponding T stage (Table 2). No significant difference in age was observed among stages T1 to T3 ($p = 0.29$). Poor adherence to guideline-recommended SLNE was observed in the SEER cohort. Among T1b patients, only 21.7% of patients underwent SLNE, which was significantly lower than the 38.2% value recorded for T2 patients ($p = 0.002$). The percentage of T1b patients who underwent SLNE did not differ significantly between 2010 and 2012, and 2013 and 2014 (23.5 vs. 19.2%, $p = 0.73$). In the academic center cohort, more than 73% of patients with T1b to T4 disease underwent SLNE. Furthermore, the risk of LNM in T1b patients was 2.23-fold ($p = 0.001$) and 6.67-fold ($p < 0.001$) higher than in T1a patients in the SEER and academic center cohorts, respectively.

In the academic center cohort, T1b was associated with poor survival, which was comparable with that associated with T3 disease (Fig. 1). The 3-year PCSS values were

TABLE 1 Demographic data of penile cancer in the SEER and academic center cohorts

Variables	SEER cohort	Academic center cohort
No. of patients	1263	296
Age (mean \pm SD)	67.01 \pm 14.02	57.21 \pm 12.77
T stage [n (%)]		
T1a	339 (26.8)	76 (25.7)
T1b	120 (9.5)	30 (10.1)
T1NOS	252 (20.0)	–
T2	306 (24.2)	111 (37.5)
T3	224 (17.7)	75 (25.3)
T4	22 (1.7)	4 (1.4)
N stage [n (%)]		
cN0	894 (70.8)	91 (30.7)
pN	138 (10.9)	84 (28.4)
cN+	55 (4.4)	–
pN1	51 (4.0)	26 (8.8)
pN2	42 (3.3)	40 (13.5)
pN3	53 (4.2)	55 (18.6)
M1 [n (%)]	30 (2.4)	3 (1.0)
Follow-up [median (95% CI)]	21 (19–23)	48.3 (41.1–55.3)
Died of penile cancer [n (%)]	128 (10.1)	69 (23.3)
Died of other cause [n (%)]	205 (16.2)	23 (7.8)

SEER Surveillance, Epidemiology, and End Results, CI confidence interval, SD standard deviation

94.4% (88.3–100), 58.8% (43.4–79.8), 78.2% (70.1–87.1), and 72.6% (62.4–84.4) for T1a, T1b, T2, and T3 disease, respectively. In univariate analyses, T1b was significantly associated with poor survival, with an HR of 9.01 (95% CI 2.99–27.15, $p < 0.001$). After adjusting for age and TNM stage, T1b remained an independent predictor of survival, with an HR of 4.10 (95% CI 1.15–14.64, $p = 0.03$). Since 69.5% of penile cancer patients in the academic center cohort underwent SLNE, we assessed the prognostic value of pathological N stages. We found that the survival rates decreased rapidly with increased nodal metastatic burden (electronic supplementary Fig. 2). Patients with pN0 disease had a 3-year PCSS of 92.2% (86.4–98.4), and treatment of minimal nodal disease (pN1) resulted in a 3-year PCSS of 80.4% (64.8–99.7). In contrast, advanced LNM, including N2 and N3 disease, was associated with survival rates of 58.8% (43.5–79.6) and 49.7% (37.2–66.4), respectively.

In the SEER cohort, 78.3% of T1b patients did not undergo SLNE at diagnosis, and we therefore evaluated the association between T stage and PCSS in men with clinical NOM0 disease. In this subgroup, the 3-year PCSS values were 95.5% (92.2–99.0), 84.0% (74.7–94.5), 94.9%

TABLE 2 The clinicopathological features of penile cancer stratified by T stage

	<i>n</i>	Age, years [mean (SD)]	Surgical lymph node evaluation (%)	N+ (%)	M+ (%)
<i>SEER cohort</i>					
T1a	339	66.96 (13.31)	8.8	7.1	1.2
T1b	120	68.09 (13.70)	21.7	15.8	4.2
T1NOS	252	67.08 (14.48)	2.8	2.8	0
T2	306	68.16 (14.43)	38.2	27.8	1.6
T3	224	65.59 (14.16)	47.8	37.1	6.2
T4	22	59.55 (11.50)	31.8	40.9	9.1
<i>Academic center cohort</i>					
T1a	76	54.69 (12.38)	44.7	13.2	2.6
T1b	30	57.31 (13.05)	100	86.7	0
T2	111	57.26 (13.00)	73.0	39.6	0.9
T3	75	59.74 (12.62)	74.7	52.0	0
T4	4	55.07 (10.95)	100	50.0	0

SEER Surveillance, Epidemiology, and End Results, SD standard deviation

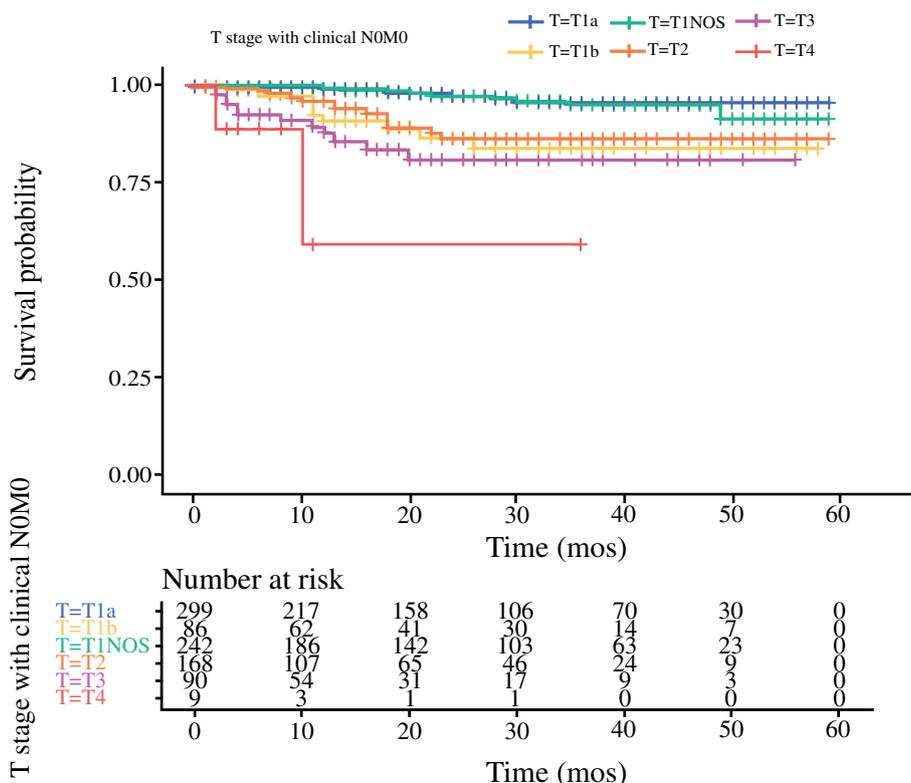
(91–98.9), 86.3% (79.4–93.8), 81.0% (71.4–92.0), and 59.3 (25.8–100.0) for T1a, T1b, T1NOS, T2, T3, and T4 disease, respectively (Fig. 2). Pairwise comparison showed significantly poorer survival for T1b disease compared with

T1a disease ($p < 0.001$). The difference between T1b and T2 disease was not significant ($p = 0.67$). We used multivariate analysis to calculate the HRs of T stages after adjusting for age. The HR of T1b was 4.40 (95% CI 1.63–11.83, $p = 0.003$) using T1a as a reference. T2 disease was not significantly different from T1b in terms of PCSS (HR 0.75, 95% CI 0.32–1.76).

Since other causes accounted for 16.2% of deaths in the SEER cohort, we performed a competing risk analysis to model the effect of T1b stratification on the cumulative incidence function. Figure 3 shows the 3-year cumulative incidence rates of cancer-specific death were 3.9% (1.67–7.58) and 14.7% (7.08–25.1%) for the T1a and T1b categories ($p < 0.001$), respectively. No difference in non-penile cancer-specific deaths was found between T1a and T1b disease (20.6% vs. 20.2%, $p = 0.57$). A multivariate competing risk analysis showed a subdistribution HR of 4.53 (1.69–12.12, $p = 0.003$) for T1b compared with T1a. Similarly, no difference was found between T1b and T2 disease for cancer-specific death ($p = 0.35$).

To test the hypothesis that early SLNE provides more prognostic information over T-stage alone, and treatment of detected minimal nodal disease may result in improved long-term survival over an initial surveillance strategy, we compared survival between patients with pN0 disease (N0 after SLNE) and those with cN0 disease, although at risk of LNM (T1b–T4). The comparison hypothesized that

FIG. 2 Kaplan–Meier curves of penile cancer-specific survival according to T stage, in patients with clinical N0M0 disease in the SEER cohort. Pairwise log-rank comparisons between different T stages are provided in the table. SEER Surveillance, Epidemiology, and End Results



untreated micrometastases (cN0) would impact survival during follow-up. We found the 3-year PCSS was 88.0% (96.2–80.5) and 83.6% (78.7–89%) for pN0 and cN0 disease, respectively (Fig. 4). Kaplan–Meier comparison showed a tendency for statistical difference ($p = 0.078$). Since the follow-up of the entire SEER cohort was 21 months (T1b was only available after 2010), our analysis was still preliminary and longer follow-up would provide more reliable information.

DISCUSSION

Our study confirms that T1b-staged primary penile tumors are significantly associated with nodal metastases and adverse outcomes compared with T1a tumors. In the North American population-based database, nearly four-fifths of T1b patients did not undergo guideline-recommended SLNE. In clinically node-negative patients, T1b disease significantly increased the risk of death from cancer 4.40-fold. In academic centers conducting rigorous evaluations of regional LNs, pN0 and pN1 patients had 3-year PCSS values of 95.5% and 84.0%, respectively. Early SLNE provides more prognostic information over T-stage alone, and the treatment of minimal nodal disease results in promising long-term survival.

This was the first study to evaluate T1a/b-staged primary penile cancer in both a population-based database and a comprehensive database of tertiary care academic centers. In both cohorts, T1b was significantly associated with an increased risk of LNM. Consistent with a previous European study, the risk of LNM in T1b is similar to, or even higher than, T2 disease in academic centers.¹⁰ The high

percentage of patients who did not undergo SLNE in the SEER cohort provides an opportunity to assess the impact of unidentified occult metastases. Kaplan–Meier curve and multivariate analyses showed that T1b patients had worse survival rates than T1a patients, and the results were similar to those in T2 patients. Similar observations were found using competing risk analyses, which accounted for the high occurrence of other causes of death in T1 disease.¹⁶ Delayed treatment of patients with occult LNM may significantly compromise survival.¹⁷ In a Netherlands cohort, applying sentinel LN biopsy in cN0 patients increased the survival rate from 85 to 92%.¹⁸ Our analysis also provides clear evidence demonstrating a decrease in survival from 80.4% in single-positive LN disease (N1) to 58.5% in multiple nodal disease (N2). Therefore, the utilization of surgical LN staging in T1b disease not only positively contributes to the early detection of LNM but may also increase survival in clinical NOM0 disease. In an untreated inguinal nodal basin, tumor recurrence can occur up to 5 years after primary tumor removal. A follow-up schedule of every 3 months for years 1–2, and every 6 months for years 3–5, should be applied to detect potential nodal recurrence.¹⁹ Accurate staging of pN0 can reduce the follow-up frequency from 14 to 7 visits.

Many reasons exist for poor adherence to guidelines. The NCCN guideline advocates LN dissection or sentinel LN biopsy for penile cancer patients;⁶ however, LN dissection is associated with considerable morbidity.²⁰ Although recent advances in minimally invasive surgery may minimize complications, this innovative approach is restricted to a few centers.²¹ Technical barriers also complicate sentinel LN biopsy. The successful European approach requires nuclear medicine, ultrasound, and dedicated pathological evaluation teams and a high case volume.²² In a previous study on the management of node-positive disease in the US, only 3.3% of centers treated four or more cases per year.²³ Therefore, adoption of SLNE in countries with a low incidence of penile cancer should prompt centralized management, which would allow standardization of treatment.

Our study was strengthened by the inclusion of a population-based database and an independent cohort from academic centers. Validation in the two groups provided strong evidence for the modification of the T1 category in the TNM staging system. The studied academic centers exhibited high adherence with the guideline recommendations. A large proportion of high-risk patients underwent SLNE, and node-positive patients were treated with standardized LN dissection. The survival curve of patients with pN disease confirmed the strong prognostic and therapeutic role of qualified LN dissection. The SEER database with population coverage of this rare cancer can overcome the selection bias observed in academic centers.²⁴ The real-

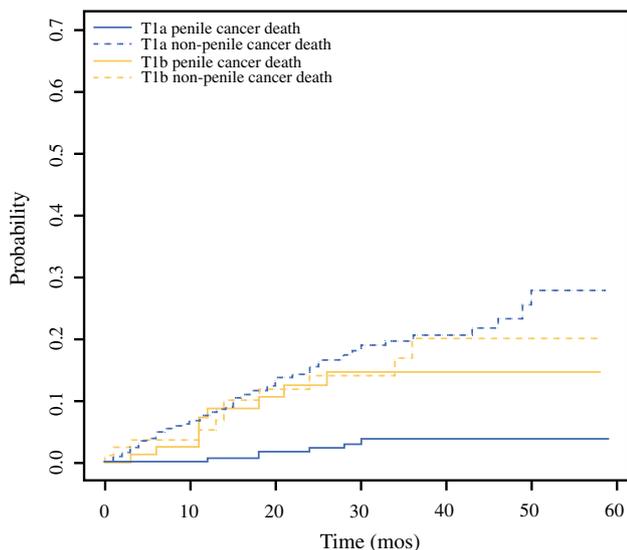
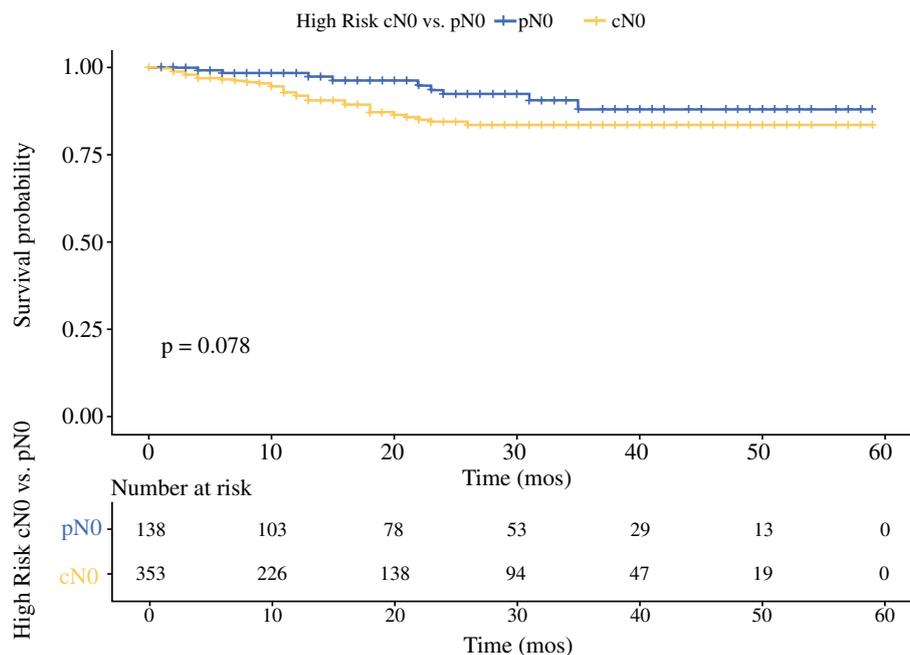


FIG. 3 Cumulative incidence of penile cancer-specific mortality and other-cause mortality in T1a/b with clinical NOM0 disease in the SEER cohort. *SEER* Surveillance, Epidemiology, and End Results

FIG. 4 Penile cancer-specific survival in T1b-4 patients who underwent SLNE (pN0) or not (cN0) in the SEER cohort. SEER Surveillance, Epidemiology, and End Results



world data not only showed the gap between the guidelines and general practice but also comparatively worse outcomes for T1b versus T1a patients managed with surveillance. Together, these data indicate the importance of T1b staging and advocate rigorous SLNE.

Several limitations should be acknowledged. First, the study was retrospectively designed. Although we used two independent cohorts and adjusted the analyses for potential confounders, we cannot completely exclude an effect of selection bias. Second, concerns exist regarding the reliability of tumor grade among different pathologists, especially in four-tiered systems (Borders' grading system²⁵ and the College of American Pathologists' grading system²⁶). Both academic institutions are referral centers for penile cancer and used the three-tiered system introduced by Velazquez et al.²⁷ The International Society of Urological Pathology experts recommend using a three-tiered grading system in which a diagnosis of grade 3 is usually straightforward, and tumor grade was assigned on the basis of the worst observed grade pattern.²⁸ The strong prognostic value of T1b stratification in the international academic centers confirmed the validity of pathological classifications. Third, since 2018, the new staging system has included perineural invasion as another criterion for T1b disease.²⁹ This modification may further define an homogenous cohort of T1a cases requiring conservative treatment. A multicenter study investigating the addition of perineural invasion and the composite value of three components to define high-risk T1 disease is ongoing. Fourth, a different risk profile between the academic center cohort and the SEER cohort was noted in our study. Academic centers are more likely to treat patients with LNM

and therefore had poorer survival compared with a population-based database. Although the adverse prognostic value of T1b was confirmed in two independent cohorts, the HRs should be interpreted cautiously in a different context. Nevertheless, our results provide useful baseline data for this rare disease and also improve the evidence for supporting T1a/b stratification in both TNM staging system and guidelines. The high risk of LNM, decreased survival outcomes, and low rate of SLNE in T1b tumors in North America should prompt the inclusion of T1b tumors in the high-risk category in future revisions of the NCCN guidelines.⁶

CONCLUSIONS

T1b penile cancer is strongly associated with nodal metastases and adverse survival outcomes in both academic centers and the SEER registry. Only one-fifth of the SEER patients with T1b disease were treated following the national guideline recommendation for SLNE. The high risk of cancer-related mortality among T1b and cN0M0 patients warrants accurate N staging in national practice.

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