Original Article

Risk factors for distant metastasis and prognosis of the penile cancer with distant metastasis

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Background: Penile cancer (PC) is a rare malignant tumor, whose distant metastasis (DM) is associated with the poorest outcomes. The risk factors associated with DM and prognosis of the PC with DM remain elusive. This study was aimed at investigating risk factors associated with DM and constructing prediction models of PC with DM.

Methods: This study analyzed data from the Surveillance, Epidemiology, and End Results (SEER) database over a period of 2000–2020, including clinical characteristics such as age, marital status, tumor size, Tumor Node Metastasis (TNM) staging, and treatment information. Utilizing univariate and multivariate logistic regression, alongside cox regression analysis, we identified independent risk factors for DM and prognosis in the total cases and the cases with DM. Nomograms were developed for predicting DM and prognosis in PC patients.

Results: Enrolling 1,488 cases, our study identified tumor size and N stage as independent predictors of DM. The predictive nomogram for DM achieved an area under the curve (AUC) of 0.904. Notably, the 1-, 3-, and 5-year cumulative survival rates for PC with DM were 35%, 17%, and 13%, respectively, with larger tumor size associated with prognosis of PC cases with DM. This study verified a correlation between advanced age and TNM stage, as well as chemotherapy with the poor PC prognosis. The nomogram yielded 0.72, 0.69 and 0.69, in predicting 1-, 3-, and 5-year overall survivals (OS), while 0.73, 0.70 and 0.69 in predicting 1-, 3-, 5-year cancer specific survivals (CSS), respectively.

Conclusions: This study investigated risk factors of PC with DM. Also, nomograms for predicting DM, OS and CSS of PC patients were developed.

Keywords: Penile cancer (PC); risk factors; prognosis; distant metastasis (DM); Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Penile cancer (PC), primarily penile squamous cell carcinoma (PSCC), is a rare malignancy that can be classified based on human papillomavirus (HPV) infection and inflammation-related etiology (1,2). A substantial proportion of cases are associated with HPV infection. Certain studies have underscored the crucial role of inflammatory factors, particularly penile infection and chronic irritation, in tumorgenesis or progression (3,4). Additionally, obesity, circumcision, and smoking are also implicated in the etiology of PC (5,6). PC may present with penile ulceration or malign priapism (3).

Low prevalence of PC has led to the management of PC is undervalued. Despite its scarcity, the global burden of PC is not negligible, with an estimated 2050 new diagnoses and 470 deaths anticipated in 2023 cancer statistics (7). Additionally, the period from 2000 to 2018 marked a notable rise in PC mortality in the United States (U.S.) (8). PC exhibits a marked epidemiological variation, significantly more prevalent in developing nations, with an incidence of 10% surpassing those in developed regions like the U.S. From 1998 to 2003, the incidence among Hispanics in the U.S. was 72% higher than that in non-Hispanics, potentially reflecting the involvement of lifestyle-related factors (9,10).

PC can be diagnosed using non-invasive imaging techniques, such as ultrasound and magnetic resonance imaging. Therapeutic strategies aim at preserving sexual and urinary function as much as possible, involving conservative to radical surgeries, or adjuvant therapies (radiation therapy, chemotherapy, etc.) (11). However, early detection is often disrupted by misdiagnosis, leading to loss of optimal opportunities for treatment (8).

Previous studies on PC prognostic factors have been limited by small sample sizes, rendering their findings less convincing. The extent of nodal metastasis, reported in previous studies, is closely associated with survival outcomes (11). Moreover, distant metastasis (DM) is associated with the poorest outcomes, evidenced by a 5-year survival rate of merely 16% (8). Risk factors including positive surgical margins were found associated with higher recurrence rate (10). Yet, risk factors about DM in PC have been rarely analyzed. This gap underscores the need for a predictive model, such as a nomogram, to enhance disease management and prognosis, an area currently under-explored in PC research. To address this, our study investigated the risk factors, utilized them to construct a nomogram for predicting the DM and prognosis in PC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-92/rc).

Highlight box

Key findings

- This study investigated risk factors of penile cancer (PC) with distant metastasis (DM). Also, nomograms for predicting DM, overall survival and cancer specific survival of PC patients were developed.

What is known and what is new?

- PC is a rare malignant tumor, whose DM is associated with the poorest outcomes. The risk factors associated with PC have been investigated.
- We expanded the array of risk factors from a larger cohort, and established N stage and tumor size as critical predictors of DM in the predicting nomogram.

What is the implication, and what should change now?

- The nomograms based on these factors exhibited a good performance in predicting PC prognosis and DM, thus benefiting disease management. External validation and complete data on metastatic sites and metastatic patterns should be needed for further improvement of the nomogram performance.

Methods

Data sources and collection

We utilized the Surveillance, Epidemiology, and End Results (SEER) database, a comprehensive source of U.S. cancer incidence and mortality data, to collect data of PC available since 1973. Specifically, we extracted data from dataset of Incidence-SEER Research Data (17 Registries, Nov 2022 Sub, 2000–2020)-Linked To County Attributes-Total U.S., meticulously selected all PC cases using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) site recode during 2000–2020. Essential data, including demographic, clinical and histopathological characteristics, and treatment-related information, were collected. Strict inclusion criteria were set as follows to ensure robust data integrity and meaningful analysis.

Inclusion criteria: (I) confirmed diagnosis of PC, with histopathological validation; (II) first-onset; (III) general data available, including age at diagnosis, race, marital status, tumor details [site, size, grade, and Tumor Node Metastasis (TNM) staging], treatment information (surgery,

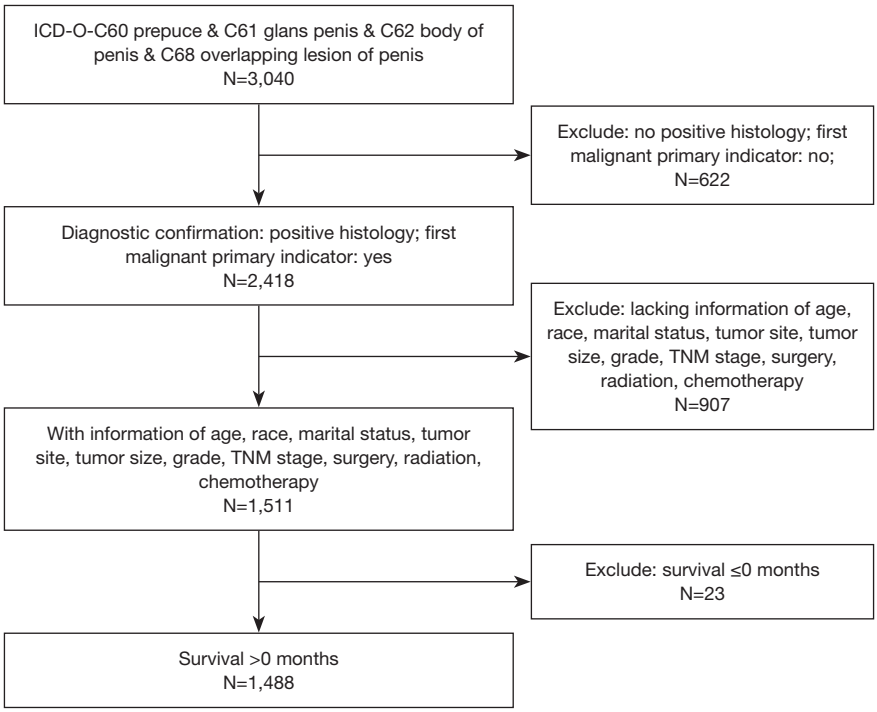

Figure 1 Flowchart of patients with penile cancer enrollment from SEER database. ICD-O, International Classification of Diseases for Oncology; TNM, Tumor Node Metastasis; SEER, Surveillance, Epidemiology, and End Results.

radiation therapy, chemotherapy, etc.), and survival outcomes (survival time, tumor-specific death status, survival status); (IV) a minimum survival time of one month. Cases not meeting these conditions were excluded. Case screening flowchart is presented in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The Kaplan-Meier method was employed for survival analysis, and the Log-rank test for comparing survival curves of overall survivals (OS) times across patient subgroups. Univariate and multivariate Cox proportional hazard regression analyses were preformed to exhibit the correlations between PC prognosis of OS and cancer specific survivals (CSS) and clinical factors. Logistic regression analysis further investigated risk factors for PC metastasis, with statistical significance set at $P<0.05$. Initial data were extracted utilizing SEER*Stat (v8.3.5), while SPSS 26.0 (IBM, Armonk, New York, USA) and R3.6.0 (Statistical Computing, Vienna, Austria) supported subsequent detailed analyses and visual representation. The receiver operating characteristic (ROC) curve determined cutoff values for continuous variables, such as age at diagnosis and tumor size.

Construction and validation of the nomograms

Following the logistic regression and the cox regression analysis, predictive nomograms were constructed. Weighted estimators of each covariate were derived from Cox regression coefficients and variance estimates. The highest b coefficient of each variable was converted into a 0–100 scale. These nomograms were run to predict CSS and OS at 1, 3, and 5 years, as well as the DM rates of PC patients. The predictive accuracy of these nomograms was evaluated by ROC curves and internal calibration curves.

Results

Clinicopathological characteristics of PC patients

In total, 1,488 PC cases were identified, with 40.7% aged over 69.5 years and 91.3% as Whites/Other (Black patients, 8.7%). The proportions of married and unmarried patients were approximately equal. A large proportion (64.6%) of

Table 1 Basic characteristics of patients' cohort

Characteristics	Value, n (%)
Age, years	
≤69.5	883 (59.3)
>69.5	605 (40.7)
Race	
White	1,276 (85.8)
Black	129 (8.7)
Other	83 (5.5)
Marital status	
Married	909 (61.1)
Other	579 (38.9)
Tumor site	
Prepuce	270 (18.1)
Glans penis	961 (64.6)
Body of penis	125 (8.4)
Overlapping lesion of penis	132 (8.9)
Tumor size, mm	
≤34.5	869 (58.4)
>34.5	619 (41.6)
Grade	
I (well differentiated)	418 (28.1)
II (moderately differentiated)	718 (48.3)
III (poorly differentiated)	341 (22.9)
IV (undifferentiated)	11 (0.7)
T stage	
Ta	3 (0.2)
T1	698 (46.9)
T2	468 (31.5)
T3	302 (20.3)
T4	17 (1.1)
N stage	
N0	1,191 (80.0)
N1	94 (6.3)
N2	111 (7.5)
N3	92 (6.2)
M stage	
M0	1,455 (97.8)
M1	33 (2.2)
Surgery	
No	17 (1.1)
Yes	1,471 (98.9)
Radiation	
Yes	131 (8.8)
No	1,357 (91.2)
Chemotherapy	
Yes	170 (11.4)
No	1,318 (88.6)

tumors originated from the glans penis. The cases were categorized into 58.4% with tumor sizes ≤34.5 mm and 41.6% with >34.5 mm. Additionally, tumors were classified into T1, T2, or T3 stages, with a majority (80.0%) with no lymph node extension. Surgery remained the primary treatment (98.9%), with radiation (8.8%) and chemotherapy (11.4%) less adopted. The clinicopathological characteristics are summarized in *Table 1*.

Prognosis of PC with DM

DM was observed in a small fraction (2.2%) of the cases, with the lung being the most frequent metastatic site (30.3%). OS rates at 1, 3, and 5 years post-diagnosis were 35%, 17%, and 13%, respectively. Nevertheless, cases with survival time exceeding 1, 3, and 5 years account for 42.4%, 12.1%, and 9.1%, respectively. Tumor size served as a significant independent prognostic factor for PC with DM (*Figure 2*).

Nomogram for DM prediction

Univariate and multivariate analyses identified larger tumor size [odds ratio (OR) 3.088; 95% confidence interval (CI): 1.281–7.443], higher N stage (N1: OR 5.148; 95% CI: 1.222–21.683; N2: OR 10.298; 95% CI: 3.163–33.533; N3:

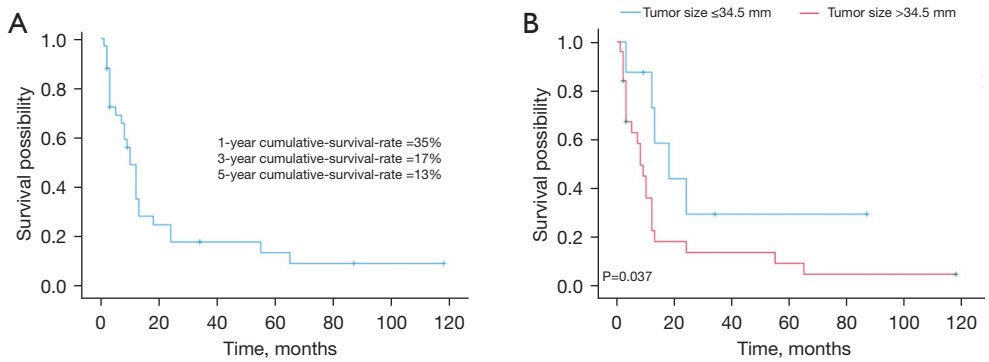

Figure 2 Overall survival rates (A) and Kaplan-Meier curves of OS (B) for PC with DM. OS, overall survival; PC, penile cancer; DM, distant metastasis.

OR 35.626; 95% CI: 12.425–102.147) as significant risk factors for DM in PC patients, with specific ORs indicating a strong association (*Table 2*). Based on the two predictors, the nomogram was established, achieving an AUC of 0.904 in predicting metastasis. The internal calibration curve further confirmed its accuracy (*Figures 3,4*).

Nomogram for OS and CSS prediction

Further multivariate analysis identified critical prognostic factors for OS and CSS in PC patients, including age (OR 2.412; 95% CI: 2.064–2.817), race (OR 1.689; 95% CI: 1.116–2.558), tumor size, TNM staging (T stage: OR 1.471; 95% CI: 1.220–1.772; N1: OR 1.602; 95% CI: 1.205–2.130; N2: OR 1.530; 95% CI: 1.152–2.033; N3: OR 1.915; 95% CI: 1.393–2.632; M stage: OR 2.419; 95% CI: 1.580–3.705), and chemotherapy (OR 1.411; 95% CI: 1.077–1.847) related to a worse OS. While age (OR 1.591; 95% CI: 1.267–1.999), tumor size (OR 1.508; 95% CI: 1.200–1.898), pathological grade (OR 1.384; 95% CI: 1.088–1.759), TNM staging (T stage: OR 1.502; 95% CI: 1.162–1.941; N1: OR 2.272; 95% CI: 1.561–3.307; N2: OR 2.341; 95% CI: 1.641–3.339; N3: OR 2.987; 95% CI: 2.026–4.405; M stage: OR 2.700; 95% CI: 1.684–4.328) and chemotherapy (OR 1.677; 95% CI: 1.215–2.315) were associated with a poor CSS (*Tables 3,4*). Consequently, we constructed nomograms predicting 1-, 3-, and 5-year OSs and CSSs, validated by ROC curves (AUC for OS: 0.72, 0.69, 0.69, respectively; AUC for CSS: 0.73, 0.70, 0.69, respectively) (*Figures 5,6*). The accuracy of these nomograms was confirmed by internal calibration curves.

Discussion

PC inflicts patients with physical dysfunction and psychological distress. Incidence of PC varies by age, race and many other factors (12,13). Despite its rarity, its aggressive behavior gives PC high propensity to DM, underscoring the necessity for enhanced management (14). The typical clinical presentations of primary PC include ulcerated lesion, while secondary penile tumors present with a persistent and painful erection. A case of primary PC with painful erection was reported and a poor prognosis was observed in it (3).

In the U.S., patients with PC DM face poor prospects, with a 5-year survival rate of merely 16% in 2022 (8). Previous research has identified age, tumor grade, size, and TNM staging as prognostic factors of PC (15,16). In contrast, here we expanded the array of risk factors from a larger cohort, thus augmenting their accuracy in nomograms in predicting patients' survival. Uniquely, our research pioneers in establishing a nomogram in predicting PC DM with a high AUC of 0.904, signifying its potential as a prognostic model. Prior research has pointed out that advanced age as a significant prognostic factor for PC. This aligns with the findings of Cancer Research UK showing that 32% of new cases during 2016–2018 aged over 75 years, and the mortality of those aged over 90 years peaked during 2017–2019 (11). Our study reaffirms this, noting a significant portion of patients aged over 69.5 years, accounting for 40.7% of the total cohort. Moreover, tumor size, pivotal in primary surgical strategy determination, was defined as a predicator for PC prognosis and DM, as evidenced by prior studies clarifying the link between smaller tumors (56–78% patients with tumor ≤5 cm) and improved 5-year survival rates (17). Additionally, Pinkheaw *et al.* have found that only advanced primary tumor stages stand out as significant prognostic markers for disease-free survival (18). In their previous work, Yang *et al.* explored

Table 2 Univariate and multivariate analysis of metastasis rate in the cohort

Factors	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P value	HR	95% CI	P value
Age of diagnosis, years							
≤69	883	1.0			1.0		
>69	605	0.831	0.406–1.701	0.612	1.283	0.579–2.844	0.540
Race							
Other	83	1.0			1.0		
White	1,276	0.598	0.178–2.010	0.406	0.442	0.115–1.699	0.235
Black	129	0.420	0.069–2.568	0.348	0.355	0.052–2.447	0.293
Marital status							
Other	579	1.0			1.0		
Married	909	0.760	0.380–1.519	0.437	0.838	0.390–1.799	0.650
Tumor site							
Prepuce	270	1.0			1.0		
Glans & body	1,086	1.567	0.541–4.541	0.408	0.809	0.246–2.659	0.727
Other*	132	2.078	0.512–8.443	0.306	0.663	0.136–3.240	0.612
Tumor size, mm							
≤34.5	869	1.0			1.0		
>34.5	619	4.530	2.029–10.111	<0.001	3.088	1.281–7.443	0.012
Grade							
I & II	1,136	1.0			1.0		
III & IV	352	2.765	1.378–5.545	0.004	1.449	0.667–3.147	0.348
T							
Ta & T1 & T2	1,169	1.0			1.0		
T3 & T4	319	3.578	1.787–7.165	<0.001	1.100	0.479–2.528	0.822
N							
N0	1,191	1.0			1.0		
N1	94	6.511	1.602–26.462	0.009	5.148	1.222–21.683	0.026
N2	111	13.283	4.387–40.284	<0.001	10.298	3.163–33.533	<0.001
N3	92	44.767	17.149–116.860	<0.001	35.626	12.425–102.147	<0.001
Surgery							
No	17	1.0			1.0		
Yes	1,471	0.356	0.046–2.765	0.323	0.293	0.031–2.784	0.285
Radiation							
No	1,357	1.0			1.0		
Yes	131	3.465	1.530–7.847	0.003	0.929	0.372–2.318	0.874

*, overlapping lesion of penis. HR, hazard ratio; CI, confidence interval.

the prognostic implications of various factors in 906 PC cases during 2010–2015 (19). Our study involved a longer array of risk factors with a larger sample size, significantly enhancing the reliability of our prognostic model. The predictive strength of our nomograms was proven by AUC values and calibration curves of OS and CSS. Furthermore, the univariate and multivariate analyses confirmed advanced age as a key prognostic indicator for poor outcomes in PC patients. Recent studies have identified cardiovascular diseases as the primary non-cancerous cause of mortality in PC patients. As patients' age grows, the occurrences of chronic conditions, such as diabetes, cardiac disorders, and hypertension, increase the risk of mortality (1,20). Notably, our findings identified tumor grade as a significant risk factor for CSS rather than OS. Particularly, patients with higher-grade tumors (Grade III & IV) demonstrated poorer CSS outcomes, compared to those with lower-grade tumors (Grade I & II), aligning with the previous results from studies on poorly differentiated and undifferentiated carcinomas. Despite gradual advancements in treatments, the paramountcy of surgery remains (19,21). The European Association of Urology-American Society of Clinical Oncology Collaborative Guideline advocates complete tumor removal, while preserving sexual and urinary functions as primary treatment goals (11). A previous clinical study in 2021 indicated that palliative care does not impact mortality rates (22). Contrastingly, our research did not corroborate treatment as an independent prognostic factor, potentially due to our limited sample size.

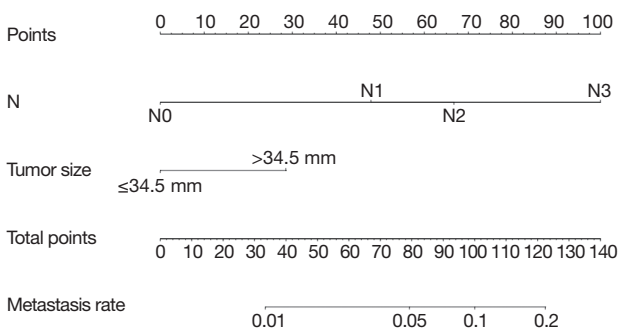

Figure 3 The nomogram for predicting distant metastasis rate of patients with PC. PC, penile cancer.

Our study reaffirms the adverse prognosis associated with DM in PC patients, emphasizing the value of early detection and tailored treatment (23). Notably, initial diagnosis shows a DM incidence of 1% to 10% in prior studies. Our nomogram may be expected to enhance the management of PC via precisely predicting DM. Consequently, DM was pathologically confirmed in 2.2% of our cases, with 1-, 3-, and 5-year survival rates of 35%, 17%, and 13%, respectively.

Notably, our analysis established N stage as a critical predictor of metastasis, signifying the role of lymph node involvement. The hazard ratio of N stage escalated with the degree of lymph node involvement. Furthermore, tumor size was proven to be a key predictor in our DM-predicting nomogram. In contrast, tumor location, though considered as a risk factor, showed minimal impact on prognosis or metastasis rate in PC (24,25). Our study acknowledges certain limitations, including the lack of external validation and incomplete data on metastatic sites and metastatic patterns. It requires further research to improve the performance of our nomogram.

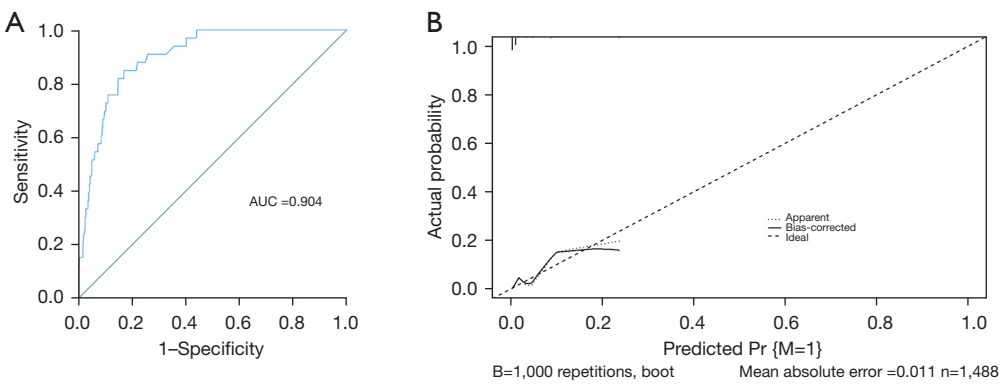

Figure 4 The calibration curves (A) and the ROC curves (B) of the nomogram predicting distant metastasis rate of patients with PC. AUC, area under the curve; ROC, receiver operating characteristic; PC, penile cancer.

Table 3 Univariate and multivariate analysis of OS in the cohort

Factors	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P value	HR	95% CI	P value
Age of diagnosis, years							
≤69	883	1.0			1.0		
>69	605	2.102	1.183–2.437	<0.001	2.412	2.064–2.817	<0.001
Race							
Other	83	1.0			1.0		
White	1,276	1.139	0.934–1.864	0.116	1.187	0.836–1.683	0.338
Black	129	1.585	1.055–2.382	0.027	1.689	1.116–2.558	0.013
Marital status							
Other	579	1.0			1.0		
Married	909	0.781	0.673–0.907	0.001	0.869	0.746–1.014	0.074
Tumor site							
Prepuce	270	1.0			1.0		
Glans & body	1,086	1.187	0.974–1.446	0.089	0.887	0.720–1.091	0.256
Other*	132	1.405	1.038–1.903	0.028	0.950	0.690–1.307	0.751
Tumor size, mm							
≤34.5	869	1.0			1.0		
>34.5	619	1.585	1.367–1.837	<0.001	1.351	1.156–1.580	<0.001
Grade							
I & II	1,136	1.0			1.0		
III & IV	352	1.505	1.278–1.772	<0.001	1.081	0.907–1.288	0.383
T							
Ta & T1 & T2	1,169	1.0			1.0		
T3 & T4	319	1.669	1.411–1.974	<0.001	1.471	1.220–1.772	<0.001
N							
N0	1,191	1.0			1.0		
N1	94	1.764	1.342–2.319	<0.001	1.602	1.205–2.130	0.001
N2	111	1.848	1.434–2.380	<0.001	1.530	1.152–2.033	0.003
N3	92	2.830	2.175–3.682	<0.001	1.915	1.393–2.632	<0.001
M							
M0	1,455	1.0			1.0		
M1	33	4.533	3.091–6.706	<0.001	2.419	1.580–3.705	<0.001
Surgery							
No	17	1.0			1.0		
Yes	1,471	0.822	0.440–1.534	0.538	0.683	0.358–1.301	0.246

Table 3 *(continued)*

Table 3 *(continued)*

Factors	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P value	HR	95% CI	P value
Radiation							
No	1,357	1.0			1.0		
Yes	131	1.474	1.164–1.868	0.001	0.871	0.655–1.158	0.342
Chemotherapy							
No	1,318	1.0			1.0		
Yes	170	1.895	1.538–2.334	<0.001	1.411	1.077–1.847	0.012

*, overlapping lesion of penis. OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table 4 Univariate and multivariate analysis of CSS in the cohort

Factors	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P value	HR	95% CI	P value
Age of diagnosis, years							
≤69.5	883	1.0			1.0		
>69.5	605	1.304	1.051–1.619	0.016	1.591	1.267–1.999	<0.001
Race							
Other	83	1.0			1.0		
White	1,276	1.254	0.758–2.074	0.379	1.215	0.729–2.022	0.455
Black	129	1.391	0.763–2.536	0.281	1.573	0.854–2.896	0.146
Marital status							
Other	579	1.0			1.0		
Married	909	0.884	0.710–1.100	0.268	1.039	0.829–1.301	0.742
Tumor site							
Prepuce	270	1.0			1.0		
Glans & body	1,086	1.564	1.136–2.153	0.006	1.062	0.759–1.485	0.726
Other*	132	2.012	1.290–3.136	0.002	1.098	0.685–1.759	0.698
Tumor size, mm							
≤34.5	869	1.0			1.0		
>34.5	619	1.942	1.566–2.408	<0.001	1.508	1.200–1.898	<0.001
Grade							
I & II	1,136	1.0			1.0		
III & IV	352	2.069	1.654–2.588	<0.001	1.384	1.088–1.759	0.008
T							
Ta & T1 & T2	1,169	1.0			1.0		
T3 & T4	319	2.305	1.836–2.895	<0.001	1.502	1.162–1.941	0.002

Table 4 *(continued)*

Table 4 *(continued)*

Factors	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P value	HR	95% CI	P value
N							
N0	1,191	1.0			1.0		
N1	94	2.885	2.021–4.118	<0.001	2.272	1.561–3.307	<0.001
N2	111	3.572	2.629–4.853	<0.001	2.341	1.641–3.339	<0.001
N3	92	5.595	4.111–7.614	<0.001	2.987	2.026–4.405	<0.001
M							
M0	1,455	1.0			1.0		
M1	33	7.182	4.687–11.005	<0.001	2.700	1.684–4.328	<0.001
Surgery							
No	17	1.0			1.0		
Yes	1,471	0.535	0.253–1.132	0.102	0.495	0.228–1.077	0.076
Radiation							
No	1,357	1.0			1.0		
Yes	131	2.174	1.617–2.923	<0.001	0.787	0.550–1.125	0.189
Chemotherapy							
No	1,318	1.0			1.0		
Yes	170	3.445	2.695–4.403	<0.001	1.677	1.215–2.315	0.002

*, overlapping lesion of penis. CSS, cancer specific survival; HR, hazard ratio; CI, confidence interval.

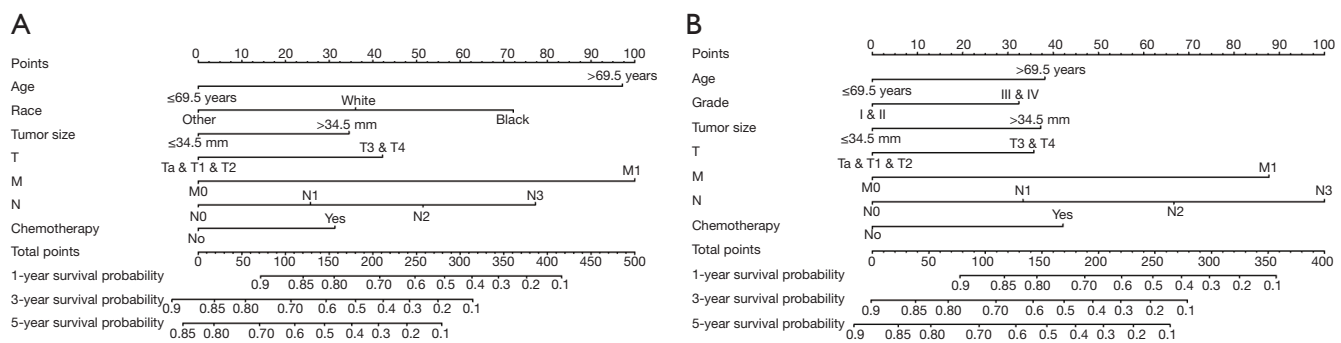

Figure 5 The nomogram for predicting 1-, 3-, and 5-year OS (A) and CSS (B) of patients with PC. OS, overall survival; CSS, cancer specific survival; PC, penile cancer.

Conclusions

This study highlighted the significant association of larger tumor sizes and higher N stages with an increased DM risk. Additionally, age, tumor size, TNM staging were identified as independent prognostic factors. The nomograms based on these factors exhibited a good performance in predicting PC prognosis and DM, thus benefiting disease management.

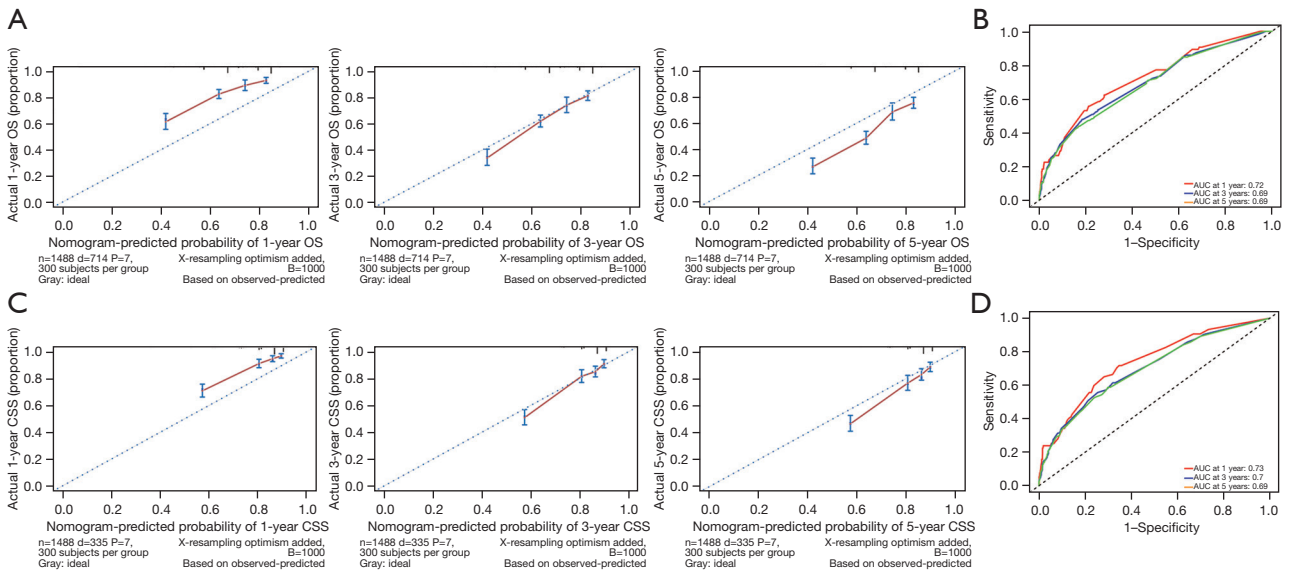

Figure 6 The calibration curves and the ROC curves of the nomogram predicting 1-year, 3-year, and 5-year OS (A,B) and CSS (C,D) of patients with PC. OS, overall survival; CSS, cancer specific survival; AUC, area under the curve; ROC, receiver operating characteristic.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-92/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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