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Proposal for reclassification of N staging system in penile cancer patients, based on number of positive lymph nodes

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In the present study, we aim to compare the rationality of proposed N classification based on the number of metastatic lymph nodes (LNs) with the current one. A total of 509 penile cancer patients at our institute were analyzed. Univariable and multivariable statistical analyses were used to assess cancer-specific survival (CSS) in 2 staging systems. Harrell's concordance index was applied to evaluate predictive accuracy of the current and proposed N classification in predicting CSS. We propose a new classification: pN1 (metastasis in 1-2 regional LNs), pN2 (metastasis in 3 regional LNs, or 3 or fewer regional lymph nodes with extranodal extension), and pN3 (metastasis in 4 or more regional LNs). According to the current and proposed N classification, the 5-year CSS of penile cancer patients with pN1, pN2 and pN3 was 85.8%, 39.0%, and 19.7%; and with pN1, pN2 and pN3 was 79.8%, 39.3% and 15.3%, which almost all showed significant difference ($P < .001$, $P = .259$) ($P < .001$, $P < .001$). Multivariable predictive accuracy of the proposed and current N staging was 76.48% and 70.92% (5.56% gain; $P < .001$). With a multivariable model of clinical features, both current (hazard ratio [HR], 7.761, 10.612; $P < .001$, $P < .001$) and proposed N stages (HR, 3.792, 3.971; $P < .001$, $P < .001$) exhibited independent effects on survival. The proposed N classification is superior to the current one, which is simpler and provides more accurate prognosis.

KEYWORDS
lymph node, neoplasm metastasis, neoplasm staging, penile neoplasm, penis

1 | INTRODUCTION

In the present study, we aimed to compare the rationality of a proposed N classification based on the number of metastatic lymph nodes (LNs) with the current one. A total of 509 penile cancer patients at our institute were analyzed. Univariable and multivariable statistical analyses were used to assess cancer-specific survival (CSS) in 2 staging systems. Harrell's concordance index was applied to evaluate the predictive accuracy of the current and proposed N classifications in predicting CSS. We propose a new classification: pN1, metastasis in 1 or 2 regional LNs; pN2, metastasis in 3 regional LNs, or 3 or fewer regional lymph nodes with extranodal extension; and pN3, metastasis in 4 or more regional LNs. According to the current N classification, the 5-year CSS of penile cancer patients with pN1,

Abbreviations: AJCC, American Joint Committee on Cancer; CSS, cancer-specific survival; ENE, extranodal extension; HR, hazard ratio; LN, lymph node; PLNM, pelvic lymph node metastasis.

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pN2, and pN3 was 85.8%, 39.0%, and 19.7%; with the proposed N classification, the 5-year CSS with pN1, pN2, and pN3 was 79.8%, 39.3% and 15.3%. All of these comparisons between pN1 and pN2 of current classification ($P < .001$), between pN1 and pN2 ($P < .001$), pN2 and pN3 ($P < .001$) of proposed classification showed significant statistical difference except comparison between pN2 and pN3 of current classification (P = .259). Multivariable predictive accuracy of the proposed and current N staging was 76.48% and 70.92% (5.56% gain; $P < .001$). With a multivariable model of clinical features, both current (hazard ratio, 7.761, 10.612; $P < .001$, $P < .001$) and proposed N stages (hazard ratio, 3.792, 3.971; $P < .001$, $P < .001$) showed independent effects on survival. The proposed N classification is superior to the current one in that it is simpler and provides more accurate prognosis.

The 8th edition of the AJCC's N staging system for penile cancer was published with 1 change: metastasis in unilateral 2 inguinal LNs was incorporated into pN1. Generally, the system follows the 2009 TNM clinical and pathological classification.[1,2] The current N classification was based mainly on a single study with some limitations.[3] A long timespan was found in collected data of the study, as the included patients were treated between 1956 and 2006. The number of dissected LNs was not specified. We know that inguinal LN dissection generally yields 8 or more resected LNs,[4] and that accurate N classification cannot be guaranteed when the number of dissected LNs is suboptimal. In addition, the distribution of patients undergoing LN dissection was not balanced; there were 20 patients with N3 classification, 7 with pN3, and 13 with estimated N3, as well as 99 patients whose regional LNs could not be assessed. We believe that there is room for improvement to the current N staging systems.

Our clinical observations include several interesting phenomena. First and foremost, there is no significant difference in survival between 1 and 2 metastatic LNs. Second, among patients with the same number of positive LNs, those with 2 or more positive LNs had no significant survival difference between those with unilateral and those with bilateral metastasis. Third, for those patients with 4 or more regional LNM, there is no significant difference in prognosis between those with PLNM and those without. Finally, we also found that the vast majority of patients with PLNM have 4 or more positive LNs.

With regard to accuracy in predicting survival, there is a trend to simplify the N classification. For example, the N staging systems of breast cancer,[5] gastric carcinoma,[6] esophageal,[7] and colon cancer[8] are all based on the number of metastatic LNs. We thus propose a novel N classification based on only the number of positive LNs to provide a more universal, precise, reproducible, and simpler classification, and to facilitate clinical staging. We also evaluate the rationality of our proposed N classification compared with the current system.

2 | MATERIALS AND METHODS

2.1 | Patient selection and pathologic features

Between January 1999 and January 2017, 556 consecutive patients with penile cancer were treated in our institution. Clinical and pathologic variables were assessed for all patients. We established the following eligibility criteria: (i) histologically confirmed penile squamous cell carcinoma; (ii) 8 or more LNs dissected if inguinal lymph node dissection is carried out;[4] and (iii) absence of distant metastasis. We identified 556 penile cancer patients, of whom 509 met the above criteria and were enrolled for this study.

2.2 | Treatments and follow-up

All of the included patients underwent standard surgery: partial/total penectomy and/or inguinal lymphadenectomy and/or pelvic lymphadenectomy with curative intent. According to a study described by Master et al[4], lymphadenectomy of 8 or more nodes could be considered extensive inguinal lymphadenectomy. The boundaries of dissection, technology, and criteria for inguinal lymphadenectomy have been discussed previously in detail.[9] If 2 or more positive inguinal LNs or 1 node with ENE are found, pelvic lymphadenectomy is indicated, simultaneously or as a secondary procedure based on definitive histology.[10] Patients with 2 or more positive LNs were treated with 5-fluorouracil and cisplatin postoperatively, based on the European guidelines.[11] The study was carried out in accordance with the principles of the Declaration of Helsinki and was compliant with the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The protocol was approved by the ethical committee or review board of our institution (approval no. B2017-095-01). All patients provided written consent before their enrollment.

Our institution has followed a standardized follow-up protocol for 18 years. Patients were, in general, assessed at 3-month intervals for the first 2 years following surgery, semiannually for the years 3-5, and annually thereafter. Follow-up evaluation included physical examination of the penis and the groin, ultrasound, and pelvic computed tomography. The survival interval was defined from the date of surgery to the date of death or the last follow-up. Cancer-specific survival was the primary end-point, and the cause of death was determined by treating physicians by chart review corroborated by death certificates, or by death certificates alone.[12] Our follow-up assessment ended in January 2017.

2.3 | Current and proposed N staging systems

The definitions of the current and proposed N staging systems are listed in Table 1.

2.4 | Statistical analysis

Continuous parametric variables were recorded as the mean value ± SD; the median value and interquartile ranges were applied in continuous non-parametric distribution. The Kaplan-Meier method was applied for calculating estimates of survival time. Patients who were alive or who had died from other causes were censored. Univariable analysis was used for comparison of survival curves with the log-rank test. A Cox proportional hazards

TABLE 1 Comparison of the American Joint Committee on Cancer (AJCC)'s 8th edition N staging system and the proposed N staging system

Stage	AJCC N staging system	Proposed N staging system
pNx	Regional lymph nodes cannot be established	Regional lymph nodes cannot be established
pN0	No lymph node metastasis	No lymph node metastasis
pN1	≤2 unilateral inguinal metastases, no ENE	Metastasis in 1-2 regional lymph nodes
pN2	≥3 unilateral inguinal metastases or bilateral metastases	Metastasis in 3 regional LNs, or ≤3 regional lymph nodes with extranodal extension
pN3	ENE of lymph node metastases or pelvic lymph node metastases	Metastasis in ≥4 regional lymph nodes

model was used to estimate the HR of prognostic factors. The Harrell c-index were used in the prognostic models.[13] Predictive accuracy was evaluated by the c-index, which ranges from 0.5 (no predictive ability) to 1.0 (perfect discrimination). All reported *P*-values are two-sided, with $P < .05$ indicating statistical significance. All data analyses were undertaken with SPSS 19.0 (IBM, Armonk, NY, USA) and R 3.2.3.

We acquired the Research Data Deposit approval number RDDA2017000381 on the Research Data Deposit public platform (www.researchdata.org.cn).

3 | RESULTS

3.1 | Patient characteristics

Table 2 summarizes the clinicopathologic characteristics of the 196 patients with penile cancer and positive LN.

3.2 | Prognosis in association with 1 and 2 involved LNs

Figure 1A shows survival curves of patients with 1 or 2 positive LNs without ENE. The 5-year CSS of patients with 1 and 2 positive LNs without ENE was 88.2% and 79.3%, respectively, indicating no statistically significant difference between them ($P = .359$). The result is consistent with the he AJCC 8th edition N classification and our proposed N classification. Moreover, according to our statistics, we found that no PLNM was detected in patients with 2 positive LNs.

3.3 | Prognosis in relation to unilateral and bilateral LNM

In 147 patients with 2 or more positive LNs, 66 and 81 patients were found to have unilateral and bilateral LNM, respectively. There was no survival difference between these 2 groups (37.9% vs 36.9%, $P = .535$; Figure 1B). According to our proposed N classification, no survival differences were reported between the patients with unilateral vs bilateral LNM in pN1, pN2, and pN3 ($P = .470$, .404, and .522, respectively) (Figures S1, S2, S3).

TABLE 2 Clinical and pathologic characteristics in 196 patients with penile cancer

Variable	Cases
Age at surgery, years, median (range)	52 (28-81)
BMI, mean ± SD	22.35 ± 3.24
No. of lymph nodes removed, median (range)	25 (10-140)
No. of positive lymph nodes, median (range)	3 (1-26)
ENE, n (%)	66 (33.7)
PLNM, n (%)	32 (16.3)
No. undergoing inguinal lymphadenectomy	405
No. undergoing pelvic lymphadenectomy	89
pT stage, n (%)	
Tis	28 (14.3)
T1	48 (24.5)
T2	100 (51.0)
T3	14 (7.1)
T4	6 (3.1)
Grade, n (%)	
G1	76 (38.8)
G2	86 (43.9)
G3-4	34 (17.3)
AJCC 8th edition pN, n (%)	
pN1	63 (32.1)
pN2	59 (30.1)
pN3	74 (37.8)
Proposed pN, n (%)	
pN1	76 (38.8)
pN2	47 (24.0)
pN3	73 (37.2)

Patients were treated at the Sun Yat-Sen University Cancer Center (Guangzhou, China). AJCC, American Joint Committee on Cancer; BMI, body mass index; ENE, extranodal extension; PLNM, pelvic lymph node metastasis.

3.4 | Prognosis between the current and proposed pN3

Our statistics show that there were 32 patients with PLNM in our study, among whom 26 patients (81.25%) were found to have 4 or more positive LNs. Another 6 patients (18.75%) were found to have 3 positive LNs. The 5-year CSS of patients with PLNM and 3 or 4 or more positive LNs was 25.0% and 12.0%, respectively, representing a statistically significant difference ($P = .025$; Figure 1C). Moreover, the 5-year CSS of the current and proposed pN3 was 18.7% and 15.3%, respectively. In addition, the proposed pN3 group showed significant homogeneity in their prognosis ($P = .480$; Figure S4). In our proposed pN3, the 5-year CSS of the 26 patients with PLNM and 47 patients without PLNM was 19.0% and 12.4%, respectively, showing no statistical difference ($P = .333$; Figure 1D).

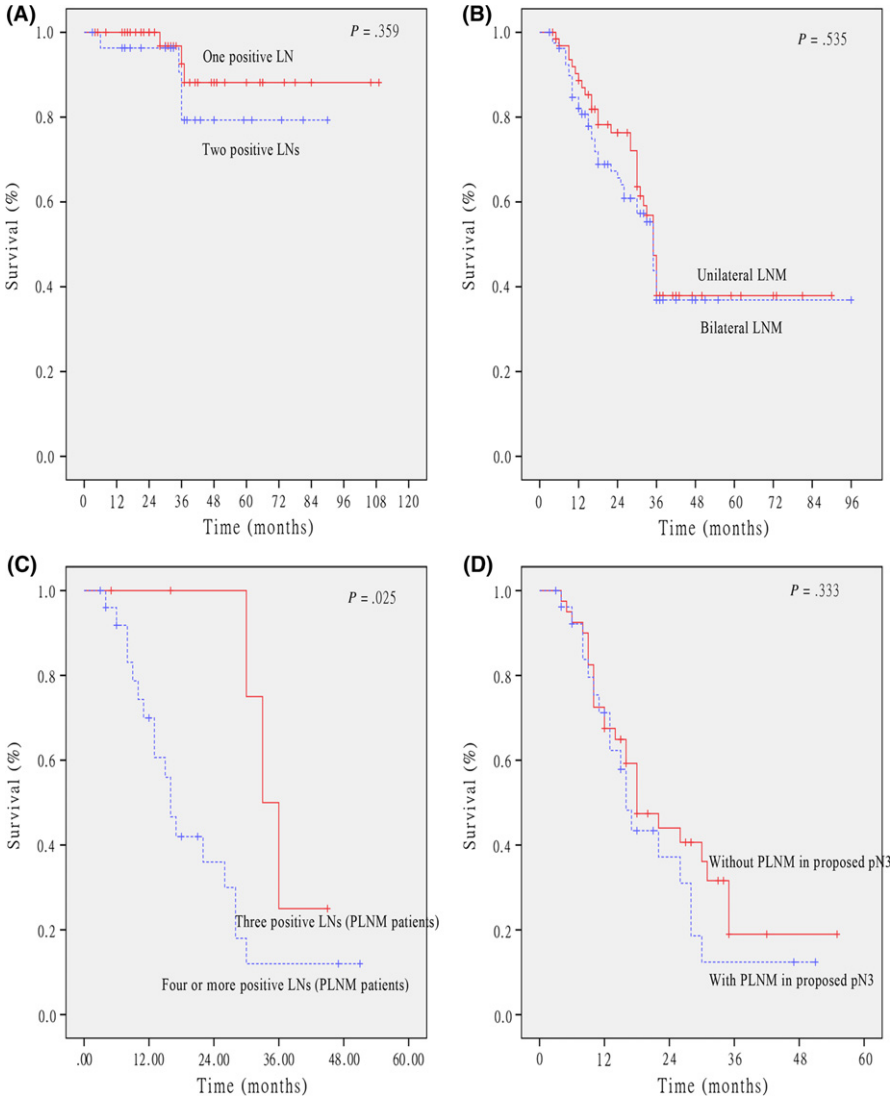

FIGURE 1 A, Survival curves of patients with penile cancer and 1 or 2 positive lymph nodes (LNs). B, Survival curves of patients with unilateral and bilateral LN metastasis (LNM). C, Survival curves of patients with 3 or 4 or more positive LNs in pelvic LNM (PLNM). D, Survival curves of patients with and without PLNM in the proposed pN3 system

3.5 | Correlation with CSS

Table 3 shows the relationship between the AJCC 8th edition N classification and our proposed N classification.

Figure 2A analyzes the association between the number of positive LNs and survival for all patients. We observed a marked linear trend for an increasing number of metastatic LNs correlated with decreasing survival times. Survival curves showed no significant difference between patients with 1 or 2 positive nodes ($P = .319$). However, significant differences were observed between patients with 2 vs 3 metastatic nodes, and 3 vs 4 positive nodes ($P = .036$ and $P < .001$, respectively), but no statistically significant difference was found between those with 4 vs 5 or more positive nodes ($P = .507$).

TABLE 3 Relationship between the American Joint Committee on Cancer (AJCC)'s 8th edition N classification and the proposed N classification for lymph node metastasis in penile cancer

Proposed N Classification	AJCC 8th edition N classification				
	pN0	pN1	pN2	pN3	Total
pN0	209	0	0	0	209
pN1	0	63	13	0	76
pN2	0	0	13	34	47
pN3	0	0	33	40	73
Total	209	63	59	74	405

Figure 2 shows survival curves based on the current and proposed N staging systems. According to the current N classification, the 5-year CSS of patients with penile cancer with pN1, pN2, or pN3 was 85.8%, 39.0%, and 19.7%, respectively, which represented a significant difference ($P < .001$ and $P = .259$; Figure 2B). On the basis of our proposed N classification, the 5-year CSS for pN1, pN2, and pN3 was 79.8%, 39.3%, and 15.3%, respectively. Statistically significant differences were found between these 2 classifications, which also showed good survival stratification ($P < .001$ and $P < .001$; Figure 2C).

Figures S2 and S3 show survival curves of 2 N classifications to analyze their respective homogeneity. We could not analyze the homogeneity of the current pN1 patient population in terms of prognosis (Figure S5). However, widely varying prognoses existed in both

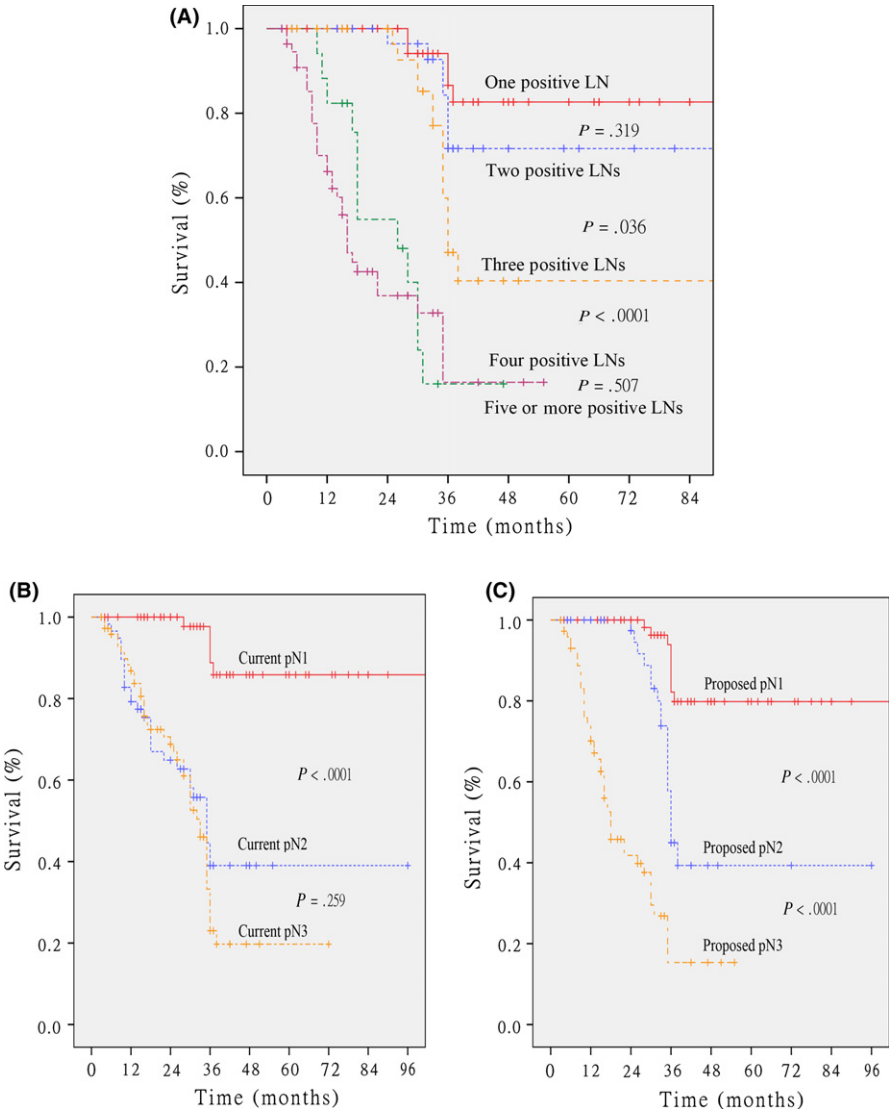

FIGURE 2 A, Association of number of metastatic lymph nodes (LNs) with cancer-specific survival (CSS) for all patients with node-positive penile cancer. B, CSS probabilities according to the current pN classification of penile cancer. C, CSS probabilities based on the proposed pN staging system of penile cancer

subgroups of the current pN2 and pN3 groups, which means that heterogeneity was found in the current pN2 and pN3 groups ($P < .001$ and $P = .002$, respectively; Figures S6, S7). The proposed pN1 and pN2 groups showed heterogeneity in their prognosis ($P = .034$ and $P = .002$, respectively; Figures S8, S9). The current pN1 and pN2 groups were the same as the proposed pN1 and pN2 patient cohorts with regard to homogeneity, whereas the proposed pN3 patient group was more homogeneous than the current pN3 cohort.

In the univariable analysis, primary T stage ($P = .002$), grade ($P = .009$), number of positive LNs ($P < .001$), and side involvement ($P = .03$) were related to CSS.

In multivariable Cox regression analysis adjusting for the effects of established clinicopathologic parameters including pT stage and tumor grade, both N classifications were independent markers for cancer-specific mortality (Table 4). On the basis of the current classification, the HRs were 7.761 (2.960-20.351, $P < .001$) for pN2/pN1 and 10.612 (4.094-27.508, $P < .001$) for pN3/pN2. According to the proposed classification, the HRs were 3.792 (2.672-5.382, $P < .001$) for pN2/pN1, 3.971 (2.827-5.578, $P < .001$) for pN3/pN2. The c-index of the base multivariable for bias-corrected prediction of CSS, including the current N classification, pT stage, and tumor grade, was 0.7092. The substitution of our proposed N classification for the current N classification to the model improved its accuracy for predicting cancer-specific mortality to 0.7648 ($P < .001$).

4 | DISCUSSION

The current TNM classification for penile cancer was based mainly on a notable study that had some limitations, including a long timespan of treating patients, a lack of specified number of retrieved LNs, and an imbalanced distribution of patients.[3] In researching our proposed classification, we found that there was room for improvement regarding clinical usefulness, predictive accuracy, and simplicity.

First and foremost, our study found no significant difference in the CSS of patients with penile cancer with 1 vs 2 positive LNs without ENE. Previous studies failed to find a significant survival difference between 1 and 2 tumor-positive inguinal nodes,[3,14-16] which

TABLE 4 Multivariable Cox regression analysis predicting penile cancer-specific mortality

	AJCC 8th edition N classification			Proposed N classification		
Variable	HR	CI (95%)	*P*-value	HR	CI (95%)	*P*-value
pT stage			.085			.421
T1 vs Tis	0.743	0.340-1.625	.457	0.803	0.365-1.765	.585
T2 vs T1	1.334	0.694-2.563	.387	1.040	0.541-1.998	.907
T3 vs T2	1.442	0.498-4.177	.500	1.368	0.477-3.923	.560
T4 vs T3	3.199	1.101-9.294	.033	2.282	0.782-6.664	.131
Grade			.267			.647
G2 vs G1	1.538	0.913-2.590	.106	1.286	0.749-2.209	.362
G3-4 vs G2	1.348	0.670-2.714	.402	1.085	0.537-2.191	.821
Current pN stage			<.001			-
pN2 vs pN1	7.761	2.960-20.351	<.001	-	-	-
pN3 vs pN2	10.612	4.094-27.508	<.001	-	-	-
Proposed pN stage			-			<.001
pN2 vs pN1	-	-	-	3.792	2.672-5.382	<.001
pN3 vs pN2	-	-	-	3.971	2.827-5.578	<.001

-, not applicable; AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio.

is consistent with our findings. Lymphatic metastasis in penile cancer follows the route of anatomical drainage. Inguinal LNs are the first echelon to manifest lymphatic metastatic spread.[17] In our research, we found that tumor-positive nodes in patients with 1 or 2 positive LNs were all inguinal nodes, and not pelvic nodes. Forty-nine and 23 patients were found to have 1 and 2 tumor-positive LNs, respectively, without ENE or PLNM, showing no statistically significant difference between them. Thus, we incorporated both 1 and 2 positive LNs into our proposed pN1 classification.

Second, our study found no significant difference in the CSS of patients with penile cancer between those with unilateral and those with bilateral LNM, which included those patients with 2 or more positive LNs (the same positive LNs). Previous studies reported that bilateral metastasis may increase the probability for migration, having a negative impact on survival.[2,3,18] When comparing the survival difference between patients with unilateral vs bilateral LNM, we considered including patients with at least 2 LNs positive for metastatic disease to be meaningful, yielding findings different from those reported previously. In 147 patients with 2 or more metastatic LNs, 66 and 81 patients were found to have unilateral and bilateral LNM, respectively, and there was no survival difference between them. On the basis of our proposed N classification, none of the patients with unilateral and bilateral LNM in pN1, pN2, and pN3 classifications showed any survival difference.

Third, our study found no significant difference in the CSS of patients with penile cancer and 4 or more positive LNs between those with and those without PLNM. In our study, most of the patients with PLNM had 4 or more positive LNs. Specifically, 26 of the 32 patients with PLNM had 4 or more positive LNs. Another 6 patients were found to have 3 tumor-positive LNs. The 5-year CSS of patients with PLNM and 3 or 4 or more positive LNs was 12.0% and 25.0%, respectively, representing a statistically difference ($P = .025$; Figure 1C). More importantly, no survival difference was found between the 6 PLNM patients with 3 metastatic LNs and our proposed pN2. Thus, it is appropriate to shift these 6 patients to a lower stage in our proposed N classification. In addition, in our proposed pN3 (4 or more regional LNMs), the 5-year CSS of the 26 patients with PLNM and 47 patients without PLNM was 19.0% and 12.0%, respectively, showing no statistically significant difference. All in all, the number of positive LNs may have a stronger impact on survival. Although the number of positive LNs may have a stronger impact on survival than PLNM, we still need to pay attention to pelvic lymph node dissection. We consider that if 3 or more positive inguinal LNs or 1 node with ENE, or preoperative imaging indicating pelvic LN enlargement are found, pelvic lymphadenectomy is indicated, simultaneously or as a secondary procedure based on definitive histology.

Finally, our study found no significant difference in the CSS of patients with penile cancer between those with metastasis in 3 regional LNs and those with metastasis in 3 or fewer regional LNs with ENE. Previous studies have assessed ENE as a prognostic factor.[12,19,20] However, most ENE is associated with fused LNs, which makes it difficult to count the number of positive LNs precisely. Among the cancers with number-based N staging systems, extranodal tumor deposits were described only in colon cancer. In colon cancer, tumor deposit in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis was defined as N1c, while metastasis in 1 regional LN and metastasis in 2 or 3 regional LNs was defined as N1a and N1b, respectively. With regard to the N classification of colon cancer, we compared the CSS in patients with 3 positive LNs with CSS in patients with 3 or fewer regional LNs with ENE, which showed no significant survival difference. Thus, they are both defined as pN2 in our proposed classification.

On the basis of our findings, we propose a simpler and more precise N classification based only on the number of positive LNs.

We acknowledge that our study is not without limitations, most notably, its retrospective design. However, the potential flaws of a retrospective study have been minimized with systematic re-evaluation of each specimen by a dedicated uropathologist blinded to clinical outcomes. Moreover, a large sample size and standard treatment approach of our study further reduce shortcomings of retrospective design. Secondly, adjuvant chemotherapy and pelvic lymphadenectomy may have an impact on survival. According to the current guidelines, for patients with 2 positive LNs, we perform pelvic lymphadenectomy and adjuvant chemotherapy,[21] which may affect their survival and lead to selection bias. However, for patients with 2 positive LNs, there was no ENE or PLNM. The final potential limitation is a relatively short follow-up time. The median time was 33 months, which may result in length time bias. It's possible that the rate of regional recurrence was underestimated. However, a prior study reported that local or regional nodal recurrences usually occur within 2 years of primary treatment.[18] Further research involving longer follow-up may help reduce bias.

In conclusion, the number-based proposed N classification represents a prognostic factor as powerful as the current N staging systems. Especially, the proposed N classification is superior to the current N classification in terms of the higher predictive accuracy and simpler way of assessing pathologic LNM. Further research may help evaluate the value of reclassification and its inclusion in future editions.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

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