

# New N Staging System of Penile Cancer Provides a Better Reflection of Prognosis

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## Abbreviations and Acronyms

AIC = Akaike information criterion

C-index = concordance index

ENE = extranodal extension

LN = lymph node

LNM = lymph node metastasis

LNR = lymph node ratio

LR = likelihood ratio

RFS = recurrence-free survival

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**Purpose:** We determined whether the new N staging system, which was introduced in 2009, leads to more specific prediction of survival in patients with penile squamous cell carcinoma.

**Materials and Methods:** We analyzed the records of 60 patients in whom node positive penile cancer was surgically resected from 1990 to 2008. All cases were staged according the 6th and 7th N staging system after pathological review. Histopathological information on the number of positive lymph nodes, lymph node metastasis laterality, extranodal extension, pelvic lymph node metastasis and lymph node ratio were also recorded. We evaluated the added information on these nodal related prognostic factors to the current N classification. Recurrence-free survival was calculated. Predictive accuracy was assessed by the concordance index.

**Results:** Disease recurred in 27 of the 60 patients (42.4%) at a median of 10 months. In the 33 patients without recurrence at the last visit median followup was 53 months. Using the 6th N classification the 3-year recurrence-free survival rate was 69.8%, 48.2% and 33.3% for the N1, N2 and N3 categories, respectively. Log rank survival analysis failed to show a statistical difference ( $p = 0.054$ ). For the new 7th N categories the 3-year recurrence-free survival rate was 87.5%, 57% and 31.8% in the corresponding N1 to N3 groups. Better survival stratification was observed on analysis ( $p < 0.001$ ). Adding lymph node metastasis laterality or lymph node ratio significantly increased the accuracy of the 7th N category to predict recurrence-free survival.

**Conclusions:** The new N staging system better reflects the prognosis in patients with penile cancer.

**Key Words:** penis, penile neoplasms, neoplasm metastasis, lymph nodes, neoplasm staging

PENILE squamous cell carcinoma is characterized by regional LN spread before distant metastases. Lymphatic mapping study found that inguinal LNs are the first echelon of LNs reached by metastasizing cancer cells from the primary tumor. Pelvic LNs, without direct drainage from the penis, are higher-tier LNs visualized after inguinal LNs.<sup>1</sup> The stepwise disseminative pattern of cancer cell in

regional LNs is further confirmed in an anatomical study of positive LNs.<sup>2</sup>

Mainstay treatment for penile cancer LNM is surgery with a limited role for radiotherapy.<sup>3</sup> It is well established that the extent of LNM has strong prognostic significance in patients with node positive penile cancer. The 5-year survival rate for patients with 1 to 3 positive inguinal LNs is 75.6% but only 8.4% in those

with 4 or 5 metastatic LNs and 0% in those with more than 5 involved LNs.<sup>4</sup> Besides the number of positive LNs other pathological features have also been suggested as prognostic factors in node positive penile cancer, such as bilateral involvement, LNR, ENE and pelvic LNM.<sup>4</sup>

The TNM staging system is widely used to indicate prognosis, classify the tumor for a treatment plan, evaluate results of different studies and facilitate the exchange of information. The 6th TNM classification introduced in 2002 for penile cancer was criticized for several shortcomings.<sup>5</sup> Thus, many groups have proposed changes in the classification to improve prognostication and facilitate staging.<sup>6,7</sup>

In 2009 a revised TNM staging system for penile cancer was published with 2 major changes in the N categories.<sup>8</sup> 1) There is no longer a staging distinction between inguinal superficial and deep LNs. 2) ENE of regional LNM is classified as N3 disease. The first change was mainly due to the difficulty in differentiating superficial and deep LNs in inguinal nodal basin.<sup>5</sup> The second change reflects accruing evidence that ENE is a strong prognostic factor of poorer survival.<sup>9</sup>

Due to variability in predicting LN status by clinical examination we discuss only pathological N staging. We reviewed the survival characteristics of patients based on the new N staging system. We studied 60 consecutive patients who underwent regional lymphadenectomy at a single institution. Other nodal related prognostic factors were also discussed.

## MATERIALS AND METHODS

The study group included 60 consecutive patients with penile squamous cell carcinoma in whom LNM was surgically resected from 1990 to 2008. Data on 24 patients treated before 2005 were collected retrospectively. Since then, all data have been recorded prospectively. All patients underwent bilateral inguinal lymphadenectomy in the prophylactic or therapeutic setting at Fudan University Shanghai Cancer Center.

Before 2005 the indication for pelvic lymphadenectomy was enlarged pelvic LNs in preoperative cross-sectional images or the involvement of Cloquet's node on frozen section. Since then, due to the low negative predictive value of the indication,<sup>10</sup> pelvic lymphadenectomy has been done when 1 or more positive inguinal LNs were found. The borders of ilioinguinal lymphadenectomy were previously described in detail.<sup>2</sup> Briefly, superficial and deep inguinal LNs were removed at inguinal LN dissection. The template of pelvic lymphadenectomy included external iliac, obturator and common iliac LNs. Chemotherapy using 5-fluorouracil and cisplatin was administered postoperatively to patients with positive margins. Since 2005, those with 2 or more metastatic LNs have also received adjuvant chemotherapy. We excluded from analysis

patients who underwent neoadjuvant chemotherapy or previous groin exploration. Informed consent was obtained from all patients and the protocol was approved by the institutional ethics committee.

After pathological review, cases were staged according to the American Joint Committee on Cancer 6th and 7th N staging system.<sup>8,11</sup> Deep inguinal LNM was defined as involvement of Cloquet's nodes or LNs located around the femoral vessel. Histopathological information on the number of positive LNs, LNM laterality, ENE and pelvic LNM were recorded for analysis. LNR was calculated by dividing the number of positive LNs by the total number of excised LNs.<sup>12</sup> The number of positive LNs and LNR were analyzed as categorical variables by grouping patients into 3 categories based on equal percents. We assessed the addition of information on these nodal related prognostic factors to the current N classification. Given the small sample size and the number of relationships examined, all analyses were considered exploratory and all results were considered hypothesis generating rather than hypothesis testing.

RFS was measured as time from operation to date of recurrence or last followup. Survival was calculated by the Kaplan-Meier method with the log rank test to assess differences between groups. The Cox proportional hazards regression model was used to estimate the HR of prognostic factors. Due to the limited number of events and the study main objective only the N staging system and another candidate predictor were included on multivariate analysis.

The criteria investigated to evaluate the prognostic models were LR chi-square, AIC and the Harrell c-index.<sup>13</sup> LR chi-square estimates the loss of adjustment by calculating the difference in the deviance between models with and without the score. A smaller AIC or a higher LR chi-square indicates a better model. Predictive accuracy was assessed by c-index, which is comparable to AIC and ranges from 0.5—no predictive ability to 1.0—perfect discrimination. Comparison of nested models was calculated by the LR test. Due to small sample size we did not compare rank concordance between unnested models. All data analysis was done using R 2.12.0<sup>14</sup> with  $p < 0.05$  considered statistically significant.

## RESULTS

Table 1 lists clinicopathological characteristics of the patient population. Disease recurred in 27 of the 60 patients (45%) at a median of 10 months (range 3 to 29). In the 33 patients without recurrence at last visit median followup was 53 months (range 15 to 171).

Disease stage was revised according to the new N classification in 16 patients (26.7%). The proportion of patients with N3 disease was remarkably increased by the reclassification. Of N1 and N2 cases 33.3% and 20.8%, respectively, were up-staged to N3 in the new categories. On the other hand, 3 cases (25%) were shifted from N3 to N2.

Figure 1 shows survival curves according to the 6th and 7th N staging systems. For the 6th N classification the 3-year RFS rate was 69.8% (95% CI

**Table 1.** Clinicopathological characteristics of 60 patients with pN+ penile cancer

Median age (range)	48	(29–84)
No. lymphadenectomy (%):		
Inguinal	31	(51.7)
Ilioinguinal	29	(48.3)
No. 6th pN stage (%):		
N1	24	(40)
N2	24	(40)
N3	12	(20)
No. 7th pN stage (%):		
N1	16	(26.7)
N2	22	(36.7)
N3	22	(36.7)
Median No. nodes (IQR)	25	(20–31.5)
No. pos nodes (No. pts):		
1st Tertile	1	(24)
2nd Tertile	2	(14)
3rd Tertile	3 or Greater	(22)
% LNR (No. pts):		
1st Tertile	Less than 6.0	(20)
2nd Tertile	6–11.1	(19)
3rd Tertile	Greater than 11.1	(21)
No. bilateral LNM (%)	18	(30)
No. ENE (%)	16	(26.7)
No. pelvic LNM (%)	8	(13.3)

53.3–91.4), 48.2% (95% CI 31.4–74.1) and 33.3% (95% CI 15.0–74.2) for the N1, N2 and N3 categories, respectively. Log rank survival analysis failed to show a statistical difference ( $p = 0.054$ ). For the new 7th N categories the 3-year RFS rate was 87.5% (95% CI 72.7–100.0), 57% (95% CI 39.0–83.2) and 31.8% (95% CI 10.4–54.9) for N1 to N3, respectively. Better survival stratification was observed on analysis ( $p < 0.001$ ). Of the 48 cases staged as N1-2 disease in the old system 13 were shifted into N3 in the new system due to ENE. Patients with up-staged disease had significantly poorer survival than those without up-staging ( $p = 0.02$ ), indicating better reclassification in patients with diverse outcomes (fig. 2).

To improve the stratification of current N staging we performed exploratory data analysis on the question of whether any other nodal related prognostic factors add to the prognostic value of current N staging.

Survival curves showed that RFS significantly differed by the number of positive LNs, LNM laterality, ENE, pelvic LNM and LNR ( $p < 0.05$ , fig. 3). Since ENE and pelvic LNM are already included in the new N staging system, the other 3 factors were added to the model based on the 7th N classification (table 2). Adding LNM laterality or LNR significantly increased the predictive accuracy of the basic model.

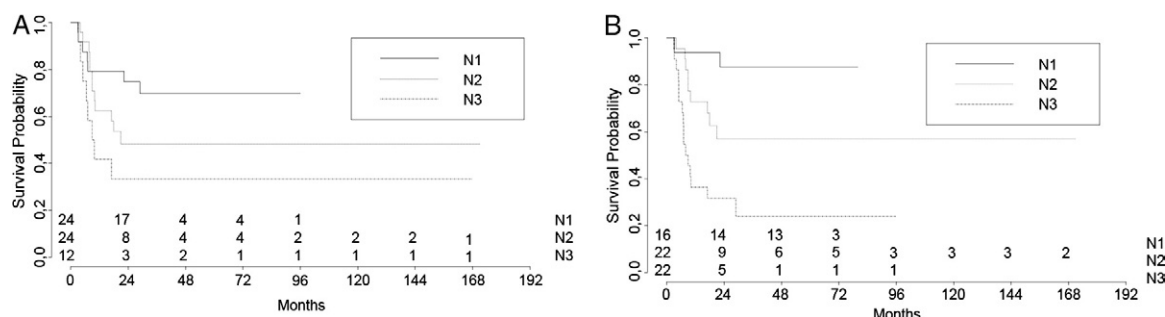
## DISCUSSION

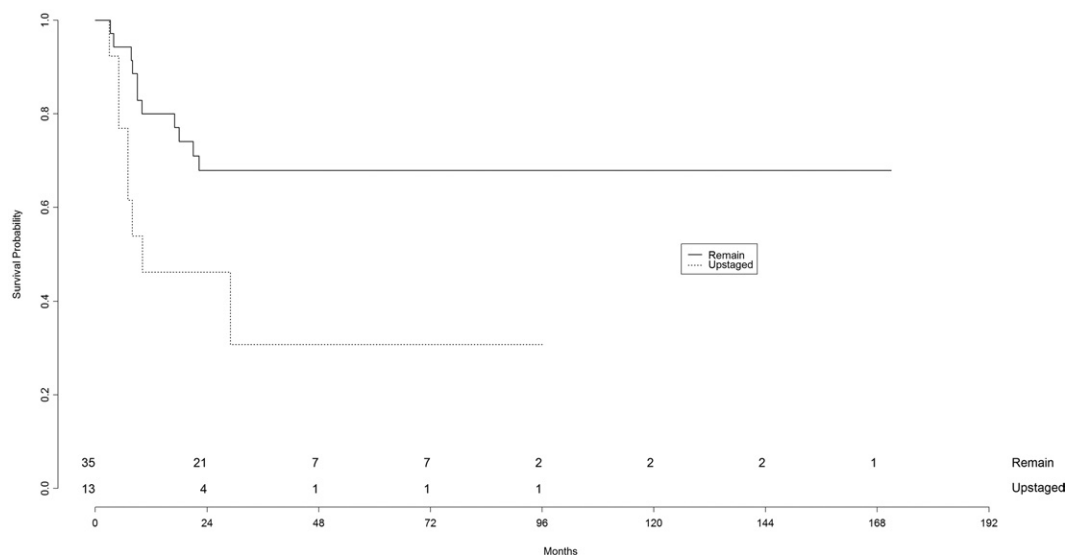
Our study shows that the new N staging system better reflected prognosis in our cohort of 60 patients with pN+ penile cancer. N stage in 16 cases (26.7%) was revised according to the new classification, including 13 that were up-staged and 3 that were down-staged. The 13 patients shifted from N1-2 to N3 disease had significantly poorer survival than those not shifted.

The improvement in reclassification was mainly due to including ENE, a strong adverse prognostic factor, as an indicator of N3 disease. Graafland et al from The Netherlands evaluated ENE as a prognostic factor in a large cohort of 156 node positive cases.<sup>9</sup> Five-year disease specific survival was distinctly different in patients without vs with ENE (80% vs 42%,  $p < 0.001$ ). Rather than the number of positive LNs and LNM laterality, ENE showed important prognostic value on multivariate analysis (HR 2.37,  $p = 0.012$ ).

In accordance with the study by Graafland et al,<sup>9</sup> Pandey et al noted 8.9% vs 90.5% 5-year overall survival in patients with vs without ENE.<sup>4</sup> ENE was identified as an independent variable in a their multivariate model (HR 9.206,  $p < 0.001$ ). In a recent report of neoadjuvant chemotherapy for penile cancer ENE in residual tumor was significantly associated with shorter survival.<sup>15</sup> Median time to progression was more than 50 months in patients without ENE after chemotherapy but only 5 months in those with the adverse feature ( $p = 0.001$ ).

Omitting the distinction between superficial and deep inguinal LNs is another advantage of the

**Figure 1.** Survival curves of patient subgroups by 6th (A) and 7th (B) N staging system



**Figure 2.** Survival curves of patients with disease up-staged from N1-2 (6th) to N3 (7th) and those with disease that remained N1-2 (7th)

current N category. In clinical practice it is hard for pathologists to distinguish the 2 groups of LNs if en bloc dissection is performed. The situation is even more difficult when a large LN is situated in the central Daseler zone.

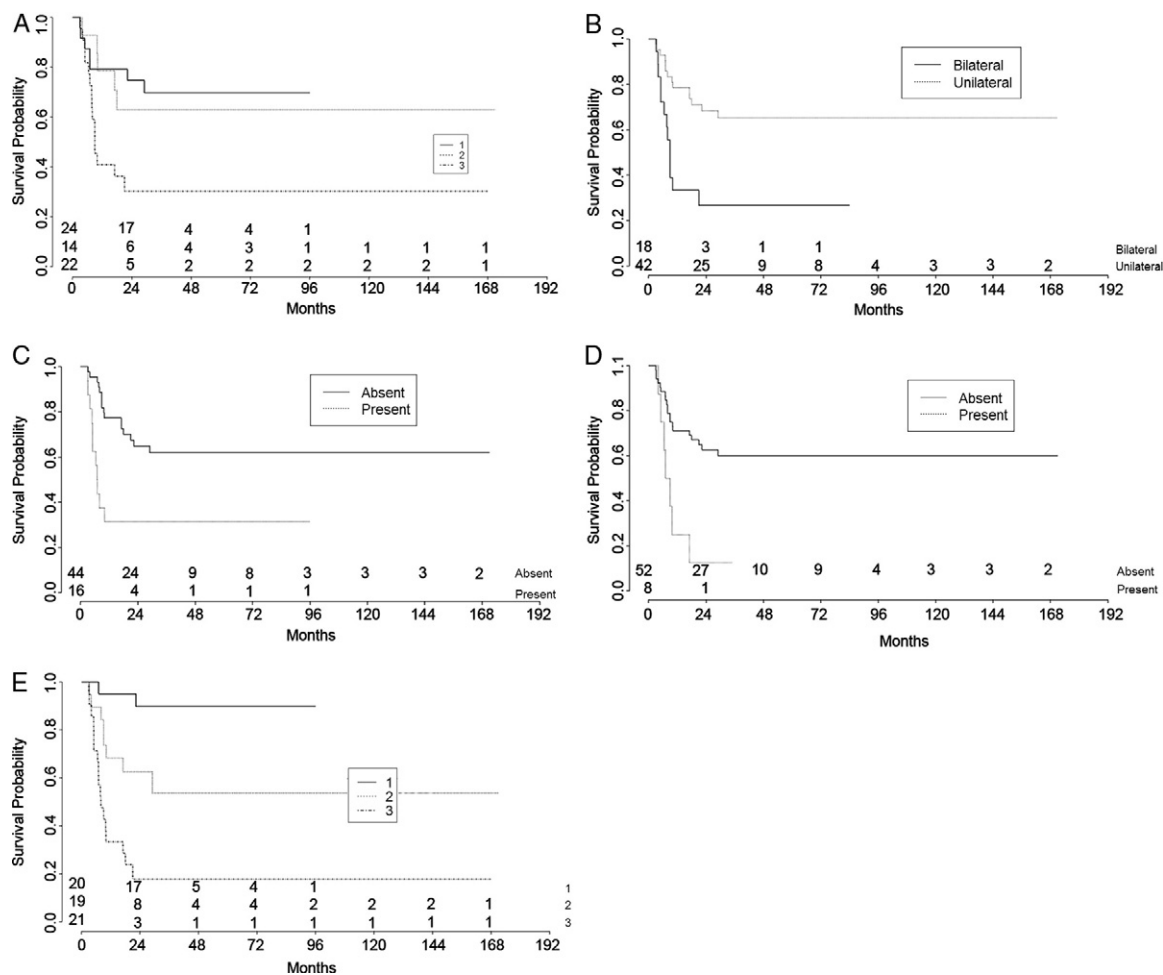
Besides better prediction, there is still room for improvement in the current N staging system. Adding LNM laterality and LNR to the 7th N classification had a positive impact on predictive accuracy. Our results are consistent with those of several previous studies.

In the study by Ravi the 5-year survival rate in patients with unilateral and bilateral inguinal LNM was 86% and 60%, respectively.<sup>16</sup> Pandey et al reported 63.1% 5-year survival in unilateral LN positive cases but only 21.2% in cases of bilateral disease.<sup>4</sup> On multivariate analysis bilaterally positive LNs were an independent factor affecting survival in node positive cases (HR 2.669,  $p = 0.007$ ). To improve the prognostic stratification of the 6th N definition Leijte et al proposed a modified N category using inguinal LNM laterality as the distinction between N1 and N2 disease.<sup>6</sup> Survival analysis of the proposed N category showed improved stratification among all strata over that of the 6th N staging system. A lymphatic mapping study revealed bilateral inguinal drainage in 89% of patients with penile cancer.<sup>17</sup> However, bilateral nodal involvement was observed in about 15% to 54% of all node positive cases in case series.<sup>4,9,16,18,19</sup> Tumor with bilateral metastasis may show increased capability for migration and, thus, have an adverse effect on survival. Further analysis of the molecular changes between unilaterally and bilaterally involved tumors may be helpful to elucidate the hypothesis.

Previous studies have proved that LNR is an excellent predictor of survival outcome in patients with colon and breast cancer.<sup>20,21</sup> LNR could consider the total number of LNs retrieved by various techniques. LNR may also accurately reflect disease severity independent of treatment modality, for example without neoadjuvant therapy and modified/standard/extended lymphadenectomy, as well as heterogeneous patient characteristics.<sup>22</sup> Svatek et al evaluated the prognostic value of LNR for penile cancer by reviewing 45 patients with node positive penile cancer from M. D. Anderson Cancer Center.<sup>12</sup> LNR was significantly associated with disease specific survival when stratified by median value or tertile. Estimated 5-year disease specific survival in patients with an LNR of 6.7% or less was 91.7% but only 23.3% in those with an LNR of greater than 6.7% ( $p < 0.001$ ). When included in a model with ENE, perioperative chemotherapy or pN staging criteria, LNR remained statistically significant and the other factors were no longer statistically significant.

A similar finding was identified on multivariate analysis in our cohort. LNR was the only statistically significant factor in the model using the 7th N staging system (HR 3.84,  $p = 0.0026$ ). Although the optimal cutoff of LNR is still undetermined for penile cancer, this prognostic factor warrants further consideration. The additional value of LNR may be more obvious in multicenter studies, in which heterogeneous patient populations and management are common.

We acknowledge some study limitations. 1) Our study population encompassed an 18-year period and 40% of the data (those before 2005) were collected retrospectively. However, there were few



**Figure 3.** Survival curves for patient subgroups by number of positive LNs (A), LNM laterality (B), ENE (C), pelvic LNM (D) and LNR (E)

changes in the surgical approach to lymphadenectomy and the histopathological evaluation of specimens at our institution. 2) Small sample size restricted the number of variables on multivariate analysis and the power of model comparisons. Thus, multivariate analysis included only 2 prognostic factors and should be interpreted as

exploratory. 3) For validation purposes we categorized the number of positive LNs and LNR in a way similar to that in a previous report.<sup>12</sup> The optimal cutoff for these predictors needs further evaluation in a large multicenter study. 4) We did not evaluate micrometastasis size since ultra-staging was not routinely done. The innovative

**Table 2.** Predictive accuracy of models including 7th N staging system alone and with other variables

Model (variables)	HR (95% CI)	p Value	AIC	LR	Predictive Accuracy	
					C- Index	p Value vs Model 1
1 (7th N)	9.30 (2.89–29.87)	0.0002	190.86	16.84	0.72 (0.63–0.81)	—
2: (7th N + LNM lat)			188.40	21.31	0.76 (0.66–0.85)	0.035
7th N	7.98 (2.34–27.16)	0.0009				
LNM lat	2.33 (1.08–5.03)	0.0316				
3: (7th N + No. pos LNs)			191.21	18.49	0.74 (0.65–0.84)	0.20
7th N	8.01 (2.29–28.03)	0.0054				
No. pos LNs	1.83 (0.71–4.72)	0.2101				
4: (7th N + LNR)			182.19	27.52	0.77 (0.69–0.86)	0.0011
7th N	3.64 (0.86–15.44)	0.080				
LNR	3.84 (1.37–10.71)	0.0026				

dynamic sentinel lymph node biopsy procedure certainly requires enhanced pathological analysis and other promising prognostic factors. In

conclusion, the new N staging system better reflects the prognosis in patients with penile squamous cell carcinoma.

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