Prognosis of the 8th TNM Staging System for Penile Cancer and Refinement of Prognostication by Incorporating High Risk Human Papillomavirus Status

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Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
C-index = concordance index
CMC = Chinese multicenter
hrHPV = high risk human papillomavirus
LND = lymph node dissection
LNM = lymph node metastasis
LR = likelihood ratio
MCC = Moffitt Cancer Center
NCCN® = National Comprehensive Cancer Network®
OS = overall survival

Purpose: We evaluated the prognostic value of the 8th TNM staging system and assessed a modified N stage incorporating high risk human papillomavirus status in a multicenter cohort.

Materials and Methods: Included in analysis were 292 patients with M0 penile squamous cell carcinoma from a total of 6 referral centers. High risk human papillomavirus status was examined. The Chinese multicenter cohort of 230 patients was used to validate the 8th TNM staging system and propose a modified N classification. The modified classification was further validated in an independent cohort of 62 patients at Moffitt Cancer Center.

Results: Median followup was 48.9 months. Of the patients 42% had node positive disease. In the primary cohort the 8th TNM staging system achieved better discriminative ability compared with the 7th edition (C-index 0.769 vs 0.751, $p=0.029$). The 8th N category better stratified survival between pN1 and pN2 ($p<0.001$) and reclassified 15% of node positive cases into pN1 with 64% 5-year overall survival. High risk human papillomavirus status further stratified pN2-3 disease ($p=0.040$) and pN2-3 high risk human papillomavirus negative status was associated with 32% 5-year survival. The newly proposed 3-tier classification (1—pN1, 2—pN2-3 high risk human papillomavirus positive and 3—pN2-3 high risk human papillomavirus negative) significantly increased the C-index from 0.620 to 0.666 compared with the 8th N classification of pN1 and pN2-3 ($p=0.04$). In the external validation cohort significantly improved results were observed using the modified N classification (C-index 0.567-0.641, $p=0.027$).

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Conclusions: The 8th edition of the AJCC (American Joint Committee on Cancer) Staging System for penile cancer showed better discriminative ability for prognostic stratification. Adding high risk human papillomavirus status further improved the prognostic stratification in patients with node positive disease.

Key Words: penile neoplasms, prognosis, Papillomaviridae, neoplasm staging, mortality

GIVEN the rarity and heterogeneity of penile cancer, prognostic prediction is difficult.[1] In the last decade the most widely used prognostic estimation tool was the 7th edition of the AJCC TNM staging system,[2] which was adopted in the NCCN guideline.

Although the 7th TNM staging system is continuously evolving, several controversies have arisen following adoption. 1) Stratification of stages T2 and T3 was based on urethral invasion. Since invasion depth was a well-established prognostic factor,[3] this T stratification contraindicated these experiences. Malignancies in the glans were likely to invade the urethra (stage T3) before the corpora cavernosa (stage T2) while malignancies which might invade the cavernosa before the urethra (the primary location in the penile body) only account for 7.3% in the SEER (Surveillance, Epidemiology, and End Results) database.[4]

2) While the guidelines drew a line between N1 and N2 disease for surgery alone or intense treatment,[2] there was much debate on N1 and N2 stage stratification. The definition of N2 stage in the 7th edition included the number of inguinal LNMs and whether they were bilateral. However, several groups have drawn conflicting conclusions, including considering that the number of LNMs has no value to adopting a cutoff greater than 3 LNMs.[5–7]

Based on these considerations the 8th TNM staging system has incorporated several modifications (supplementary Appendix, https://www.jurology.com).[8] Although the 8th TNM staging system recommends collecting the status of hrHPV infection in clinical practice, the prognostic value of hrHPV in penile cancer remains controversial.[9,10] Recently Yuan et al found that hrHPV status could predict a chemoradiotherapy benefit in node positive penile cancer cases.[11] However, as in other studies,[9,10] this conclusion was hindered by the low number of node positive cases (67 or less overall). Supplementary table 1 (https://www.jurology.com) shows the literature review. Moreover, how to combine N stage and hrHPV status in clinical practice awaits studies with adequate cases of node positive disease and qualified lymphadenectomy.

The objective of this study was to evaluate the prognostic value of the 8th TNM staging system in a multicenter study. A modified N stage including hrHPV status was proposed and its clinical value was assessed. An independent cohort from the United States was included to validate the proposed modified classification.

MATERIALS AND METHODS

Patient Cohorts and Data Collection

We identified 318 patients with penile cancer who underwent surgical treatment at a total of 6 referral centers between 1998 and 2015. After applying the exclusion criteria 292 patients with nonmetastatic penile squamous cell carcinoma remained in the final cohort (supplementary methods, https://www.jurology.com). Information on pretreatment and therapy related findings was recorded. The study protocol was approved by the local Institutional Review Board (IRB No. 050432-4-1008A). The study was performed according to institutional ethical guidelines based on sound clinical practice. Informed consent was waived because of the retrospective nature of this study.

In the evaluation of the 8th staging system and the discovery of the modified N classification 230 patients were included from the institutional database of a total of 5 referral centers in China between 2005 and 2015 (supplementary methods, https://www.jurology.com). To validate the modified N classification 62 patients from MCC with nonmetastatic penile squamous cell carcinoma between 1998 and 2014 were also included in study.

Treatment and Followup Strategy

In the entire CMC and MCC cohort surgery was the mainstay treatment of penile cancer. Primary disease was treated with local excision in 4.1% of cases and partial or total penectomy in 96%. Prophylactic inguinal LND was recommended in patients with pT2 or higher disease plus all grade 3 tumors while therapeutic LND was performed in clinical node positive cases. Overall 74% of patients with pT1b-4 disease underwent inguinal LND while 51% with 2 inguinal or more LNMs underwent pelvic LND.

A median of 19 lymph nodes (IQR 13–24) were removed. Adjuvant therapy, including chemotherapy and/or radiotherapy, was performed in 32% of patients with pN2/3 disease. The multimodality treatment pattern fulfilled the 2018 version 2 of the NCCN guidelines in 59% of patients. The supplementary methods (https://www.jurology.com) show the followup scheme.

Histopathological Evaluation

At the diagnosis stages pT and N in each patient were initially recorded according to the AJCC TNM staging system.[2,12] The supplementary methods (https://www.jurology.com) show details of the sample reevaluation and the central pathology review. All histopathological findings in the CMC cohort were reviewed by an experienced oncologic pathologist (QW) blinded to other clinical information.

High Risk Human Papillomavirus Examination

The supplementary methods (https://www.jurology.com) show the details of hrHPV examinations in the CMC cohort. In MCC patients hrHPV status was determined using frozen tissues as previously described.[11] We defined

hrHPV positive tumors as those positive for DNA of hrHPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 66 or those showing positive p16 expression.

Statistical Analysis

Categorical data are shown as the frequency and percent, and continuous data are shown as the median and IQR. The main outcome was OS, defined as from diagnosis to death. The OS distribution was estimated by the Kaplan-Meier method. The log rank test was performed to compare survival differences among the curves. Univariate and multivariate Cox regression analyses were done to estimate the HR and 95% CI of covariates in the survival model. The Uno C-index was calculated to evaluate model discrimination.[13]

The LR chi-square test for nested models was used to compare goodness of fit in competing models and assess whether new variables added predictive value to the baseline models. An adequacy index using LR methods was used to quantify the percent of variation explained by a subset of the individual predictors compared with the information contained in the full set of predictors. Analyses were done with SPSS®, version 22 and R, version 3.1.2 (https://www.r-project.org/) with $p \leq 0.05$ considered statistically significant.

RESULTS

Patient Characteristics

All 292 patients had pathologically confirmed penile squamous cell carcinoma and 45% were hrHPV positive. Median followup in the entire cohort was 48.9 months (IQR 28.1–84.7) and 85 patients had died by the time of the last followup. Supplementary table 2 (https://www.jurology.com) lists baseline characteristics.

Analyses

American Joint Committee on Cancer Stage Group. The 8th edition stage categories provided good OS stratification (log rank $p < 0.001$, fig. 1, *A*). Multivariate analysis incorporating pT and pN stages showed

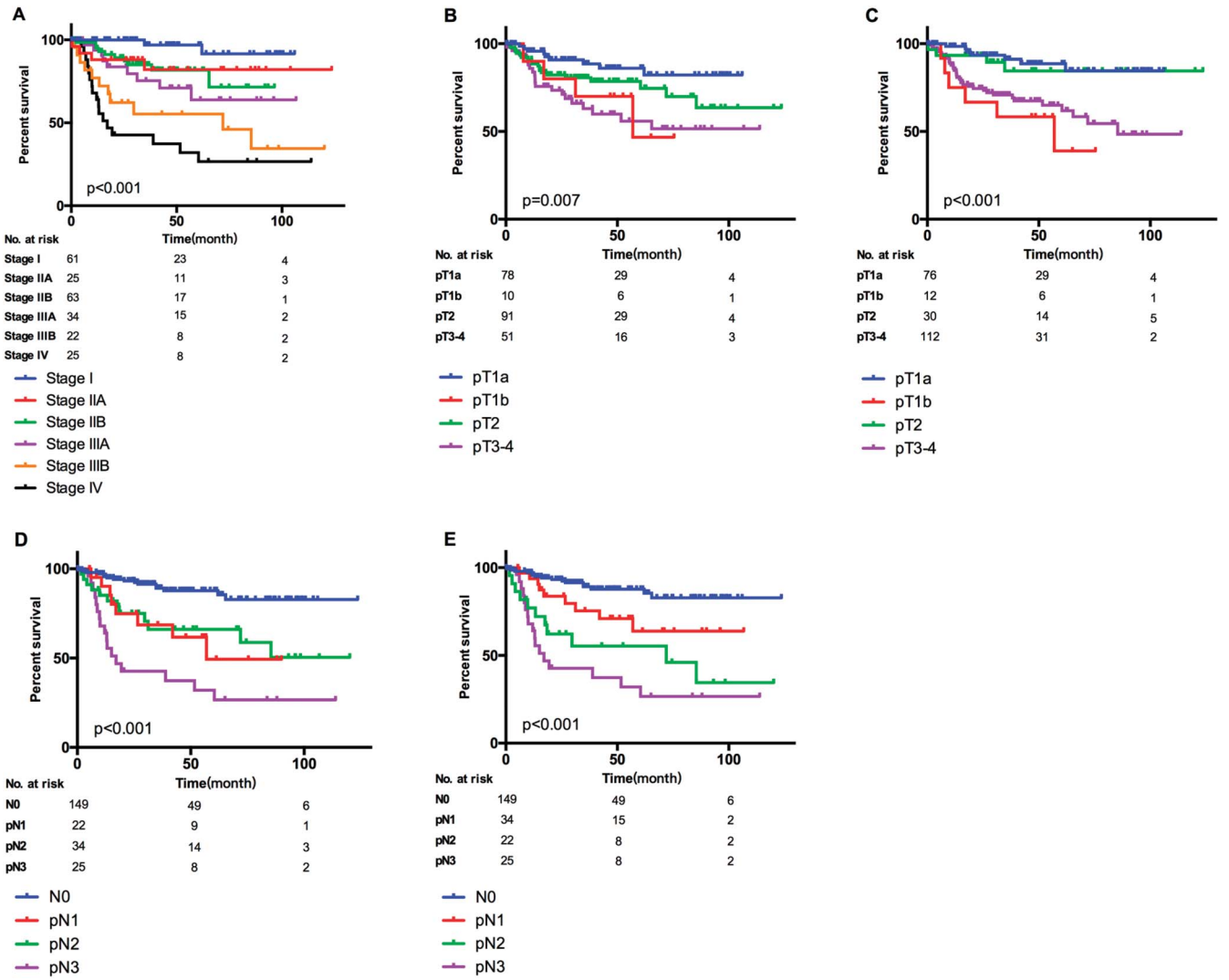

Figure 1. Kaplan-Meier OS curves by CMC cohort staging categories. *A*, 8th edition stage group. *B*, 7th edition pT category. *C*, 8th edition pT category. *D*, 7th edition N category. *E*, 8th edition N category.

that the 8th edition staging system achieved better discriminative ability than the 7th edition as evidenced by a higher C-index of 0.755 vs 0.737 (LR chi-square test p = 0.03, table 1).

pT Category. The 7th and 8th editions had inadequacies in stratifying patients by pT stage. Specifically the outcome of pT1b disease was worse than that of pT3/4 disease as evidenced by 5-year OS data including pT1a disease in 89% of patients, pT1b in 39%, pT2 in 85% and pT3/4 in 65%. Poor survival in the pT1b category may be explained by the relatively higher 83% rate of LNM caused by selection bias at academic centers (supplementary table 3, https://www.jurology.com).

N Category. The N stage of the 8th edition staging system provided better survival stratification than the 7th edition as shown by the Kaplan-Meier curves (fig. 1, *D* and *E*). The N category of the 7th edition demonstrated inadequacy for stratifying patients. That is, similar 2-year OS and worse 5-year OS were observed in patients with pN1 vs pN2 disease (supplementary table 4, https://www.jurology.com). No such defect was observed for the 8th edition, which revealed a sequential OS decrease from N0 to pN3 and a sequential increase in HR from pN1 to pN3 compared with N0 (HR 2.47, 5.30 and 8.50 for pN1, pN2 and pN3, respectively, p <0.001, supplementary table 4, https://www.jurology.com). Supplementary table 5 and supplementary figure 1 (https://www.jurology.com) show similar results in the MCC cohort.

Next we performed decision based stratification analysis to determine how many patients would have a treatment shift after revision using the 7th edition. While good prognostic stratification was retained in terms of 5-year OS, according to the 8th edition 15% of the patients with node positive disease would have been de-intensified to curative surgery alone instead of adjuvant treatment (table 2).

Improvement by Adding High Risk Human Papillomavirus Status to Current System

Finally, we examined whether adding hrHPV status would improve the prognostic estimations of the 8th edition staging system. A total of 130 cases were hrHPV positive, including 112 (86%) hrHPV DNA and p16 positive, 8 (6.2%) hrHPV DNA negative and p16 positive, and 10 (7.6%) hrHPV DNA positive and p16 negative. We found that patients with pN2-3 disease could be further stratified by incorporating hrHPV status into each N category (fig. 2, *F*). OS was significantly poorer in pN2-3 hrHPV negative patients (5-year OS in 32%) than in hrHPV positive patients (table 2 and fig. 2, *F*).

We then modified the classic N stage by incorporating hrHPV status into the pN2-3 category. The HR of each category in the modified 4-tier classification of 1—N0, 2—pN1, 3—pN2-3 and hrHPV positive, and 4—pN2-3 hrHPV negative sequentially increased even after adjusting for the known prognostic factors patient age and T stage (table 2). The modified 4-tier classification increased the C-index from 0.713 (95% CI 0.641–0.785) to 0.728 (95% CI 0.654–0.802) compared with the 8th edition N classification of N0, pN1 and pN2-3. The LR chi-square test demonstrated that the discriminative ability of the modified classification was significantly better than that of the 8th edition N classification (p = 0.04, fig. 2, *A*). Similar results were obtained when we compared the 2 models in node positive cases only (C-index 0.666 vs 0.620, LR chi-square test p = 0.04, fig. 2, *B*).

We further validated the modified N classification in the MCC cohort. The modified classification outperformed the 8th edition N stage in the entire MCC cohort and in node positive cases with a C-index of 0.651 (95% CI 0.502–0.800, LR chi-square test p = 0.011) and 0.641 (95% CI 0.477–0.805, LR chi-square test p = 0.027), respectively (fig. 3, *C* and *D*). The calibration of predicted and observed 5-year OS was close in the MCC cohort (supplementary fig. 2, https://www.jurology.com). Patients in the MCC cohort with pN2-3 hrHPV negative disease had extremely poor outcomes. None of them survived beyond the 5-year time point (supplementary table 6, https://www.jurology.com).

Table 1. *Multivariate analysis and discriminative evaluation using different AJCC TNM Staging System editions in Chinese multicenter cohort of 230 patients*

	HR (95% CI)	p Value
	7th Edition	
T stage:*		0.14
T1a	Referent	
T1b	1.44 (0.42–4.90)	
T2	1.67 (0.76–3.69)	
T3	2.33 (1.03–5.26)	
T4	6.16 (1.20–31.68)	
N stage:		<0.001
N0	Referent	
N1	3.52 (1.46–8.50)	
N2	3.02 (1.40–6.47)	
N3	6.96 (0.38–14.31)	
C-index	0.737 (0.660–0.814)	
	8th Edition	
T stage:*		0.06
T1a	Referent	
T1b	3.19 (1.01–10.05)	
T2	1.30 (0.38–4.50)	
T3	2.61 (1.13–6.04)	
T4	8.23 (1.53–44.44)	
N stage:		<0.001
N0	Referent	
N1	2.07 (0.87–4.90)	
N2	3.83 (1.73–8.51)	
N3	5.86 (2.80–12.25)	
C-index	0.755 (0.678–0.832)	

* No stage T1.

Table 2. *N category decision based stratification in Chinese multicenter cohort of 230 patients*

Decision* (decision based stratification)	% N+	% 5-Yr Survival	HR vs N0 (95% CI)	
			Vs N0	Adjusted† vs N0
		7th Edition		
Surgery alone (pN1)	27	49	3.68 (1.57–8.60)	–
Multimodality treatment/clinical trial:				–
pN2-3	73	51	5.21 (2.82–9.60)	
pN2-3 (HPV pos)	–	–	–	
pN2-3 (HPV neg)	–	–	–	
		8th Edition		
Surgery alone (pN1)	42	64	2.47 (1.09–5.58)	–
Multimodality treatment/clinical trial:				–
pN2-3	58‡	42	6.86 (3.70–12.71)	
pN2-3 (HPV pos)	–	–	–	
pN2-3 (HPV neg)	–	–	–	
		8th Edition + HPV		
Surgery alone (pN1)	42	64	2.47 (1.09–5.58)	2.53 (1.11–5.75)
Multimodality treatment/clinical trial:				
pN2-3	–	–	–	–
pN2-3 (HPV pos)	30	51	4.60 (2.13–9.92)	3.94 (1.80–8.65)
pN2-3 (HPV neg)	28	32	10.14 (5.10–20.17)	8.35 (4.09–17.06)

* According to EAU (European Association of Urology) and NCCN Guidelines.
† Adjusted for patient age and T stage.
‡ After revision 15% of patients (73% to 58%) with node-positive disease were de-intensified to curative surgery alone instead of adjuvant treatment.

DISCUSSION

In this study we validated the 8th TNM staging system in patients with penile cancer treated with surgery. Of those with high risk primary disease 80% underwent inguinal LND and the median number of removed lymph nodes was 19 (IQR 13–24). Thus, our study included a surgically treated population with a high rate of compliance with the NCCN guidelines,

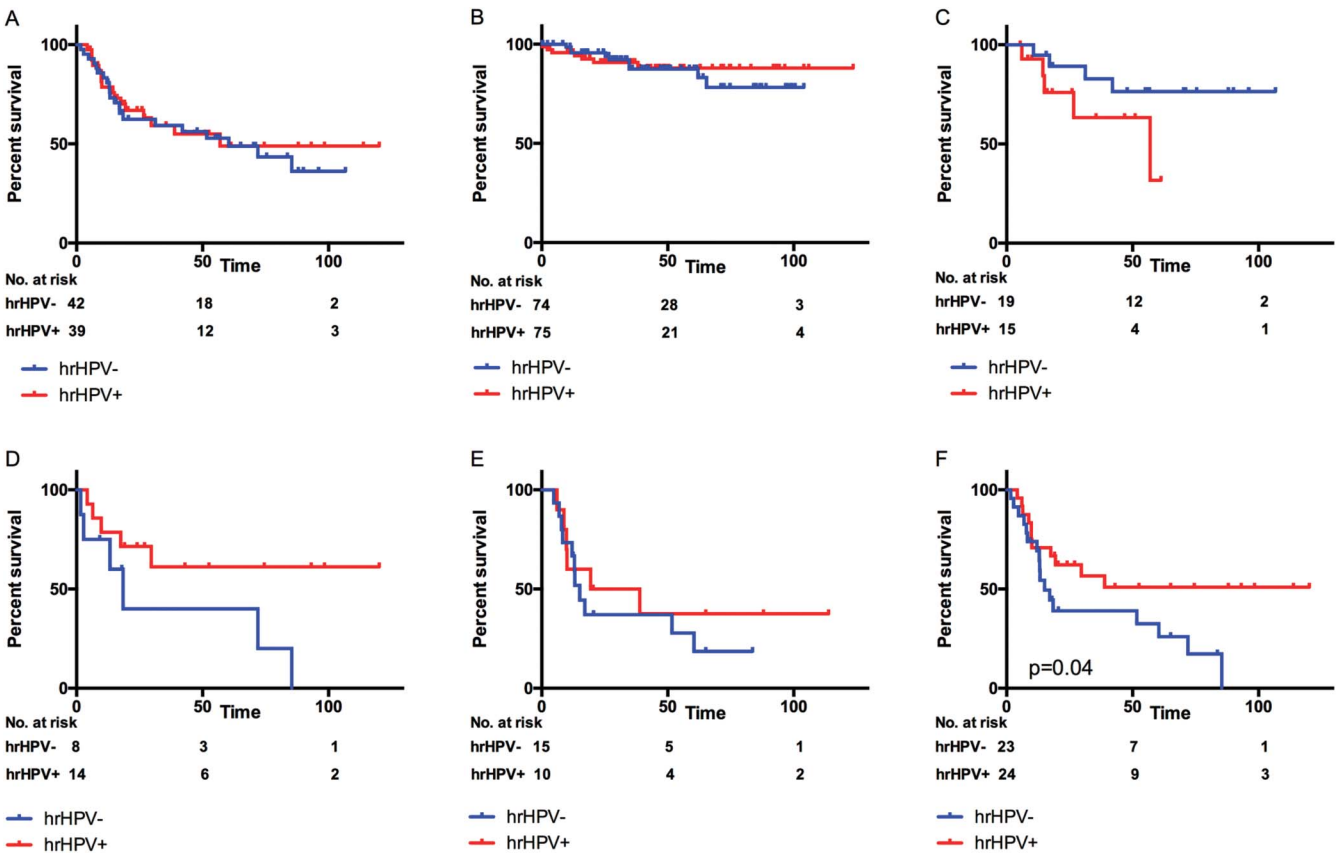

Figure 2. Kaplan-Meier OS curves in CMC cohort by hrHPV status. *A*, category N+. *B*, category pN0. *C*, category pN1. *D*, category pN2. *E*, category pN3. *F*, category pN2-3.

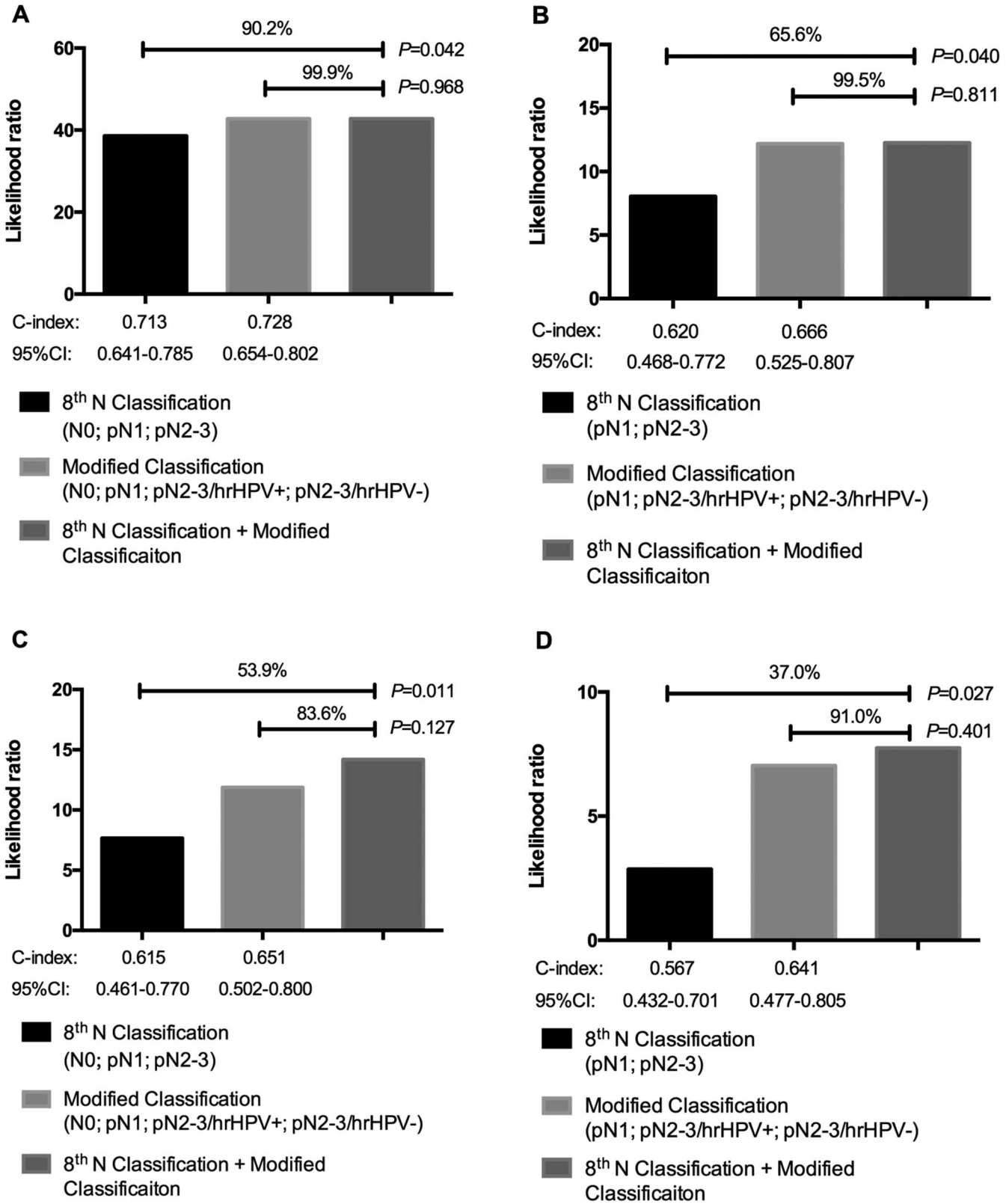

Figure 3. Likelihood chi-square test of modified classification vs 8th edition N classification for OS. *A*, all CMC cohort cases. *B*, CMC cohort node positive cases. *C*, all MCC cohort cases. *D*, MCC cohort node positive cases.

reinforcing the value of the 8th staging system in state-of-the-art clinical practice. Most importantly, by incorporating hrHPV status with N stage we identified a patient subgroup (pN2-3 and hrHPV negative) with poor outcomes after surgery. The modified classification would help not only with prognostication but it could also serve as a strong candidate for predicting the treatment response. Different treatment approaches may be developed because different progression mechanisms were observed.[10]

Significant effort has been made to improve the TNM staging system for rare cancers since it is the most widely used prognostic estimation tool for these malignancies. Our study confirmed the value of the 8th TNM staging system after modification. The C-index of the stage group improved from 0.737 to 0.755 after revision. As most of our patients underwent surgical LN staging, the prognostic influence of LN status has surpassed that of the pT2/pT3 modification. However, we still observed slightly better stratification using univariate Kaplan-Meier analysis for the 8th pT2/pT3 compared with the 7th edition.

The pN1/pN2 modification generated more instructive prognostic implications for clinical practice. 1) A more equally distributed HR was observed for the 8th N staging system (HR pN1 2.47, pN2 5.30 and pN3 8.50 vs N0, $p < 0.001$). 2) A slight survival increase was observed in the pN1 category after revision. The cause of this finding may not be that more treatment was administered in patients with 2 LNMs according to the 7th TNM staging system since no patient with 2 unilateral inguinal LNMs underwent adjuvant therapy in the CMC cohort. Furthermore, we found a similar lymph node ratio (number of positive nodes/number of examined nodes) in patients with 1 and with 2 unilateral LNMs (median lymph node ratio 0.081 vs 0.085), suggesting that the true metastatic burden was similar in the 2 groups. This observation was also reported by Li et al, who found a significant survival difference between patients with 1 or 2 vs 3 unilateral inguinal LNM in the context of qualified LND (median 21 removed nodes).[14]

Our modification of the N staging system was easy to use as it only incorporates hrHPV stratification in pN2-3 disease. The proposed modification identified a high risk group with extremely poor outcomes after surgery. Its predictive accuracy was confirmed in the CMC cohort and externally validated in the MCC cohort. Furthermore, the hrHPV positive rate was 50% in the CMC cohort and 26% in the MCC cohort. The wide range of HPV infection rates indicated distinct patterns of carcinogenesis and only the anatomy based N staging system is likely to be influenced by the HPV prevalence, which could be compromised after generalizing the HPV vaccine.[15] Finally, Ottenhof et al found that immunological contexts were different in HPV negative and HPV positive tumors.[10] A different mutational pattern of tumor suppressor genes as well as a different pattern of methylation was also observed between these 2 subgroups.[16,17] Given the profound predictive value of HPV in head and neck squamous cell carcinoma,[18] the newly proposed modified N staging system may be used to guide inclusion criteria in adjuvant therapy trials.

Our study has certain strengths. 1) Qualified surgery as recommended by the recent NCCN guidelines was performed in the majority of patients. This provided accurate staging information and improved the validity of the N category. 2) Because 5 or more penile cancer cases per year have been treated at only 1.7% of centers in America, the disease has been poorly evaluated and heterogeneous management was commonly observed in previous studies.[19] Our study included high volume centers so that we recruited 123 node positive cases, nearly twice the number in previous studies, providing urgently needed data (supplementary table 1, https://www.jurology.com). 3) Finally, the HPV evaluation offered more biological information for prognostication and improved the N staging system using a new perspective which to our knowledge has been overlooked in previous studies.

The major limitation lies in the retrospective nature of the study. Although statistical significance was observed when applying the LR chi-square test, further validation is needed in prospective trials such as the InPACT (International Penile Advanced Cancer Trial).[20] The stratification of pN1 and pN2-3 was also used in InPACT to randomize subsequent treatment after LND. Therefore, it will be interesting to test the modified N classification proposed in this study in such trials. Moreover, the selection bias due to including tertiary centers may have contributed to a relatively smaller proportion of patients with early stage disease.

CONCLUSIONS

The newly released 8th edition of the AJCC staging system for penile cancer showed better discriminative ability for prognostic stratification than the 7th edition, especially for the N category. Further modification by adding hrHPV status would improve the prognostic stratification of the current system. This finding awaits validation in large cohorts.

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