

Validation of predictors for lymph node status in penile cancer: Results from a population-based cohort

X. Melody Qu, MD MPH¹; D. Robert Siemens, MD²; Alexander V. Louie, MD, MSc PhD³; Darwin Yip, MD¹; Aamer Mahmud, MD¹

¹Department of Oncology, Queen's University, Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON; ²Department of Urology, Queen's University, Kingston General Hospital, Kingston, ON; ³Department of Radiation Oncology, Western University, London Health Sciences Centre, London, ON; Canada

Cite as: *Can Urol Assoc J* 2018;12(4):119-25. <http://dx.doi.org/10.5489/cuaj.4711>

Published online December 22, 2017

See related commentary on page 126

Abstract

Introduction: The ability to predict lymph node (LN) status is essential in the management of men with localized squamous cell carcinoma (SCC) of the penis. There has been limited external validation of available risk stratification tools, particularly in routine clinical care. The objective of this study was to evaluate the predictive variables of LN metastases within a large population-based cohort of patients.

Methods: In this population-based cohort study, surgical pathology reports were linked to the population-based Ontario Cancer Registry to identify all patients who were diagnosed with penile cancer in Ontario, Canada. Multivariable analyses were performed to evaluate predictive variables for LN involvement. Three contemporary risk stratification schemes used to predict LN status were analyzed by logistic regression.

Results: The study included 380 localized penile SCC cases treated between 2000 and 2010. Sixty-three (17%) had pathologically confirmed LN metastases. Among these, 35 (56%) were diagnosed within three months of the initial penile SCC diagnosis and these patients had a worse five-year disease-specific survival (43%; 95% confidence interval [CI] 26–64) compared to patients who were diagnosed at a delayed LN dissection. On multivariable analysis, age (odds ratio [OR] 0.68; 95% CI 0.52–0.88), pathological stage (\geq pT1b; OR 3.32; 95% CI 1.38–8.01), and tumour grade (Grade 2 OR 2.98; 95% CI 1.26–7.62; Grade 3 OR 3.97; 95% CI 1.32–11.9) were associated with an increased risk of LN metastases. Candidate risk stratification schemes demonstrated moderate to good property, with C-statistics ranging from 0.662–0.747.

Conclusions: Using a population-based cohort of penile cancer patients with a relatively low proportion of patients with pathologically confirmed LN involvement, we confirm and externally validate the importance of age, stage, and grade of the primary tumour in predicting nodal status.

Introduction

The presence of lymph node (LN) metastases is highly prognostic in patients with squamous cell carcinoma (SCC) of penis.¹ In clinically LN-negative patients, an early or prophylactic dissection may confer a survival benefit compared to a delayed or therapeutic dissection at the time of recurrence.^{2–4} However, inguinal LN dissections are associated with a significant morbidity,⁵ with reported complications as high as 25%.^{6,7} Despite the potential benefits of an early LN dissection, it may be viewed as overtreatment in the 75–90% of patients without micrometastasis.⁸

Factors associated with an increased risk of LN metastases in penile cancer include advanced pathological tumour (pT) stage, higher grade, presence of lymphatic and/or vascular invasion, and certain histological subtypes.¹ Solsona et al originally described a predictive model, stratified by stage and grade, which was based on a cohort of 66 patients and was prospectively validated by the same group with a cohort of 37 patients.^{9,10} To our knowledge, three contemporary risk stratification schemes based on these factors have been proposed to estimate the risk of LN status in these patients (Table 1). The schemes endorsed by European Association of Urology (EAU), International Consultation on Urological Diseases (ICUD), and National Comprehensive Cancer Network (NCCN) are based on the literature synthesis.^{9,11–14} Potential limitations of these tools include the small number of cases used to create stratifications and a lack of external validation.^{11,14,15}

Population-based cohorts serve as the ideal populations to be used for external validation of stratification schemes, as they provide larger sample sizes, capture all patients in routine clinical practice, and minimize sources of selection and referral biases inherent to single-institution studies. Thus, the objective of the present study is to use a large population-based cohort to evaluate these predictive variables in routine clinical practice and compare these available risk stratification schemes that estimate risk of LN metastasis in penile SCC.

Table 1. Contemporary risk stratification schemes for lymph node metastases in penile cancer

Risk groups			
Low	Intermediate	High	
ICUD ¹¹	pTis , pTa,pT1, no LVI	pT1G2,T2G1, no LVI	pT2-4, G2-3, LVI
EAU ^{12,13}	pTis, pTa,pT1 G1	pT1 G2	pT1G3, pT2-pT3
NCCN ¹⁴	Tis,Ta T1a	T1b	≥T2, or G3 or G4

EAU: European Association of Urology; ICUD: International Consultation on Urological Diseases; NCCN: National Comprehensive Cancer Network.

Methods

Patient population

In this Queen’s University health sciences and affiliated teaching hospitals research ethics board-approved study, all patients diagnosed with penile cancer between January 1, 2000 and December 31, 2010 were identified from the Ontario Cancer Registry (OCR). Ontario is a province of Canada with a population of 13.5 million people and a single-payer universal health insurance program, and the OCR captures diagnostic and demographic information on approximately 98% cases of cancer within the province.¹⁶ Eligible patients were identified using international classification of diseases,¹⁰th revision (ICD-10) C.60-malignant neoplasm of penis codes. All available corresponding pathology reports were obtained through Cancer Care Ontario (CCO). The date of diagnosis, vital status, cause of death, and date of death were obtained from OCR. The following patients were excluded: non-SCC histology, initial presentation with an unknown primary, and clinical primary penile tumour without pathological confirmation of malignancy.

Pathology data

All pathology reports were reviewed by two physicians, audited by a third, with discrepancies settled via consensus. Date of diagnosis based on pathology reports was used. All surgical procedures that occurred within the three months of diagnosis were considered as initial management that provided pathological staging information according to the American Joint Committee on Cancer (AJCC) 7th edition. Cases with pT1 lesion and no documentation of lymphovascular invasion status within the abstracted pathology reports were assigned a stage of pT1a for the purposes of this analysis. Given the lack of clinical LN staging in this dataset, patients who did not undergo upfront surgical nodal staging (pNx) were considered N0 for overall staging and compared to those with pathologically confirmed LN metastases.

Treatment data

Details on collecting treatment information has been previously described.¹⁷ In brief, the information on surgical procedures was obtained from pathology reports. The radiation record was obtained from CCO and matched with OCR based on a unique identifier. Chemotherapy record was not collected.

Statistical analysis

Time-to-event analyses were defined from the date of pathological diagnosis and were estimated using the Kaplan-Meier method. Overall survival (OS) was censored on December 31, 2012, whereas disease-specific survival (DSS) was censored on December 31, 2010, as there is a two-year lag on available data for causes of death. LN recurrence was censored on December 31, 2010. The reverse Kaplan-Meier method was used to estimate the length of followup.

Univariable logistic regression was used to identify associations between clinical and pathological variables with LN status. Continuous variables, such as tumour thickness and tumour size, were dichotomized using cutpoints reported in the literature. A p value of 0.05 was considered to be statistically significant. Variables that were found to be significantly associated with nodal disease on univariable analysis were further examined in multivariable analysis through backward elimination. Both logistic regression models and Cox proportional hazard models were fitted and compared by considering LN positivity as event only (yes/no) and time-to-event outcome, respectively. The final model was built by selection for variables based on previous clinical dogma and statistical properties. Kernel estimation was used to examine the hazard rate over time, as well as through the assessment of proportional hazard assumption. C-statistics were used as a global measure of model discrimination.¹⁸ The C-statistic from the Cox proportional hazard model was obtained by the method described by Liu et al¹⁹

We assessed three contemporary risk stratification schemes in this patient population.^{9,11-14} The logistic regression method was chosen, as the stratification schemes were originally derived or adapted from studies using logistic regression. We used various risk stratification schemes to estimate the risk of nodal disease at three months, one year, two years, and overall for each risk groups to assess calibration. The C-statistic was used to compare these schemes. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc).

Results

Patient characteristics

A total of 533 patients were identified from OCR between January 2000 and December 2010 using the ICD-10 C.60

code. Of the 469 patients with available pathology reports, 795 unique pathology reports were identified. After applying the exclusion criteria (n=50, ineligible cases; n=35, missing pathology on primary tumour records; n=4, unknown primary with LN metastases), 380 patients were eligible for analysis. A flowchart of the patient cohort selected for final analysis is presented in Supplementary Fig. 1.

Baseline characteristics of patients, stratified by the presence of LN involvement, are summarized in Table 2.

The median followup for all patients was 4.5 years (range 0–10.9), and the five-year DSS and OS were 81% and 59%, respectively.

Seventy-four patients (19%) underwent inguinal nodal surgical procedure, including biopsy only (n=13, 3%), sentinel lymph node biopsy only (n=1, <1%), ipsilateral inguinal LN dissection (n=13, 3%), and bilateral inguinal LN dissection (n=47, 12%). The median number of inguinal nodes removed was 10 (range 1–29). Pelvic nodal dissection was

Table 2. Baseline characteristics and univariable analysis of factors associated with lymph node metastasis

Variables	No pathologic lymph node involvement (N0, Nx) (n=317)	Lymph node positive (≥N1) (n=63)	OR (95% CI)	p
Age (median, range)	69 (26–99)	62 (31–93)		0.0019
Grade				
1	118 (37%)	8 (13%)	1	
2	114 (36%)	31 (49%)	4.01 (1.77–9.10)	0.0009
3	49 (15%)	20 (32%)	6.28 (2.49–14.59)	<0.0001
Missing	36 (11%)	4 (6%)		
Vascular invasion				
Absent	137(43%)	22 (35%)	1	
Present	26 (8%)	14 (22%)	3.35 (1.52–7.39)	0.003
Missing	154 (49%)	27 (43%)		
Lymphatic invasion				
Absent	111 (35%)	16 (25%)	1	
Present	22 (7%)	11 (17%)	3.47 (1.42–8.48)	0.006
Missing	184 (58%)	36 (57%)		
Perineural invasion				
Absent	24 (8%)	10 (16%)	1	
Present	24 (8%)	14 (22%)	1.40(0.52–3.77)	0.51
Missing	269(85%)	39 (62%)		
pT stage				
pTa/pTis	22 (7%)	1(2%)	0.63 (0.076–5.23)	0.67
pT1a	125 (39%)	9 (14%)	1	
pT1b	25 (8%)	6 (10%)	3.33 (1.09–10.2)	0.035
pT2	61 (19%)	18 (29%)	4.10 (1.74–9.65)	0.001
pT3/4	36 (11%)	15(24%)	5.79 (2.34–14.3)	0.0001
pTx	48 (15%)	14 (22%)		
Histological subtype				
SCC NOS	276 (87%)	56(89%)	1	
Verrucous	31 (10%)	2 (4%)	0.32 (0.074–1.37)	0.12
Basaloid/spindle	6 (2%)	5 (8%)	4.11 (1.21–13.9)	0.023
SCC in situ	4 (1%)	0 (0%)	<0.001	0.99
Tumour size				
≤3 cm	103(32%)	14(12%)	1	
>3 cm	75(24%)	22(35%)	2.16(1.04–4.49)	0.040
Missing	139(44%)	27(43%)		
Tumour thickness				
≤5 mm	28 (9%)	4 (6%)	1	
>5 mm	57 (18%)	10 (16%)	1.23 (0.35–4.26)	0.75
Missing	239 (73%)	49 (78%)		

CI: confidence interval; OR: odds ratio; NOS: not otherwise specified; SCC: squamous cell carcinoma.

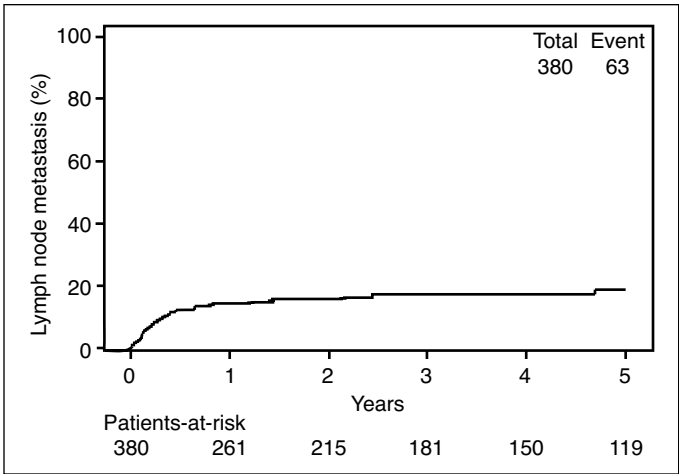


Fig. 1. Time to lymph node metastasis from date of pathological diagnosis.

conducted in 20 patients (5%). The median number of pelvic nodes removed was six (range 2–17).

Sixty-three patients (17%) had pathological evidence of LN metastases (Fig.1). Among these, 35 (56%) were diagnosed within three months of the primary diagnosis (early) and 28 (44%) beyond three months of the initial diagnosis (late), with a median time of nine months (range 3–106). The five-year DSS for patients with an earlier diagnosis of LN positivity was significantly worse (43%; 95% confidence interval [CI] 26–64) than patients with either a later diagnosis (65%; 95% CI 49–87; logrank $p=0.01$) or without nodal confirmation on pathology (N0, Nx, 87%; 95% CI 83–91; logrank $p<0.0001$) (Fig. 2). The LN distribution of malignancy were as follows: 90% ($n=57$) inguinal, 3% ($n=2$) pelvic, and 6% both nodal regions ($n=4$). Ninety percent ($n=57$) of LN positive cases occurred within two years after primary diagnosis and the five-year LN failure rate was 18%.

Prognostic factors of LN status

On univariable analysis, younger age (≤ 60 years), higher tumour grade, vascular invasion, lymphatic invasion, pathologic T stage, SCC variants (basaloid/spindle) and tumour size $>3\text{cm}$ were found to be significant predictors for the presence of LN metastases (Table 2).

In the multivariable analyses, the models from logistic regression confirm that patients with a pathological tumour (pT) stage of at least pT1b (odds ratio [OR] 3.32; 95% CI 1.38–8.01) and higher grade (Grade 2 OR 2.98; 95% CI 1.26–7.62; Grade 3 OR 3.97; 95% CI 1.32–11.9) were found to have an increased risk of LN metastases. Younger age remained significantly associated with an increased risk of LN metastasis, with an OR for every 10 years of 0.68 (95% CI 0.52–0.88; $p=0.0035$). The time-to-event analyses in the Cox proportional hazard model demonstrated similar results (Table 3).

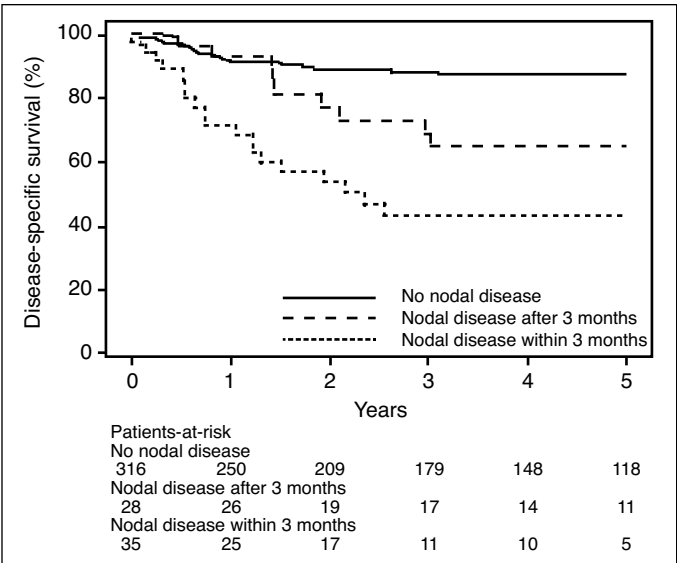


Fig. 2. Disease-specific survival for patients with no lymph node metastases (N0/NX) and those with pathological positive lymph nodes ($\geq N1$) within three months or after three months from diagnosis of the primary penile cancer.

Validation of risk stratification schemes

The performance of the three contemporary risk stratification schemes assessed in this study cohort is summarized in Table 4. The ORs for LN risk of the intermediate-risk group ranged from 1.60–2.94 and 4.94–6.89 for the high-risk group when compared with the low-risk group. All published risk stratification schemes demonstrated moderate to good C-statistics without statistically significant difference among them (Table 5). There was a consistent trend of decreasing performance in the assessment of later LN recurrence among all risk tools. Although this suggests limited utility in this cohort, this finding could be due to several methodological factors, including the small numbers of cases with a delayed diagnosis.

Discussion

As the presence of LN metastases is highly prognostic in SCC of the penis, we sought to externally validate clinico-pathological variables associated with published risk stratification schemes using a population-based cohort that represents care in a real-world setting. Our findings confirm the ability of age, pathological stage, and grade of the primary cancer to predict for LN status and, in addition, we demonstrate the good discrimination of available stratification tools. In this cohort of all men treated with SCC of the penis from 2000–2010, 56% of pathologically positive LNs were diagnosed within three months and these men had an inferior DSS than those diagnosed later, likely due to a higher burden of LN metastases at presentation. Considering the rarity of penile SCC, the use of population cohorts for external validation of risk stratification models is ideal given the larger number of patients, reflection

Table 3. Multivariable analysis of predictors for lymph node metastases

	Logistic model		Cox model	
	OR (95% CI)	p	HR (95% CI)	p
≥pT1b	3.32(1.38–8.01)	0.0075	3.35 (1.50–7.48)	0.0032
Grade				
Grade 1	1 (reference)		1 (reference)	
Grade 2*	2.98 (1.26–7.62)	0.023	3.14 (1.32–7.49)	0.0098
Grade 3*	3.97 (1.32–11.9)	0.014	3.67 (1.38–9.73)	0.0090
Age (increase q10 y)	0.68 (0.52–0.88)	0.0035	0.74 (0.60–0.91)	0.0049

*Grade 2 and 3 were not significantly different from each other. CI: confidence interval; HR: hazard ratio; OR: odds ratio; q10 y: every 10 years.

of real-world outcomes, and heterogeneity of case mix within academic and community practices.

The present study builds on the existing literature on risk prediction of LN positivity in penile SCC. The contribution of pathological variables to predict for LN status, based on previously published risk tools, have been previously evaluated in a smaller cohort of 175 patients, with C-statistics ranging from 0.632–0.697.¹⁵ However, some authors have suggested that the available tools lack sufficient predictive accuracy based on the definition by Collinson, whereby a C-statistic of 0.5–0.7 is considered low, 0.7–0.9 moderate and >0.9 highly accurate.^{15,20,21} A nomogram, constructed from eight variables derived from the same cohort of patients achieved a C-statistic of 0.876,²² however, has not been externally validated. We were unable to validate this particular nomogram due to the lack of certain required parameters. The growth pattern is not routinely reported in clinical practice and the clinical nodal status is not available to us, as we are limited by the nature of this registry-based study. Previous work has demonstrated that a prediction model with perfect reliability in risk assessment can only achieve a maximum C-statistic of 0.83;²³ therefore, the models evaluated in this study should be considered as moderate to good in this clinical context when a balance between discrimination and reliability in risk assessment is desired.

The reliability of estimating the risk of LN involvement is important for clinicians in determining the need of LN dissection, as it is central to the decision-making process, balancing the potential benefits (particularly with non-palpable lymph nodes) and risks of surgery. This present work can be considered as a calibration of the available models, which has been

largely overlooked in penile cancer literature. The reported risk of nodal involvement in penile SCC in the literature varies, a finding limited by the small sample sizes.^{9,24–27} In contrast, this population-based cohort captured a broad range of stages of penile cancer in a large population where cancer data is recorded and accurate for 98% of the residents.¹⁶ The LN risk observed in this cohort was lower than in several published series: even in the high-risk group there was a point estimate of 27% in contrast to the 46–83% range in previous reports.^{10,15} Although this observation could be secondary to a suboptimal rate of LN dissection or biopsy in this series, it is also possible that our results are more consistent with disease characteristics presenting in routine clinical care as compared to those in more specialized referral practices.

There were some candidate variables that were not found to be predictive of LN metastases in our multivariable analyses. As an example, there are conflicting reports of the significance of the primary tumour thickness of ≤5 mm vs. >5 mm.^{25,28} Our data did not find a significant association between tumour thickness and LN metastases, although this could be related to an under-reporting of this pathological characteristic in this cohort. Lymphovascular invasion has previously been shown to have an independent prognostic value in two large cohorts by Zhu et al (n=110) and Ficarra et al (n=175).^{22,25,29} This was reflected in AJCC 7th edition separating pT1b from pT1a based on lymphovascular invasion or high grade. Although lymphovascular invasion in our multivariable models was not found to be an independent factor predicting for LN status, this is potentially secondary to its incorporation into the staging of pT1 tumours (pT1b), with less relevance for those at higher pathological stage. Finally, we did demonstrate an association of older age with a decreased risk of LN metastases. This disparate finding may be secondary to confounding by indication, where older patients could have been managed less aggressively with LN dissection. This is supported by our previous findings that older patient had worse DSS in this cohort.¹⁷

In this cohort, we found that patients who were found to have pathologically confirmed LN metastases at the time of diagnosis (within three months) have significantly worse survival outcome compare to patients who were found to have LN failure beyond three months. We previously reported that LN involvement is one of the most important prognostic factors for DSS, with a hazard ratio (HR) of 4.7 (95% CI 2.8–7.7) on multivariable analysis.¹⁷ Earlier time to

Table 4. Odds ratio for lymph node metastases by contemporary risk stratification schemes

	n*	Low	Intermediate		High	
		OR	OR (95% CI)	p	OR (95% CI)	p
ICUD ¹¹	223	1	1.60 (0.31–8.42)	0.58	6.20 (1.41–27.27)	0.016
EAU ^{12,13}	306	1	2.41 (0.65–8.96)	0.19	6.89 (2.38–20.0)	0.0004
NCCN ¹⁴	326	1	2.94(0.31–27.6)	0.35	4.94 (2.38–10.3)	<0.0001

*Number of patients with sufficient information to be stratified according to each scheme.

CI: confidence interval; EAU: European Association of Urology; ICUD: International Consultation on Urological Diseases; NCCN, National Comprehensive Cancer Network; OR: odds ratio.

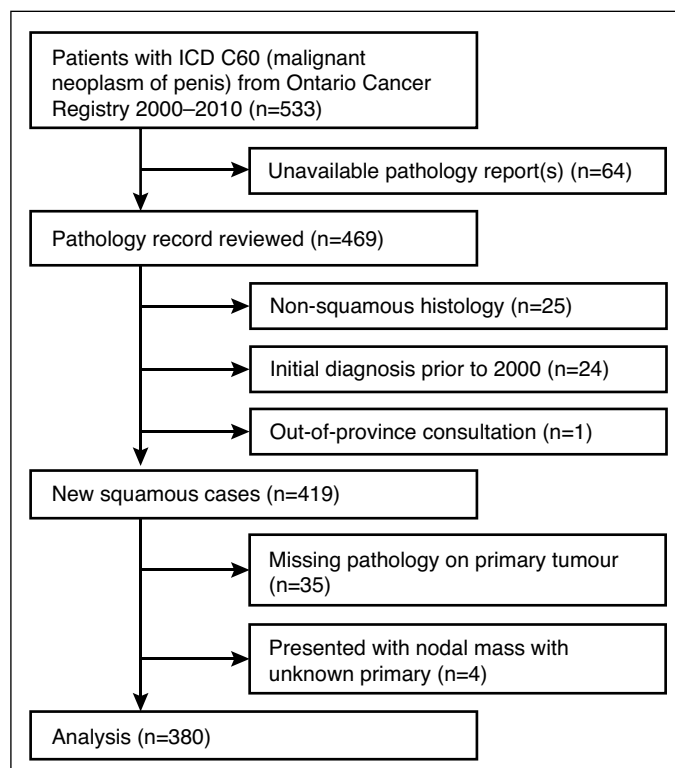
Table 5. Validation and calibration of lymph node status risk stratification schemes for men with penile cancer

	Overall	Nodal recurrence risk (n, %)			C-statistic (95% CI)
	(n, %)	Low	Intermediate	High	
International Consultation on Urological Diseases(2010) ¹¹					
Patients	223	33	64	126	
pN+ occur within 3 months	26 (12%)	0 (0%)	2 (3%)	24 (19%)	0.709 (0.659–0.799)
pN+ occur within 1 year	38 (17%)	1 (3%)	4 (6%)	33 (26%)	0.688 (0.624–0.751)
pN+ occur within 2 years	39 (17%)	1 (3%)	4 (6%)	34 (27%)	0.691 (0.628–0.953)
pN+ ever occurred	44 (20%)	2 (6%)	6 (9%)	36 (29%)	0.662 (0.594–0.730)
European Association of Urology (2004–2015) ^{12,13}					
Patients	306	86	57	163	
pN+ occur within 3 months	30 (10%)	0 (0%)	2 (4%)	28 (17%)	0.733 (0.689–0.776)
pN+ occur within 1 year	44 (14%)	2 (2%)	4 (7%)	38 (23%)	0.703 (0.648–0.759)
pN+ occur within 2 years	46 (15%)	3 (4%)	4 (7%)	39 (24%)	0.693 (0.634–0.752)
pN+ ever occurred	51 (17%)	4 (5%)	6 (11%)	41 (25%)	0.674 (0.613–0.734)
National Comprehensive Cancer Network (2015) ¹⁴					
Patients	326	157	6	163	
pN+ occur within 3 months	30 (9%)	1 (1%)	1 (17%)	28 (17%)	0.747 (0.701–0.794)
pN+ occur within 1 year	44 (14%)	5 (3%)	1 (17%)	38 (23%)	0.715 (0.658–0.772)
pN+ occur within 2 years	47 (14%)	7 (5%)	1 (17%)	39 (24%)	0.697 (0.637–0.758)
pN+ ever occurred	52 (16%)	10 (6%)	1 (17%)	41 (25%)	0.675 (0.612–0.738)

LN metastases in this cohort was likely indicative of more aggressive disease and more advanced stage at presentation. Unfortunately, this particular dataset does not include clinical or radiological assessment of LN status at the time of original presentation. The median time for those men with a more delayed documentation of LN metastases was nine months ranging to 106 months. We have observed that 90% of nodal disease occurred within the first two years of the initial diagnosis, reinforcing the need for close followup during this time period if expectant management is planned.

The limitations include the inherent retrospective nature of this study and use of an administrative database. There was lack of information in terms of clinical history, comorbid conditions, clinical LN status (palpable inguinal lymphadenopathy) and patient's willingness to undergo certain treatments. A small proportion of patients who were diagnosed with metastatic disease clinically without tissue confirmation may be misclassified. The primary sources of information were the pathology reports and the provincial registry database, which could be subject to a risk of missing cases due to miscoding. There were a small proportion of pathology reports that were missing in the registry. In addition, the completeness and accuracy of these findings are related to the quality of the pathology reports. Incomplete pathological reporting in this cohort might limit the power to detect independent association of other features with the risk of nodal disease. The quality of pathology reports on penile cancer in Ontario has been reported and there is a trend of improvement.¹⁷ The presence of LN metastases reported was likely an underestimate of the true rate, as some patients may not have had biopsy, were not surgical candidates, and/or were

managed on clinical grounds only. Despite these potential criticisms, the present study represents one of the larger series of SCC penile cancer to date and provides credence to the generalizability of availability risk stratification models to routine clinical use.

**Supplementary Fig. 1.** Flowchart of study.

Conclusion

We compared and validated previously published risk stratification schemes for predicting LN risk among patients diagnosed with SCC of the penis using a large population-based cohort. All compared favourably. The tumour grade and pathological T stage in this cohort were the most informative factors predicting presence of LN status and validates their utility in routine clinical care.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

References

1. Ficarra V, Akduman B, Bouchot O, et al. Prognostic factors in penile cancer. *Urology* 2010;76:S66-73. <https://doi.org/10.1016/j.urology.2010.04.008>
2. Leijte JA, Kirrander P, Antonini N, et al. Recurrence patterns of squamous cell carcinoma of the penis: Recommendations for followup based on a two-centre analysis of 700 patients. *Eur Urol* 2008;54:161-8. <https://doi.org/10.1016/j.eururo.2008.04.016>
3. Ornellas AA, Kinchin EW, Nobrega BL, et al. Surgical treatment of invasive squamous cell carcinoma of the penis: Brazilian National Cancer Institute long-term experience. *J Surg Oncol* 2008;97:487-95. <https://doi.org/10.1002/jso.20980>
4. Kirrander P, Andren O, Windahl T. Dynamic sentinel node biopsy in penile cancer: Initial experiences at a Swedish referral centre. *BJU Int* 2013;111:E48-53. <https://doi.org/10.1111/j.1464-410X.2012.11437.x>
5. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: The role and technique of lymph node dissection. *BJU Int* 2001;88:473-83. <https://doi.org/10.1046/j.1464-410X.2001.00379.x>
6. Koifman L, Hampl D, Koifman N, et al. Radical open inguinal lymphadenectomy for penile carcinoma: Surgical technique, early complications and late outcomes. *J Urol* 2013;190:2086-92. <https://doi.org/10.1016/j.juro.2013.06.016>
7. Yao K, Tu H, Li YH, et al. Modified technique of radical inguinal lymphadenectomy for penile carcinoma: Morbidity and outcome. *J Urol* 2010;184:546-52. <https://doi.org/10.1016/j.juro.2010.03.140>
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29. <https://doi.org/10.3322/caac.21254>
9. Solsona E, Iborra I, Ricos JV, et al. Corpus cavernosum invasion and tumour grade in the prediction of lymph node condition in penile carcinoma. *Eur Urol* 1992;22:115-8. <https://doi.org/10.1159/000474736>
10. Solsona E, Iborra I, Rubio J, et al. Prospective validation of the association of local tumour stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. *J Urol* 2001;165:1506-9. [https://doi.org/10.1016/S0022-5347\(05\)66337-9](https://doi.org/10.1016/S0022-5347(05)66337-9)
11. Heyns CF, Fleshner N, Sangar V, et al. Management of the lymph nodes in penile cancer. *Urology* 2010;76:S43-57. <https://doi.org/10.1016/j.urology.2010.03.001>
12. Solsona E, Algaba F, Horenblas S, et al. EAU guidelines on penile cancer. *Eur Urol* 2004;46:1-8. <https://doi.org/10.1016/j.eururo.2004.03.007>
13. Hakenberg O, Comperat E, Minhas S, et al. Guidelines on penile cancer. European Association of Urology; 2015. Available at http://uroweb.org/wp-content/uploads/12-Penile-Cancer_LR1.pdf. Accessed June 15, 2015.
14. National Comprehensive Cancer Network. Penile Cancer (Version 3.2015). 2015. Available at http://www.nccn.org/professionals/physician_gls/PDF/penile.pdf. Accessed June 6, 2015.
15. Novara G, Artibani W, Cunico SC, et al. How accurately do Solsona and European Association of Urology risk groups predict for risk of lymph node metastases in patients with squamous cell carcinoma of the penis? *Urology* 2008;71:328-33. <https://doi.org/10.1016/j.urology.2007.09.055>
16. Clarke EA, Marrett LD, Krieger N. Cancer registration in Ontario: A computer approach. In: Jensen OM, Parkin DM, MacLennan R, eds. *Cancer Registration Principles and Methods*. Lyon, France: IARC; 1991. p. 246-57.
17. Mahmud A, Qu X, Yip D, et al. The patterns of practice and outcomes of penile cancer in Ontario. *Clin Oncol (R Coll Radiol)* 2017;29:239-47. <https://doi.org/10.1016/j.clon.2016.12.006>
18. Pencina MJ, D'Agostino RB Sr. Evaluating discrimination of risk prediction models: The C statistic. *JAMA* 2015;314:1063-4. <https://doi.org/10.1001/jama.2015.11082>
19. Liu L, Forman S, Barton B. Fitting Cox model using PROC PHREG and beyond in SAS; 2009. Available at <http://support.sas.com/resources/papers/proceedings09/236-2009.pdf>. Accessed June 12, 2015.
20. Collinson P. Of bombers, radiologists, and cardiologists: Time to ROC. *Heart* 1998;80:215-7. <https://doi.org/10.1136/hrt.80.3.215>
21. Ficarra V, Novara G, Boscolo-Berto R, et al. How accurate are present risk group assignment tools in penile cancer? *World J Urol* 2009;27:155-60. <https://doi.org/10.1007/s00345-008-0274-z>
22. Ficarra V, Zattoni F, Artibani W, et al. Nomogram predictive of pathological inguinal lymph node involvement in patients with squamous cell carcinoma of the penis. *J Urol* 2006;175:1700-4. [https://doi.org/10.1016/S0022-5347\(05\)01003-7](https://doi.org/10.1016/S0022-5347(05)01003-7)
23. Diamond GA. What price perfection? Calibration and discrimination of clinical prediction models. *J Clin Epidemiol* 1992;45:85-9. [https://doi.org/10.1016/0895-4356\(92\)90192-P](https://doi.org/10.1016/0895-4356(92)90192-P)
24. Slaton JW, Morgenstern N, Levy DA, et al. Tumour stage, vascular invasion and the percentage of poorly differentiated cancer: Independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. *J Urol* 2001;165:1138-42. [https://doi.org/10.1016/S0022-5347\(05\)66450-6](https://doi.org/10.1016/S0022-5347(05)66450-6)
25. Ficarra V, Zattoni F, Cunico SC, et al. Lymphatic and vascular embolizations are independent predictive variables of inguinal lymph node involvement in patients with squamous cell carcinoma of the penis: Gruppo Uro-Oncologico del Nord Est (Northeast Uro-Oncological Group) Penile Cancer data base data. *Cancer* 2005;103:2507-16. <https://doi.org/10.1002/cncr.21076>
26. Naumann CM, Alkatout I, Al-Najar A, et al. Lymph-node metastases in intermediate-risk squamous cell carcinoma of the penis. *BJU Int* 2008;102:1102-6. <https://doi.org/10.1111/j.1464-410X.2008.07744.x>
27. Hughes BE, Leijte JA, Kroon BK, et al. Lymph node metastasis in intermediate-risk penile squamous cell cancer: A two-centre experience. *Eur Urol* 2010;57:688-92. <https://doi.org/10.1016/j.eururo.2009.07.004>
28. Lopes A, Hidalgo GS, Kowalski LP, et al. Prognostic factors in carcinoma of the penis: Multivariate analysis of 145 patients treated with amputation and lymphadenectomy. *J Urol* 1996;156:1637-42. [https://doi.org/10.1016/S0022-5347\(01\)65471-5](https://doi.org/10.1016/S0022-5347(01)65471-5)
29. Zhu Y, Zhang HL, Yao XD, et al. Development and evaluation of a nomogram to predict inguinal lymph node metastasis in patients with penile cancer and clinically negative lymph nodes. *J Urol* 2010;184:539-45. <https://doi.org/10.1016/j.juro.2010.03.145>

Correspondence: Dr. Aamer Mahmud, Department of Oncology, Queen's University, Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; aamer.mahmud@krcc.on.ca