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ANATOMICAL PATHOLOGY

Histopathological risk scoring system as a tool for predicting lymph nodal metastasis in penile squamous cell carcinoma

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Summary

Penile cancer is an aggressive neoplasm and nodal metastasis is a key factor in determining the outcome. While there is a paucity of tools predicting nodal metastasis, an elective groin node dissection (GND) may cause severe morbidity. We aimed to devise a histopathology-based risk stratification system to predict the risk of nodal metastasis in penile squamous cell carcinoma (SCC) patients.

In this retrospective clinicopathological analysis, consecutive penile SCC patients who had undergone primary surgical treatment with GND from 2007 to 2012 were included. Histopathology slides were reviewed and a histopathological risk scoring system (ranging from 3 to 9) was devised by adding the values assigned to the following pathological variables: tumour grade (1–3); anatomical level of infiltration (1–3); and tumour infiltration pattern (1–3). Three risk groups were created based on histopathological risk scores. Final scores and risk groups were correlated with nodal metastasis, disease-free survival (DFS) and overall survival (OS). We also validated the earlier described prognostic index score (PIS) on our set of patients and compared it to our proposed scoring system.

A total of 162 cases of primary penile resections with unilateral or bilateral groin node dissection were identified during the study period. Sixty-two of 68 patients (91.17%) and 58 of 94 patients (61.7%) had nodal metastasis on upfront and follow-up nodal basin surgeries, respectively. Chances of nodal metastasis for each risk group were as follows: low risk (score 3 and 4) 14.3%; intermediate risk (score 5) 52.6%; and high risk (scores 6–9) 83.7%. Follow-up was available in 145 patients (89.5%). Median follow-up was 21 months (1–96 months). The histopathological scoring system (p=0.04) and risk groups (p=0.005) had a statistically significant correlation with DFS but not with OS. Logistic regression model demonstrated that this stratification system was a good predictor of nodal metastasis. Further, this scoring system had better predictive sensitivity for detecting true node-negative cases and marginally better accuracy in detecting nodal metastasis as compared to the PIS.

Our study demonstrates that the histopathological risk stratification can predict nodal metastasis and aid in planning management of penile cancer patients with judicious implementation of the morbid procedure of GND.

Key words: Penile cancer; lymph node metastasis; penile squamous cell carcinoma; prognosis; risk stratification; scoring system.

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INTRODUCTION

Primary penile cancer, though a rare disease in developed countries, constitutes significant health and social problem in many regions of the developing world.[1,2] It is prevalent in regions such as Asia, Africa, and Latin America.[3,4] Inguinal lymph node metastasis is the single most important factor predicting survival in patients of penile carcinomas.[5] The 5-year survival drastically drops from 95.7% to 51.1% with the involvement of the groin node basin.[6] About 28–60% of patients present with clinically palpable nodes; however, in only 47–85% of these patients the cause of lymphadenopathy is metastasis.[7] Carcinoma of the penis can be treated by wide local excision or by partial or total penectomy. Most authors advocate elective groin node dissection (GND) except for very small and early lesions.[8,9] Studies have advocated prophylactic lymphadenectomy to achieve superior survival rates compared with patients who undergo lymphadenectomy for clinically evident metastatic disease.[10,11] However, the procedure of lymphadenectomy is not entirely innocuous and about half of the patients develop post-operative complications and morbidity.[12,13] Hence, the decision to address the groin requires clinical tools to predict nodal metastasis.[14] We hereby present a histopathological risk scoring system (HRS) designed to aid treating surgeons make decisions regarding the nodal basin in penile cancer patients. We also use this opportunity to compare and validate the earlier described prognostic index score (PIS) as applied to our cohort of patients[15] and compare both risk stratification systems.

MATERIALS AND METHODS

Retrospective histopathology review of patients diagnosed with penile squamous cell carcinoma (SCC) who had undergone primary surgical treatment (penectomy and/or circumcisions) with either upfront or follow-up

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unilateral/bilateral GND was carried out for a period of 6 years from 2007 to 2012. The study was reviewed and approved by the institutional review board and the local ethics committee (TMH IEC Project No.1329).

Histopathology slides of primary resections were reviewed by two pathologists (AS and SM). To avoid observer bias, one of the authors (SM) was blinded to the status of nodal dissection. Clinicopathological data analysed were: clinical nodal stage, tumour grade, anatomical level of infiltration, the tumour infiltration pattern, lymphovascular emboli (LVI), perineural invasion (PNI) and pathological lymph nodal status. Cases were considered clinically node-negative (cN0) when there were no definite palpable nodes and/or no radiological evidence for metastasis. The cases were considered clinically node positive (cN+) when the clinical index of suspicion was high (based on palpable nodes) in combination with radiological evidence suggesting metastasis.

The HRS was constructed by combining the values assigned to the tumour grade (1–3), anatomical level of infiltration (1–3) and tumour infiltration pattern (1–3). The tumour was graded according to the criteria laid down by Velazquez *et al.*[16] as follows. Grade 1: well differentiated cells with minimal cytological atypia, almost indistinguishable from normal squamous cells (Fig. 1A,B). Grade 3: anaplastic cells with little/no keratinisation, scanty/minimal amount of cytoplasm, nuclear enlargement with thick nuclear membrane, nuclear pleomorphism, clumped chromatin, prominent nucleoli, and numerous mitosis (Fig. 1E,F). Grade 2: all cases not included in criteria for grade 1 and grade 3 tumour (Fig. 1C,D). A cut-off of 10% anaplasia was taken as a criterion to label tumour as grade 3. Tumour infiltration patterns and values assigned to them were as follows (Fig. 2A–D): 1, bulbous or broad-based; 2, cords/trabeculae; and 3, single cell infiltration. The pattern was called bulbous or broad-based when the infiltrating front comprised broad/bulbous tumour fronts with the well-defined tumour-host interface (Fig. 2A), whereas it was labelled cords/trabeculae when the infiltrating front formed strands of tumour cells creating finger-like infiltration pattern (Fig. 2B). Single cell infiltration was identified when the infiltrating front had discohesive, singly scattered cells or clusters containing $\leq$5 cells (Fig. 2C,D). The anatomical level of infiltration was assessed differently in the glans and prepuce as described by Chaux *et al.*[15] (Fig. 3A–D). Glans: 1, lamina propria (LP); 2, corpora spongiosa (CS); 3, corpora cavernosa (CC). Prepuce: 1, LP; 2, dartos; 3, skin. CC was identified by virtue of complex, muscular and interanastomosing vessels (Fig. 4A,C), whereas CS was identified by straight and thin vascular spaces with relatively more connective tissue matrix between vascular channels as compared to CC (Fig. 4B,C). The HRS (ranging from 3 to 9) was calculated by adding the individual values assigned to the above parameters. Based on these scores (3–9), for statistical analysis we created 'risk groups' as follows: low risk group (score 3,4), intermediate risk group (score 5), high risk group (score 6–9). The PIS and the corresponding risk categories were also calculated as described previously.[15]

The clinicopathological variable, PIS, HRS and risk groups were correlated with nodal metastasis, disease-free survival (DFS) and overall survival (OS). For statistical analysis SPSS statistics software (version 20.0; IBM, USA) was used. For assessing the association of various pathological and clinical variables, chi-square test, Fisher's exact test, and Pearson's correlation coefficient test were used. The strength of association was calculated using Goodman and Kruskal's gamma (γ). Univariate and multivariate analysis was performed using logistic regression. Both the scoring systems were compared using receiver operating characteristics (ROC) curves. The area under the curve (AUC) and the 95% confidence intervals (CI) were noted. ROC curves were compared to obtain the accuracies (ACC) of both the scoring systems by using StAR software web server, which in turn is based on Mann–Whitney U-statistics for comparing the distribution of values from two samples.[17] The entire tests were applied at 5% significance level. Survival curves were calculated using the Kaplan–Meier method and Cox regression method. Comparisons between curves were performed using the Mantel–Cox (log-rank) test.

RESULTS

Clinicopathologic characteristics, histopathological risk scores, risk groups, nodal metastasis and outcome

A total of 162 cases of partial or total penectomy with unilateral or bilateral GND were reviewed. Histologically confirmed lymph node metastasis was observed in 120/162 cases (74%) studied. Further, 62/68 patients (91.17%) and 58/94 patients (61.7%) had nodal metastasis on upfront and follow-up nodal basin surgeries, respectively. The distribution of pathological nodal stage (pN) for the whole cohort was as follows: N0, 25.9%; N1, 4.3%; N2, 4.9%; and N3,

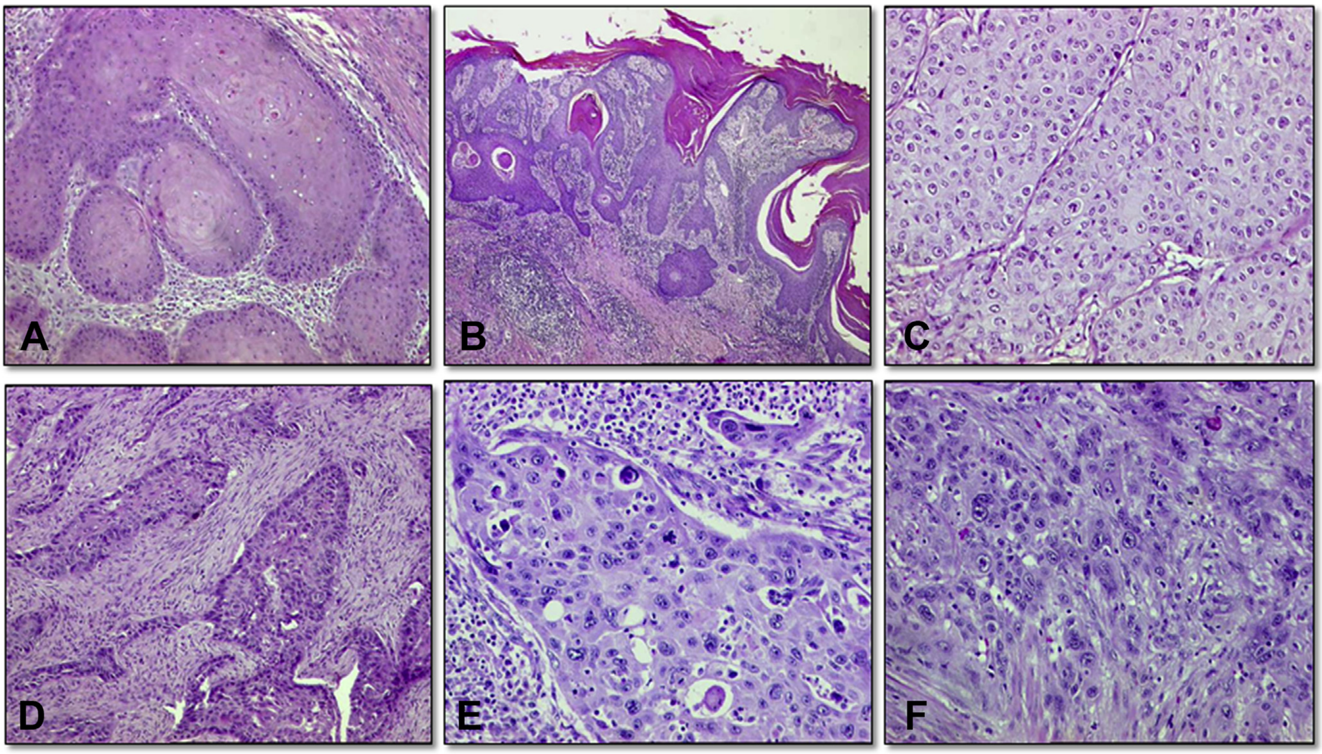

Fig. 1 Grade of tumour (H&E). (A,B) Well-differentiated SCC; striking resemblance to normal squamous cells and minimal atypia. (C,D) Moderately differentiated SCC; abundant keratin and notable atypia. (E,F) Poorly differentiated SCC; prominent nuclear atypia and numerous mitosis.

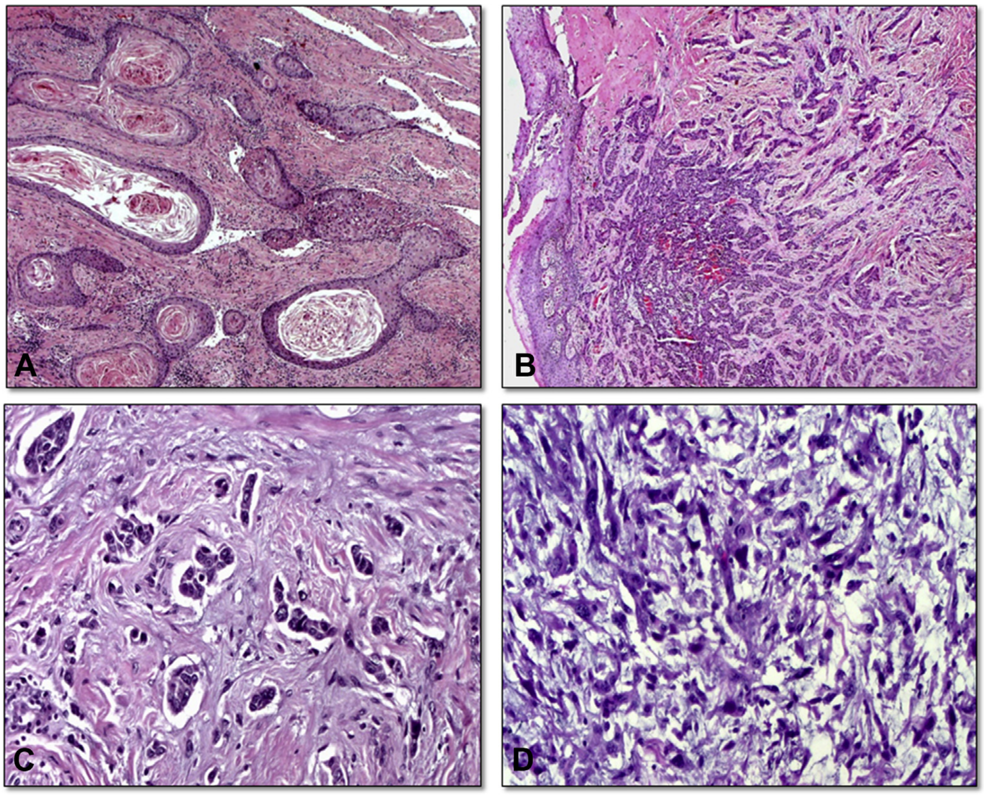

Fig. 2 Tumour infiltration pattern (H&E). (A) Bulbous/broad-based: infiltrating front in the form of broad tumour blocks. (B) Cord/trabeculae: tumour cells with finger-like projections. (C,D) Single cell infiltration: single discohesive tumour cells.

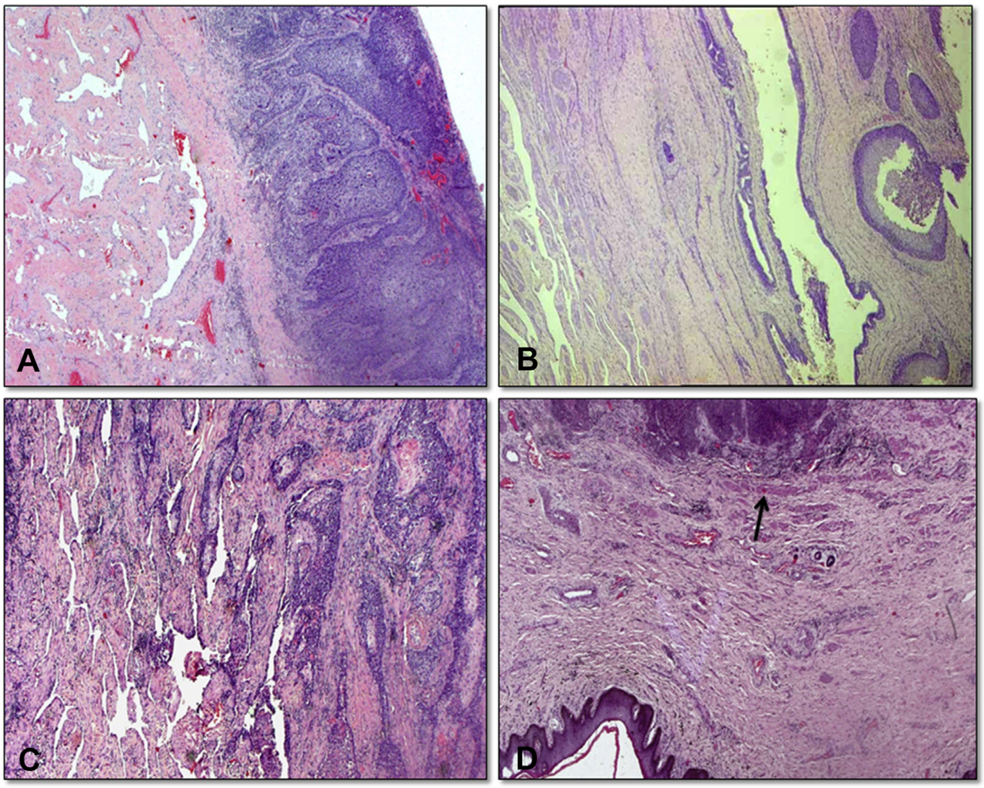

Fig. 3 Anatomical level of infiltration (H&E). (A) Infiltration of lamina propria of glans. (B) Infiltration into corpora spongiosa. (C) Infiltration of corpora cavernosa. (D) Infiltration of the tumour up to dartos muscle (black arrows) in prepuce.

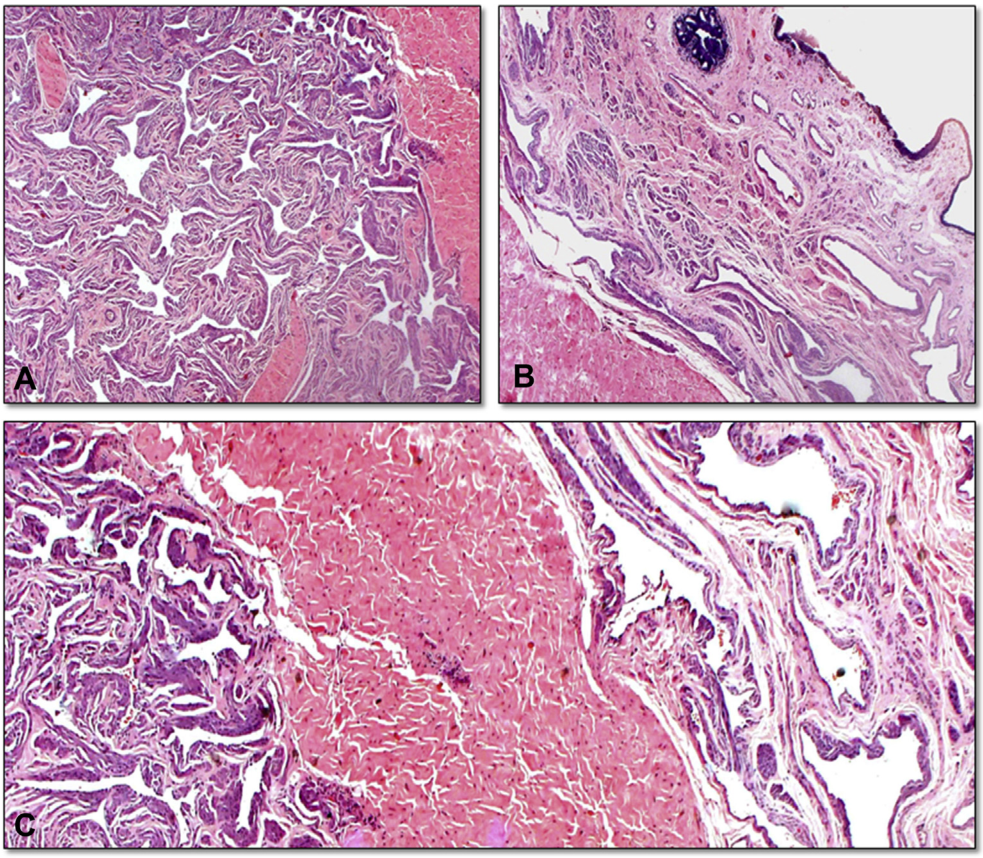

Fig. 4 Normal corpora (H&E). (A) Corpora cavernosa (CC): note the complex, thick and interanastomosing vasculature of CC. (B) Corpora spongiosa (CS): note the vascular channels with abundant intervening fibrous tissue. Urethra and periurethral gland are also seen. (C) CS is seen on the right while CC is seen on the left half of the figure; separating these two is pink fibrous tunica.

64.8%. Clinically 58 cases (35.8%) were suspected to have cN0 disease, while 104 cases (64.2%) were expected to have the cN+ disease.

Each case was scored based on the values assigned to the above mentioned parameters. The distribution of cases for the individual scores were: score 3, 3 (2%); score 4, 11 (7%); score 5, 19 (12%); score 6, 58 (36%); score 7, 49 (30%); score 8, 20 (12%); score 9, 2 (1%). The distribution of cases for the risk groups created based on the scores were: low risk, 14 (9%); intermediate risk, 19 (12%); high risk, 129 (79%).

Presence of nodal metastasis had a statistically significant relationship with tumour grade ($p<0.001$), anatomical level of infiltration ($p=0.002$), the tumour infiltration pattern ($p<0.001$), LVI ($p=0.01$), PNI ($p<0.001$) and the HRS ($p<0.001$) (Tables 1 and 2). Moreover, the HRS significantly predicted pelvic nodal involvement with an increment in the score ($p=0.02$) (Table 2).

The risk groups had a significant correlation with nodal metastasis ($p<0.001$) (Table 3). In addition to predicting the risk of nodal involvement, these risk groups demonstrated a

Table 1 Cross tabulation of histopathological variables with lymph nodal metastasis

Pathological variables	Nodal involvement (n=162)						p value (γ)
	Nodes involved		Nodes uninvolved		Total		
	No. cases (n=120)	% of cases	No. cases (n=42)	% of cases	No. cases (n=162)	% of cases	
Grade of tumour							
Grade 1	3	20	12	80	15	100	<0.001 (0.49)
Grade 2	76	78.4	21	21.6	97	100	
Grade 3	41	82	9	18	50	100	
Anatomical level of infiltration							
Lamina propria	7	41.2	10	58.8	17	100	0.002 (0.47)
Corpora spongiosa/dartos muscle	75	75	25	25	100	100	
Corpora cavernosa/skin epidermis	38	84.4	7	15.6	45	100	
Tumour infiltration pattern							
Bulbous/broad front	13	41.9	18	58.1	31	100	<0.001 (0.62)
Cords/trabeculae	96	81.4	22	18.6	118	100	
Single cell infiltration	11	84.6	2	15.4	13	100	

Table 2 Cross tabulation of histopathological risk score with nodal involvement

Histopathological risk score[a]	Nodal involvement				p value (γ)	Groin nodes vs pelvic nodes involvement				p value (γ)
	Nodes involved		Nodes not involved			Groin nodes		Pelvic nodes		
	No. cases (n=120)	% of cases	No. cases (n=42)	% of cases		No. cases (n=89)	% of cases	No. cases (n=31)	% of cases	
3	0	0	3	100	<0.001 (0.54)	0	0	0	0	0.02 (0.36)
4	2	18.2	9	81.8		2	100	0	0	
5	10	52.6	9	47.4		9	90	1	10	
6	48	82.8	10	17.2		38	79.2	10	20.8	
7	41	83.7	8	16.3		29	70.7	12	29.3	
8	17	85	3	15		10	58.8	7	41.2	
9	2	100	0	0		1	50	1	50	

[a] Histological grade + anatomical level of infiltration + tumour infiltration pattern.

Table 3 Cross tabulation of risk groups for histopathological risk score with nodal involvement

Histopathological risk groups	Nodal involvement				p value (γ)
	Nodes involved		Nodes uninvolved		
	No. cases (n=120)	% cases	No. cases (n=42)	% cases	
Low risk group (score 3 and 4)	2	14.3	12	85.7	<0.001 (0.79)
High risk group (score 5)	10	52.6	9	47.4	
Very high risk group (score 6–9)	108	83.7	21	16.3	

Table 4 Cross tabulation of risk groups for histopathological risk scores with nodal (N) stage

Histopathological risk scores (p<0.001) (γ=0.72)	Nodal stage							
	N0		N1		N2		N3	
	No. cases	% cases	No. cases	% cases	No. cases	% cases	No. cases	% cases
Low risk group (score 3 and 4)	12	78.6	0	7.1	0	0.0	2	14.3
High risk group (score 5)	9	47.4	1	5.3	1	5.3	8	42.1
Very high risk group (score 6–9)	21	16.3	6	4.7	7	5.4	95	73.6

statistical correlation with the pathological N-stage with 79% low risk category patients presenting as pN0 disease and 74% high risk patients having pN3 disease (p<0.001) (Table 4). Nineteen of 58 (32.75%) cN0 cases had pathological node positive (pN+) disease and this was statistically significant when stratified as per risk groups (p=0.007) (Table 5).

Follow-up was available in 145 patients (89.5%) with a median follow-up of 21 months (1–96 months). Median DFS for the whole group was 8 months, while the OS was 23 months. Median OS with and without nodal metastasis was 18 months and 30 months, respectively. The HRS (p=0.04) as well as the histopathological risk groups (p=0.004) significantly correlated with the DFS (Fig. 5A,B). The HRS (p=0.02) but not histopathological risk groups (p=0.15) correlated with OS (Fig. 5C,D).The 5-year survival for the low risk group was 100%, for the intermediate risk group was 59% and for the high risk group was 65%.

Univariate and multivariate logistic regression models for predicting nodal metastasis and outcome

Nodal metastasis

On univariate logistic regression models tumour grade (p<0.001), anatomical level of infiltration (p<0.001), tumour infiltration pattern (p<0.001), PNI (p=0.01), and LVI (p<0.001), all showed statistically significant correlation with

Table 5 Cross tabulation of risk groups for histological risk scores with pathological nodal involvement in clinically node-negative patients (cN0) (n=58)

Histopathological risk groups (p=0.007) (γ=0.78)	Pathological nodal involvement			
	Nodes involved		Nodes not involved	
	Count	Column N %	Count	Column N %
Low risk group (score 3 and 4)	1	8%	12	92%
Intermediate risk group (score 5)	1	10%	9	90%
High risk group (score 6–9)	17	49%	18	51%

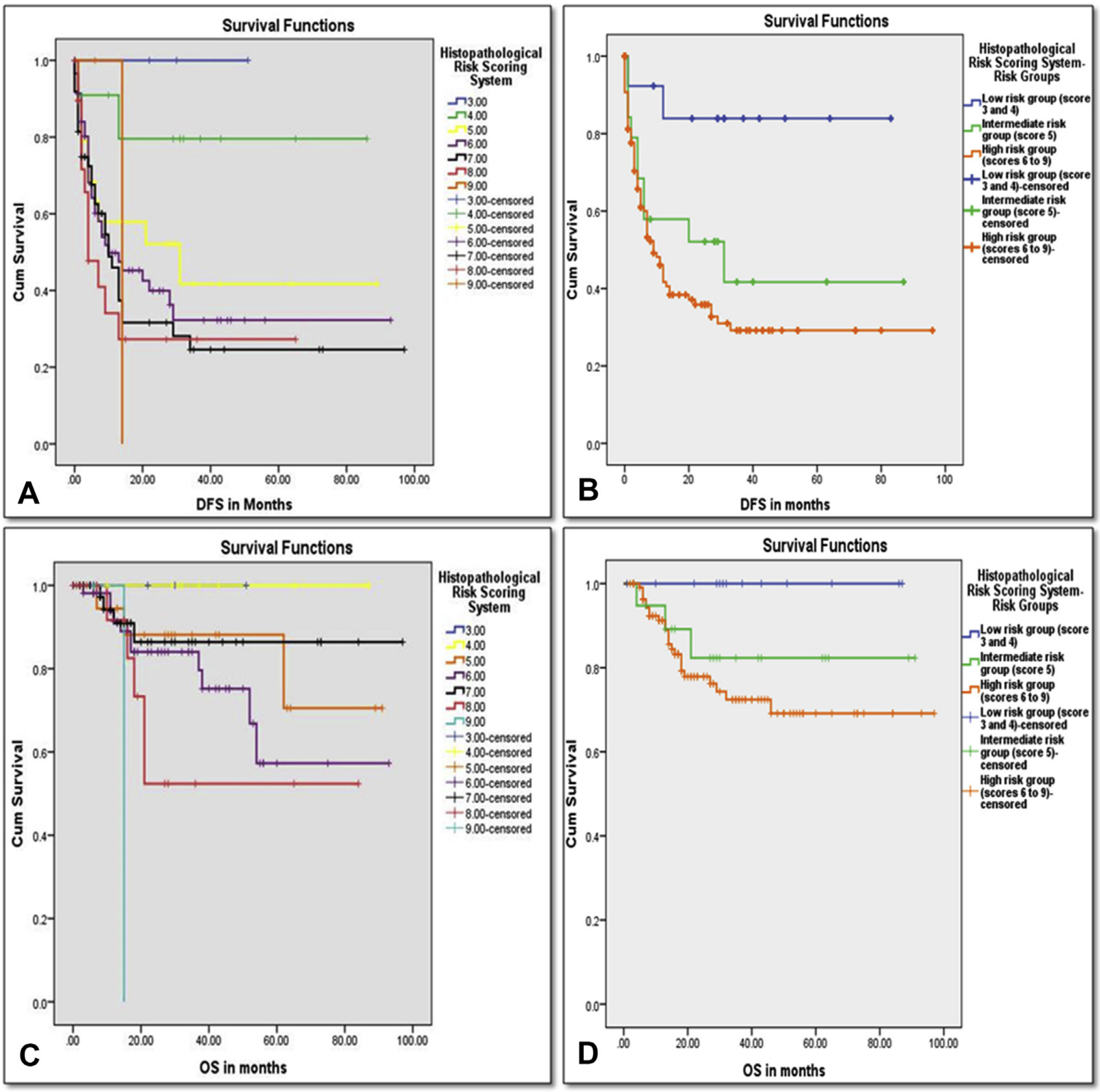

Fig. 5 Kaplan–Meier graphs. Disease-free survival (A) for histopathological risk scores (p=0.04) and (B) for histopathological risk groups (p=0.004). Overall survival (C) for histopathological risk scores (p=0.02) and (D) for histopathological risk groups (p=0.15).

nodal metastasis. However only tumour grade (p=0.02) retained this significant correlation with nodal metastasis when these parameters were analysed together on the multivariate model. Further, two multivariate models were created: one consisting of tumour grade, anatomical level of infiltration and tumour infiltration pattern; and the other comprising tumour grade, anatomical level of infiltration and PNI. Tumour grade (p<0.001, p=0.01) was significantly associated with nodal metastasis in both of the above models. In the former model anatomical level of infiltration (p=0.05) but not the tumour infiltration pattern (p=0.07) showed a statistical correlation with nodal metastasis, while in the latter model neither anatomical level of infiltration (p=0.06) nor the PNI (p=0.11) showed any statistical correlation with the nodal metastasis.

Outcome (DFS)

The univariate survival analysis models showed statistical association between DFS and tumour grade (p=0.02), tumour infiltration pattern (p=0.04) and nodal metastasis (p<0.001) but not anatomical level of infiltration (p=0.13), PNI (p=0.15) and LVI (p=0.25). Based on this finding two multivariate survival models were created: one consisting of tumour grade, anatomical level of infiltration, tumour infiltration pattern, PNI, LVI, and nodal metastasis; and the other consisting of HRS and nodal metastasis. In both models, only nodal metastasis showed a statistically significant influence on DFS.

Outcome (OS)

Univariate survival analysis for OS was significantly associated with nodal metastasis (p=0.03). Tumour grade, anatomical level of infiltration, tumour infiltration pattern, PNI, and LVI did not have any statistically significant correlation with OS in univariate analysis.

Histopathological risk scores and prognostic index

PIS had a comparable effect on nodal metastasis and outcome. In univariate logistic regression both PIS and HRS showed >98% predictive sensitivity for detecting node-

Table 6 Comparison of increment in risk of lymph nodal involvement for the prognostic index score and histopathological risk score

Prognostic index score			Histopathological risk score		
Score	No. cases	Risk of nodal involvement	Score	No. cases	Risk of nodal involvement
2	0/4	0%	3	0/3	0%
3	8/16	50%	4	2/11	18.2%
4	27/43	62.8%	5	10/19	52.6%
5	49/59	83.1%	6	48/58	82.8%
6	27/30	90%	7	41/49	83.7%
7	9/10	90%	8	17/20	85%
			9	2/2	100%

positive disease. However, the predictive sensitivity for detecting node-negative disease for PIS was 9% while that for HRS was 29%. Further, we created two multivariate logistic regression models for predicting nodal metastasis: the first comprising of PIS and tumour infiltration pattern and the second consisting of HRS and PNI. In the first model tumour infiltration pattern (p=0.03) and not PIS (p=0.17) was associated with the nodal metastasis, while in the latter HRS (p<0.001) and not PNI (p=0.25) was associated with the risk score. When compared to HRS, the increased risk of nodal metastasis with the increment in the score was abrupt for PIS (Table 6). Performing ROC curves analysis for predicting nodal metastasis, both scoring systems showed comparable AUC (both 0.72) and 95% CI (HRS 0.62–0.82; PIS 0.63–0.81), with HRS (ACC=0.80) showing slightly better accuracy than PIS (ACC=0.76). Both stratification systems had similar AUC (0.63) for predicting outcome (DFS).

DISCUSSION

The management of penile carcinomas is largely based on surgical procedures with a limited role for chemotherapy and radiotherapy in advanced disease.[18] Regional lymph nodal metastasis is the most important risk factor for predicting survival in penile SCC patients.[5,19,20] However, the survival advantage gained by GND, even in clinically node-negative patients, should be carefully balanced by the severe comorbidity associated with it.[21,22] Moreover, 15–53% patients presenting with clinically palpable nodes in penile cancer may have an underlying inflammatory pathology.[23] Hence, optimal patient selection for GND is necessary. Physical examination is associated with high false-negative rates (11–62%). Other staging strategies, including ultrasonography and minimally invasive methods like fine needle aspiration cytology (FNAC), image-guided FNAC and sentinel lymph node biopsy (SNB) are also associated with false-negative findings.[24,25] Dynamic SNB (DSNB), contemplated as a replacement for SNB has been quoted to have false-negative rates as high as 43%.[26] In current practice, contemporary superficial or modified GND with intraoperative frozen section remains the gold standard for identifying microscopic groin nodes metastasis.[27] However, frozen section facility and expertise is not readily available in developing countries. Many researchers have tried to develop prediction models based on different pathological variables.[10,23,28] However, recently it has been shown that most of these systems have poor accuracy for predicting nodal metastasis.[29] Chaux *et al.* proposed the 'prognostic index' comprising of three parameters: histological tumour grade, anatomical level of infiltration and PNI.[15] The PIS was calculated from the above pathological parameters and further risk groups were constructed as low (index 2–3), intermediate (index 4), and high (index 5–7). However, this index was not validated in other studies, probably owing to the low incidence of penile cancer in most parts of the world. This PIS, when applied to our cohort, showed an abrupt increment in the risk of nodal metastasis from 0% to 50% as the score increased from 2 (minimum score) to score 3. In comparison, in HRS, the corresponding increment of nodal positivity was from 0% to 18.2% (score 3 to score 4) and further to 52.6% in score 5. It can well be argued that tumour infiltration pattern would correlate with tumour grade and depth of anatomical compartment involvement. However, we did see two cases of grade 1 lamina invasive squamous carcinoma which surprisingly had cords and trabeculae like tumour infiltration pattern. We also tried adding the parameter of tumour infiltration pattern to the PIS; the scoring system devised did not aid in delineating the lower scores accurately, and on the contrary, incorporation of the additional pathological variable to the scoring system further increased the chances of interobserver variability. Thus, our system of scoring appears to be advantageous in delineating the lower scores into more precise groups of clinical relevance. Further, HRS also seems to have better sensitivity in predicting true node-negative cases as compared to PIS.

In the current study, we propose three risk categories based on the scores: low risk, intermediate risk, and high risk. The low risk group (scores 3 and 4) had a probability of nodal metastasis of 0–18%, whereas the high risk group (scores 6–9) had >80% chances of nodal metastasis. The 5-year survival was 100% for the low risk group (score 3 and 4), 59% for the intermediate risk group (score 5) and 65% for the high risk group (score 6–9). The paradox of high risk group patients having slightly better survival than the intermediate group may be attributed to the use of chemotherapy/radiotherapy concomitantly in many of the high risk group patients.

Addressing the nodal basin in the clinically node-negative (cN0) setting is a challenge. It has been estimated that approximately 20–25% of cN0 patients harbour micrometastasis.[30] Subjecting all of the cN0 penile cancers patients to elective GND would mean overtreating almost 75% patients. Hence, the decision to address the groin nodes in cN0 patients should be made wisely considering the morbid complications of GND. Although the technique of DSNB assures a promising future in this aspect, it is associated with a learning curve and installation of sophisticated instruments requiring trained personnel and cost.[31–33] Furthermore, DSNB is not widely used even in developed countries such as the USA, where most of the patients with a high risk of micrometastasis are subjected to GND.[30] Our risk grouping, on the other hand, can identify at least 49% of potentially metastatic cN0 cases (Table 5). Hence, with limited availability of frozen section and DSNB in low resource centres, this scoring system can aid in decision making in cN0 disease.

Pelvic lymph node involvement in penile cancer carries an extremely poor prognosis. The 5-year survival is almost 0% if pelvic nodes are involved, in comparison to 64% with only the inguinal basin being involved.[6] We observed a proportional incremental risk of pelvic node involvement with increasing scores (0–50% as scores increase from 3 to 9) as per our system, which is a novel finding of clinical importance.This can be of immense utility to the surgeon/treating oncologist to decide upon curative surgery vis-a-vis palliative chemotherapy.

Our study has inherent drawbacks associated with any retrospective study design and there may have been limitations due to referral bias, especially suboptimal/inadequate sections for review of pathology material sent from referring institutes. The proposed scoring system would need a prospective validation which would strengthen its clinical utility. Recently, Chaux *et al.* compared the three established risk stratification systems with a conclusion that all of them had poor accuracy in predicting the risk of nodal metastasis.[29] Surprisingly, the PIS was not included in this comparison. It would be interesting to compare both PIS and HRS in this set of patients since we have already compared and established the marginal superiority of HRS in our cohort. In comparison to previous studies, this is a single institution cohort with a larger number of patients and a smaller time frame of inclusion.[10,15]

In summary, we propose a risk stratification approach to address the nodal basin in penile cancer. Based on the risk groups, patients with score 3 and 4 (low risk group) may be spared the morbid procedure of bilateral GND. This group of patients may be best followed up closely with clinical examination and radiological investigations such as groin node USG, and if deemed necessary, FNAC. Patients with score 5 have a 50% chance of nodal metastasis, and a modified GND with intraoperative frozen sections seems to be the best option in such patients, the alternative being DSNB if available. Patients with score 6–9 are at high risk of nodal metastasis and should undergo early planned elective GND. These risk groups can be of immense help to surgeons in the cN0 setting, as well in deciding management in cases with a high probability of pelvic nodal metastasis.

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