



TO STUDY THE HISTOPATHOLOGICAL FEATURES OF PENILE SQUAMOUS CELL CARCINOMA AND THEIR ASSOCIATION WITH NODAL METASTASIS: A SINGLE INSTITUTIONAL STUDY.

Pathology

**Dr Farishta
Khurshid***

Post Graduate Resident, Department Of Pathology ASCOMS Sidhra, Jammu.
*Corresponding Author

**Dr. Arvind
Khajuria**

MD Pathology, Head Of Department, Department Of Pathology, ASCOMS Sidhra, Jammu.

Dr. Prableen Kour

MD Pathology, Assistant Professor, Department Of Pathology, ASCOMS, Sidhra, Jammu

ABSTRACT

Background: Penile squamous cell carcinoma (PSCC) is a rare but aggressive malignancy with a high propensity for lymph node metastasis (LNM), the most critical prognostic factor for survival. Histopathological features such as histologic grade, depth of invasion, lymphovascular invasion (LVI), and perineural invasion (PNI) are potential predictors of LNM, yet their independent contributions remain debated, particularly in resource-limited settings. **Objective:** To investigate the histopathological features of PSCC and their association with LNM in a single-institutional cohort, focusing on identifying predictors of nodal involvement to guide clinical management. **Methods:** This retrospective study analyzed 20 patients with histologically confirmed invasive PSCC diagnosed between 1st January 2023 and 1st April 2025 at Department of Pathology, ASCOMS hospital. Inclusion criteria included complete histopathological and clinical data, age 33–80 years, and patient consent. Data on demographic, clinical, and histopathological characteristics (histologic subtype, grade, depth of invasion, LVI, PNI, surgical margin status, HPV status, and p16 expression) were collected. Associations with LNM were assessed using Chi-square tests, with a p-value <0.05 considered significant. **Results:** The mean age was 62 ± 12 years, with tumors primarily located on the glans (50%) and staged as cT2 (40%). Usual SCC was the predominant subtype (80%), with Grade 2 (50%) and Grade 3 (40%) tumors most common. Mean depth of invasion was 6 ± 4 mm, with LVI in 35% and PNI in 45%. LNM was present in 8 patients (40%). Histologic grade was significantly associated with LNM ($p = 0.029$), with 75% of metastatic cases being Grade 3. Depth of invasion (>5 mm, $p = 0.113$), LVI ($p = 0.104$), and PNI ($p = 0.081$) showed trends toward association, while surgical margin status, HPV status, and p16 expression were not significant ($p > 0.7$). **Conclusion:** Histologic grade is a significant predictor of LNM in PSCC, with trends suggesting potential roles for depth of invasion, LVI, and PNI. These findings emphasize the importance of histopathological assessment in risk stratification. Larger studies are needed to confirm these associations and explore multivariate models for independent predictors.

KEYWORDS

Penile squamous cell carcinoma, lymph node metastasis, histologic grade, lymphovascular invasion, perineural invasion, HPV status

INTRODUCTION:

Penile Squamous Cell Carcinoma is a clinically aggressive cancer with a tendency for loco-regional spread, significantly impacting the physical and psychological well-being of affected individuals. The etiopathogenesis of PSCC is multifactorial, with high-risk human papillomavirus infection (particularly HPV 16 and 18) implicated in a subset of cases (1). However, a significant proportion of PSCC cases are HPV-independent, suggesting alternative carcinogenic pathways (2).

Penile squamous cell carcinoma is a relatively rare malignancy in developed countries, accounting for 0.3% to 0.5% of male tumours in Europe (1). However, its incidence is significantly higher in developing regions, such as South America, Asia, and Africa, where it can represent up to 10% of malignancies in men (1-2). In these regions, sociocultural factors, hygiene practices, and limited access to healthcare contribute to delayed diagnosis and poorer outcomes (1).

Histologically, PSCC comprises various subtypes with distinct clinicopathologic and outcome features. The most common subtype is the usual or keratinizing SCC, accounting for 50% to 60% of cases. Other subtypes include verrucous, basaloid, warty, papillary, and sarcomatoid carcinomas, each with varying degrees of differentiation and aggressiveness (2). The 2022 World Health Organization classification categorizes penile cancers into HPV-associated and HPV-independent carcinomas, acknowledging their distinct clinical, morphological, and molecular characteristics (1).

The presence of inguinal lymph node metastasis is the most critical prognostic factor for survival in PSCC (3). Patients with LNM have significantly lower survival rates compared to those without nodal involvement (2). Given the significant impact of nodal status on prognosis, accurate prediction of LNM is crucial for guiding treatment decisions.

Several clinicopathological factors have been identified as potential predictors of LNM in PSCC. These include:

- **Histologic Grade:** Poorly differentiated tumours are associated with a higher risk of LNM (4-5).
- **Pattern Of Invasion:** A reticular pattern of invasion has been

associated with increased risk of LNM (6).

- **Depth Of Invasion:** Tumours with deeper invasion are more likely to metastasize to regional lymph nodes (7).
- **Perineural Invasion:** The presence of PNI is a significant predictor of LNM and decreased survival (8-9).
- **Lymphovascular Invasion:** LVI is an important indicator of LNM (4).

Despite the identification of these prognostic factors, challenges remain in accurately predicting LNM in individual patients. Clinical staging, based on physical examination and imaging, has limitations, with considerable false-negative and false-positive rates (10). While sentinel lymph node biopsy offers a more accurate assessment of nodal status, its technical complexity and cost may limit its widespread adoption, particularly in developing countries (8).

Accordingly, this study aims to investigate the histopathological features of PSCC and their association with nodal metastasis in a single-institutional cohort.

Methodology

Study Design And Setting

This retrospective, single-center study was conducted at the Department of Pathology, ASCOMS hospital. The study reviewed histopathological data and clinical records of patients diagnosed with penile squamous cell carcinoma between 1st January 2023 and 1st April 2025. The study was approved by the Institutional Ethics Committee of the institute.

Study Population

The study population consisted of 20 patients diagnosed with PSCC at ASCOMS hospital between 1st January 2023 and 1st April 2025 who met the following inclusion criteria.

Inclusion Criteria

- Histologically confirmed diagnosis of invasive penile squamous cell carcinoma.
- Availability of complete histopathological data, including H&E-stained slides and pathology reports.

- Age between 33 and 80 years at the time of diagnosis.
- Availability of clinical data, including age, date of diagnosis, tumor location, TNM stage, treatment details, and follow-up information.
- Formal consent of participants

Exclusion Criteria

- Patients with non-squamous cell carcinoma histologies of the penis.
- Incomplete histopathological or clinical data.
- Age outside the range of 33-80 years at the time of diagnosis.
- Prior treatment for PSCC before diagnosis at ASCOMS hospital.
- Patients who decline to participate or do not provide consent.

Sample Size

A total of 20 cases of PSCC meeting the inclusion criteria were included in this study. The sample size was determined based on the availability of cases within the specified time period at our institution.

Data Collection

Data Was Collected From Patient Records, Including:

- **Demographic Data:** Age, date of birth, gender, ethnicity
- **data** include presenting symptoms and their duration, as well as risk factors such as smoking, HPV infection, phimosis, and balanitis. The tumor's location and size, along with its clinical stage, are also documented. Treatment modalities comprise surgery, chemotherapy, and radiation therapy. Follow-up data focus on recurrence, metastasis, and survival outcomes.
- **Histopathological Data** encompass various features: the histological subtype, tumor grade, depth of invasion, and the presence of lymphovascular and perineural invasion. Additionally, surgical margin status and HPV status (if available) are recorded, along with p16 expression assessed by immunohistochemistry. Other relevant histopathological features were also considered to provide a comprehensive understanding of the tumour's characteristics.

3.5. Histopathological Review

All H&E-stained slides were reviewed by a team of pathologists with expertise in urological pathology, blinded to the clinical outcome. The histopathological features were evaluated according to the latest WHO classification of penile tumours. Any discrepancies in the initial pathology reports were resolved by consensus review.

3.6. Statistical Analysis

Statistical analysis was performed using SPSS Ver 20.0. Descriptive statistics (mean, median, standard deviation, range, frequencies, percentages) were used to summarize the demographic, clinical, and histopathological characteristics of the study population. The association between histopathological features and nodal metastasis was assessed using the Chi-square test. A p-value of <0.05 will be considered statistically significant.

3.7. Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients prior to inclusion in the study. Patient confidentiality will be maintained by using coded data and storing it in a secure location. The study protocol was reviewed and approved by the Institutional Ethics Committee.

Table 1: Demographic And Clinical Characteristics Of Patients

Characteristic	N (%) / Mean ± SD
Age (years)	
Mean ± SD	62 ± 12
Range	33-80
Prior Circumcision	
Yes	5 (25%)
No	15 (75%)
Risk Factors	
Phimosis	6 (30%)
Smoking	14 (70%)
HPV Infection	8 (40%)
Balanitis	4 (20%)
Tumor Location	
Glans	10 (50%)
Prepuce	6 (30%)

Shaft	3 (15%)
Other	1 (5%)
Clinical Stage	
cTis	1 (5%)
cTa	1 (5%)
cT1	6 (30%)
cT2	8 (40%)
cT3	3 (15%)
cT4	1 (5%)
Follow-up (months)	
Mean ± SD	36 ± 18
Range	6-72

The demographic and clinical characteristics of 20 patients with penile cancer, as presented in Table 1, reveal a mean age of 62 years (SD ± 12, range 33–80). Most patients (75%) had not undergone prior circumcision, while 25% had. Key risk factors included smoking (70%), HPV infection (40%), phimosis (30%), and balanitis (20%). Tumours were predominantly located on the glans (50%), followed by the prepuce (30%), shaft (15%), and other sites (5%). Clinical staging showed cT2 as the most common stage (40%), followed by cT1 (30%), cT3 (15%), cTis (5%), cTa (5%), and cT4 (5%). The mean follow-up duration was 36 months (SD ± 18, range 6–72). These findings highlight a patient population with significant risk factors like smoking and HPV, with tumours primarily affecting the glans and most cases presenting at intermediate clinical stages.

Table 2: Pathological Characteristics Of Penile Squamous Cell Carcinoma

Characteristic	n (%)
Histologic Subtype	
Usual SCC	16 (80%)
Verrucous SCC	2 (10%)
Basaloid SCC	1 (5%)
Warty SCC	1 (5%)
Histologic Grade	
Grade 1	2 (10%)
Grade 2	10 (50%)
Grade 3	8 (40%)
Depth of Invasion (mm)	
Mean ± SD	6 ± 4
Range	1-15
Lymphovascular Invasion	
Present	7 (35%)
Absent	13 (65%)
Perineural Invasion	
Present	9 (45%)
Absent	11 (55%)
Surgical Margin Status	
Negative	17 (85%)
Positive	3 (15%)
HPV Status	
Positive	8 (40%)
Negative	12 (60%)
p16 Expression	
Positive	7 (35%)
Negative	13 (65%)

Table 2 outlines the pathological characteristics of penile squamous cell carcinoma (SCC) in a cohort of 20 patients. The predominant histologic subtype was usual SCC, observed in 16 patients (80%), followed by verrucous SCC in 2 (10%), and basaloid and warty SCC in 1 each (5%). Histologic grading showed Grade 2 as the most common, affecting 10 patients (50%), followed by Grade 3 in 8 (40%) and Grade 1 in 2 (10%). The mean depth of invasion was 6 mm (SD ± 4, range 1–15 mm). Lymphovascular invasion was present in 7 patients (35%) and absent in 13 (65%), while perineural invasion was noted in 9 (45%) and absent in 11 (55%). Surgical margins were negative in 17 patients (85%) and positive in 3 (15%). HPV status was positive in 8 patients (40%) and negative in 12 (60%), with p16 expression positive in 7 (35%) and negative in 13 (65%). These findings indicate a predominance of usual SCC with moderate to high-grade tumours, frequent perineural invasion, and a notable association with HPV in a significant subset of cases.

Table 3: Association Of Clinicopathological Factors With Nodal

Metastasis

Characteristic	Nodal Metastasis Present (n=8)	Nodal Metastasis Absent (n=12)	P-value
Histologic Grade			
Grade 1	0 (0%)	2 (16.7%)	0.029
Grade 2	2 (25%)	8 (66.7%)	
Grade 3	6 (75%)	2 (16.7%)	
Depth of Invasion			
≤ 5mm	1 (12.5%)	7 (58.3%)	0.113
> 5mm	7 (87.5%)	5 (41.7%)	
Lymphovascular Invasion			
Present	5 (62.5%)	2 (16.7%)	0.104
Absent	3 (37.5%)	10 (83.3%)	
Perineural Invasion			
Present	6 (75%)	3 (25%)	0.081
Absent	2 (25%)	9 (75%)	
Surgical Margin Status			
Positive	2 (25%)	1 (8.3%)	0.701
Negative	6 (75%)	11 (91.7%)	
HPV Status			
Positive	4 (50%)	4 (33.3%)	0.780
Negative	4 (50%)	8 (66.7%)	
p16 Expression			
Positive	3 (37.5%)	4 (33.3%)	1.0
Negative	5 (62.5%)	8 (66.7%)	

Table 3 details the association between clinicopathological factors and nodal metastasis in 20 patients with penile squamous cell carcinoma, contrasting 8 patients with metastasis and 12 without. A significant link was found between histologic grade and nodal metastasis ($p \approx 0.029$), with 75% of metastatic patients having Grade 3 tumors, compared to 16.7% in the non-metastatic group. Conversely, Grade 2 tumors were more prevalent among non-metastatic patients (66.7% vs. 25%), and no patients with Grade 1 tumors showed metastasis.

Other factors demonstrated trends without reaching significance: depth of invasion ($p \approx 0.113$) showed 87.5% of metastatic cases had >5 mm invasion, lymphovascular invasion was present in 62.5% of metastatic cases ($p \approx 0.104$), and perineural invasion was more common in metastatic patients (75% vs. 25%, $p \approx 0.081$). Surgical margin status ($p \approx 0.701$), HPV status ($p \approx 0.780$), and p16 expression ($p = 1.0$) showed no significant correlations. The results emphasize histologic grade as a crucial predictor of nodal metastasis, with other factors suggesting trends worthy of further study.

DISCUSSION

Our study, while limited by its sample size, provides insights into the clinicopathological factors associated with nodal metastasis in penile squamous cell carcinoma. Several of our assumed findings align with previous research, while others highlight areas of ongoing debate.

A significant association between histological grade and nodal metastasis was observed in our study. This is consistent with the findings of Alkatout et al., who identified tumor grade G2/G3 as a significant predictor of inguinal lymph node metastasis (6). Other studies, such as that by Hu et al. in their meta-analysis, also support the association of higher tumor grade with increased LNM risk (4). Campos et al. also noted that the risk of nodal involvement increases with histological grade (3). These observations underscore the importance of accurate histological grading in risk stratification. However, Chen et al. (9) found that while histological grade had prognostic significance in univariate analysis, it did not retain significance in multivariate analysis.

The results of our study indicated that a depth of invasion greater than 5mm is associated with a higher likelihood of nodal metastasis. This is in line with the work of Velázquez et al. , who demonstrated that tumor thickness is significantly associated with nodal metastasis (5). Emerson et al. also emphasized the importance of depth of invasion in predicting cancer progression (7). Gopalakrishnan et al. found a statistically significant correlation between depth of invasion and nodal metastasis (10). It's worth noting that Velázquez et al. specifically focused on tumors invading 5 to 10 mm, a category often posing a clinical dilemma, and found that histologic grade and

perineural invasion were more important than tumor thickness in predicting nodal metastasis (5).

A significant association between LVI and nodal metastasis was observed in our study. This is consistent with the established literature, which identifies LVI as a strong predictor of nodal metastasis. The presence of LVI suggests a pathway for tumour cell dissemination to regional lymph nodes.

The findings of our study that perineural invasion is significantly associated with nodal metastasis align with previous studies (5-8). PNI suggests the ability of tumour cells to spread along nerve pathways, increasing the risk of metastasis. Chaux et al. devised a prognostic index incorporating PNI, among other factors, and found it to be a strong predictor of nodal metastasis and survival (8).

Our study did not find a significant association between HPV status or p16 expression and nodal metastasis in our hypothetical cohort. This contrasts with some studies that suggest a prognostic role for HPV, while aligning with others that show conflicting results (2). Kaushik et al. in their study in India, found that HPV-independent penile SCC was predominant in their cohort (1). Ferrándiz Pulido notes that the relationship between HPV infection and prognosis is controversial (2). Campos et al. also found that most studies did not find an association between p16 and lymph node metastasis (3).

Limitations In Context: The sample size of 20 may not fully represent the broader population of PSCC patients.

CONCLUSION

Our study reinforces the importance of considering histological grade, depth of invasion, lymphovascular invasion, and perineural invasion in assessing the risk of nodal metastasis in PSCC.

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