

## ORIGINAL RESEARCH

**Histopathology of Intraepithelial and Invasive Penile Squamous Cell Carcinomas, and its Prognostic Significance****Dr. Omkar Rama Krishna Puvvala<sup>1</sup>, Dr. Divya Prakash<sup>2</sup>, Dr. Chatura K.R.<sup>3</sup>**<sup>1</sup>Associate Professor, Department of pathology, Xavier University School of Medicine, Aruba, Netherland Caribbean.<sup>2</sup>Assistant Professor, Department of Pathology, Dr. Moopens Medical College, Wayanad, Kerala, India<sup>3</sup>Professor, Department of Pathology, JJM Medical College, Karnataka, India.**Corresponding author:**Dr. Divya Prakash,

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**ABSTRACT**

**Background:** Penile cancers are one of the dangerous, aggressive and mutilating cancers, of which squamous cell carcinoma is the common malignancy. Penile SCC is an unacknowledged disease and has a limited burden on urban and rural populations in the Indian subcontinent, hence requires a better understanding.

**Objectives of the study:** Histomorphology of variants in intraepithelial and penile invasive squamous cell carcinomas Prognostic index and outcome of the patients

**Methods:** The case and specimen details were collected from department archives between July 2012 to June 2017. After fixation in 10% formalin, specimens have been studied. Representative areas were sampled, and sections obtained, and

**Statistical analysis:** The Chi-square test and the Fischer exact test have been used to evaluate the associations between variables.

**Results:** Out of the 55 study cases, 49 (89%) cases were diagnosed as penile squamous cell carcinoma (PSCC) and 6 (11%) cases were diagnosed as a penile intraepithelial lesion (PeIN). Most common location was over glans (24 cases), followed by foreskin mucosal surface (15 cases). The majority of cases were classified as usual squamous cell carcinoma (33 cases) followed by verrucous carcinoma (7 cases), warty carcinoma (4 cases), Sarcomatoid variant (2 cases), one case each of pseudoglandular variant, basaloid variant and mixed carcinoma of usual with basaloid variant.

**Conclusion:** Routine histomorphology is useful in diagnosis of several variants of PSCC, which can be confirmed by p16 and the prognostic index provides a better perspective of the patients condition.

**Keywords:** Histomorphology, Penile squamous cell carcinoma, Prognostic Index(PI), Perineural invasion(PNI), Lymphovascular invasion(LVI).

**INTRODUCTION**

One of the deadliest cancers that profoundly affects the patient's self-esteem is penile cancer.<sup>(1)</sup> It is an aggressive and mutilating disease. Despite the presence of other types of penile cancers, Squamous cell carcinoma (SCC) is the most common type of malignancy contributing to 95% of all penile cancers. Some of the usual sites of penile SCC are the epithelium of the glans and the inner side of the prepuce. The natural history is similar to those occurring in other body sites.<sup>(2,3)</sup> Premalignant lesions like PeIN and other associated diseases like Lichen sclerosis have been known to progress to PSCC and hence require early diagnosis and treatment. SCC has a limited burden on urban and rural populations in the Indian subcontinent, a better understanding is required for specialized management and treatment.

**OBJECTIVES OF THE STUDY**

1. Histomorphology of variants in intraepithelial and invasive squamous cell carcinomas of penis
2. Prognostic index and outcome of the patients

**MATERIALS AND METHODS**

**Source of data :** Patients in the Department of Pathology, diagnosed with penile intraepithelial and invasive carcinoma from July 2012 to June 2017 were included.

**Method of collection of data (including sampling, procedure, if any) :** The case and specimen details were collected from department archives between July 2012 to June 2017. After fixation in 10% formalin, specimens have been studied. Representative areas were sampled, and sections obtained. H&E stain has been performed. To stratify the cases, a detailed analysis of microscopic features has been done. By addition of the numerical values assigned to histological grade, anatomical level of maximum tumor extent, and perineural invasion, the prognostic index has been obtained.

**Statistical analysis:** The Chi-square test and the Fischer exact test have been used to evaluate the associations between variables. Predictable features were grouped into clinical features (age and environmental factors), and pathological features (histologic subtype, anatomical site, anatomical level, histological grade, tumor thickness, tumor invasion of penile urethra, lymphovascular invasion, perineural invasion, and inguinal lymph node metastasis)

**Sample size:** 55

**Inclusion criterion:** Resection specimens like circumcisions, glansctomy, orpenectomies with or without dissection of the inguinal lymph node. Intra epithelial and invasive penile squamous cell carcinoma.

**Exclusion criterion:** Glandular tumors Metastatic tumors

## RESULTS

CHARACTERISTIC	N (%)
Age(years), median age (range)	55, 35– 82 years
Histological subtype(%)	
Usual SCC	33(68)
Verrucous carcinoma	7(14)
Pseudoglandular carcinoma	1 (2)
Sarcomatoid carcinoma	2 (4)
Basaloid carcinoma	1 (2)
Warty carcinoma	4 (8)
Mixed carcinoma ( <b>Basaloid + usual SCC</b> )	1 (2)
Histological grade	
Well differentiated (Grade 1)	30 (61)
Moderately differentiated (Grade 2)	15 (31)
Poorly differentiated (Grade 3)	4 (8)
Anatomical site	
Glans	24 (49)
Inner foreskin	15(31)
Glans + Foreskin	7(14)
Glans + coronary sulcus + inner foreskin	1 (2)
Outer foreskin	1 (2)
Shaft	1 (2)
Lymphovascular invasion (%)	
Yes	7 (14)
No	42 (86)
Perineural invasion (%)	
Yes	5 (10)
No	44 (90)

**Table 1: Demographic and clinicopathological characteristics of PSCC**

A total of 55 cases were analyzed from July 2012 to June 2017, three years were of retrospective and two years of prospective study. 49 (89%) cases were diagnosed as penile squamous cell carcinoma (PSCC) and 6 (11%) cases were diagnosed as a penile intraepithelial lesion (PeIN) of 55 cases. The median age of incidence for PeIN and PSCC was 55 years with a range of 35-82 years. Age had a linear relationship with the lesion; older individuals had an increased likelihood of developing the disease, with a majority of cases diagnosed in the 6<sup>th</sup> to 7<sup>th</sup> decade of life. A total of 65 specimens were received during the study period. This included 22 partial penectomies, 9 total penectomies, 23 incisional / excisional biopsies, 7 circumcisions and 4 lymph node biopsies. Of 23 incisional / excisional biopsies, 6 were diagnosed as PSCC and followed by either partial or total penectomy. 4 lymph node biopsies were sent post penectomy as part of patient follow-up. Six cases were diagnosed as PeIN, with two specimens each of incisional /excisional biopsies, partial penectomies, and circumcision. PSCC was diagnosed in 49 cases. Cases of PeIN presented with lesion over foreskin mucosal surface (three cases), glans (two cases) and glans plus foreskin (one case). Three were diagnosed as differentiated PeIN and three were diagnosed as warty type undifferentiated PeIN. A majority of PSCC cases presented with a lesion over the glans (24 cases) underwent predominantly partial penectomy (16 cases). Most patients with lesion over the foreskin mucosal surface (15 cases) underwent incision/excision biopsy (10 cases). Patients with lesions involving the multiple compartments or shaft of the penis underwent either partial penectomy (four) or total penectomy (five).The current study received 49 cases of PSCC with 7 distinct histomorphological entities.(Table 1) The majority of cases were classified as usual squamous cell carcinoma (33 cases) followed by verrucous carcinoma (7 cases), warty carcinoma (4 cases), Sarcomatoid variant (2 cases), one case each of pseudoglandular variant, basaloid variant and mixed carcinoma of usual with basaloid variant. All PSCC cases were graded on basis of microscopic criteria into grade 1 or well-differentiated (30 cases), grade 2 or moderately differentiated (15 cases) and grade 3 or poorly differentiated (four cases). Lymphovascular invasion was seen in seven cases, whereas the perineural invasion was identified in five cases.Of the 55 cases, only

five cases (4 cases were usual SCC and one was a verrucous variant) were associated with other non-malignant conditions such as Lichen sclerosis (LS). Lymph node metastasis was seen in 7 out of 49 cases of PSCC, and they were also associated with infiltration of erectile tissue (corpora spongiosa and corpora cavernosa). Of 49 PSCC cases, 33 were diagnosed as usual SCC variant, 17 cases were well differentiated, 12 cases were moderately and the remaining 4 cases were diagnosed as poorly differentiated. The remaining 16 PSCC cases diagnosed as verrucous carcinoma (7 cases), warty carcinoma (4 cases), sarcomatoid carcinoma (2 cases), pseudoglandular, basaloid, mixed basaloid-usual SCC one case each. Lymph node metastasis was seen in seven cases, of which six cases were Usual SCC and one case was a basaloid variant.

**Prognostic index:** The prognostic index score (G+A+P) was calculated by adding scores given for grading of the tumor (G), anatomical level of invasion (A), and perineural invasion (P). (Table 2) The range for the prognostic index was from a minimum of two to a maximum of seven. A prognostic index score of 2 was calculated for a third of all cases with a score of 7 accounting for only a single case in the current study. PNI was seen in 4 cases (40%) and LVI in 6 cases (60%) with a prognostic index score of 5. Prognostic index score 7 included only a solitary case with features of both PNI and LVI. (Table 3) The prognostic index was correlated with nodal metastasis and patient outcome details. (Table 4) Six patients with prognostic index 5 developed nodal metastasis, with a single death attributed to the disease. The solitary case with a prognostic index of 7 developed nodal metastasis with his death directly attributed to the disease.

SCORE	TOTAL	%	COMBINATIONS(G+A+P)
2	16	33	1+1+0
3	12	25	1+2+0, 2+1+0
4	8	16	2+2+0, 1+3+0
5	10	20	2+3+0, 1+3+1
6	2	4	3+3+0
7	1	2	3+3+1

**Table 2: Prognostic index distribution**

PI	Total	PNI (%)	LVI (%)
2	16	0 (0)	0 (0)
3	12	0 (0)	0 (0)
4	8	0(0)	0 (0)
5	10	4(40)	6 (60)
6	2	0(0)	0(0)
7	1	1(100)	1(100)

**Table 3: Prognostic index and pathological data**

PNI: Perineural invasion; LVI: Lymphovascular invasion

PI Score	No. of cases	No. of cases Positive Node (%)	Dead of disease
5	10	6 (60%)	1
6	2	0	0
7	1	1(100%)	1

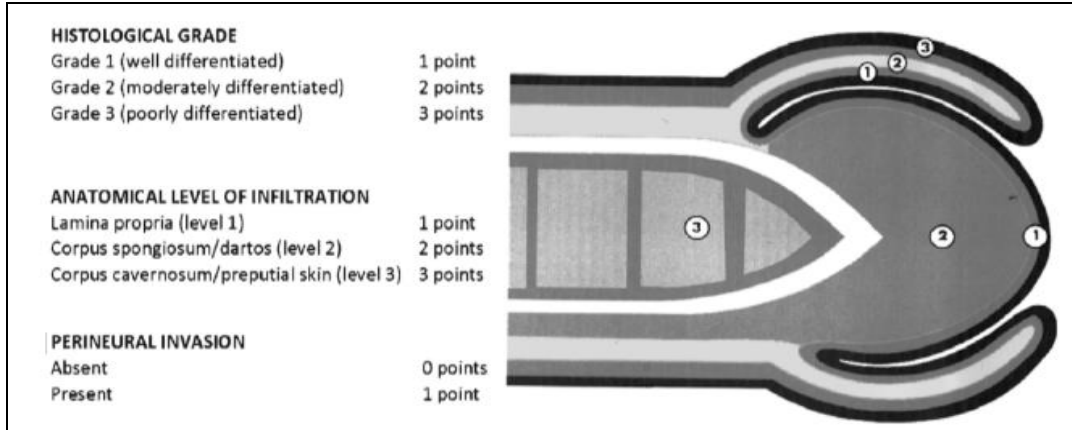
**Table 4: Prognostic index, Nodal metastasis, and Outcome**

**The outcome of patients with PI scores 4,5,6 and 7:** In this study of 49 PSCC cases, 21 patients were categorized under PI 4 to 7 (8 cases of PI 4, 10 cases of PI 5, 2 cases of PI 6, and 1 case of PI 7). PI was correlated with 9 categories of outcomes. PI score 4 patients had variable outcomes. Out of 10 patients with a PI score of 5, 4 patients were lost to follow-up. 2 out of 2 patients with a PI score of 6 were lost to follow-up, and a solitary patient with a PI score of 7 died due to disease. (Table 5)

Sl. No.	Outcome	Patients with PI=4	Patients with PI=5	Patients with PI=6	Patients with PI=7
1	Disease free survival	2	2	0	0
2	Mortality due to disease	0	1	0	1
3	Mortality due to non cancer Cause	1	0	0	0
4	No further treatment	2	0	0	0
5	Developed lymph node metastasis	2	0	0	0
6	< 1 year follow up	1	0	0	0

7	Unavailability of information (Referred cases)	0	2	0	0
8	Local recurrence	0	1	0	0
9	Lost to follow up	0	4	2	0
10	<b>Total</b>	<b>8</b>	<b>10</b>	<b>2</b>	<b>1</b>

**Table 5: PI and outcome of the patients**



**Figure 9: Schematic picture for prognostic index calculation**

**DISCUSSION**

Penile cancer is an uncommon and aggressive cancer in men accounting for 6% of all malignancies in india.<sup>(4)</sup> The rural population shows a higher prevalence of the disease when compared to urban populations. Due to its superficial location, penile cancer lends itself to early detection and management. The disease is more commonly seen in the elderly population.<sup>(5)</sup> The mean age at diagnosis of patients with penile cancer is 60 years and the age-related incidence is highest at 70 years.<sup>(4,5)</sup>

PeIN which is deemed to be a precursor lesion of penile cancer, is sub-classified into undifferentiated and differentiated PeIN based on histomorphology irrespective of HPV status.<sup>(6,7)</sup> In our current study median age of incidence of PeIN and PSCC was 55 years. A similar study conducted at New Delhi by Girotra et al showed that the mean age for incidence in the study was 56.11 years with more than 75% of cases seen in individuals above the age of 50 years.<sup>(4)</sup>

The current study received 55 specimens. The most commons specimens were incisional/excisional biopsies accounting for 23 cases followed by partial penectomies (22 cases). The others were total penectomies, circumcision, and lymphadenectomy specimens. Of the 23 biopsies, 2 were diagnosed as PeIN and the remaining as PSCC. Of the 21 patients, diagnosed with PSCC on biopsy only 6 underwent further surgical intervention for management of the disease. Of the remaining 15 cases, 10 did not require further management and were on surveillance, 2 were lost to follow up and 3 refused surgery in our institute. During the follow-up period, 4 patients with a previous positive diagnosis of PSCC underwent lymph node dissection. These specimens accounted for all lymphadenectomy specimens received during the study period. The specimens were all positive for nodal metastasis.

**PeIN:** PeIN accounted for a total of 6 cases. The most common site was the mucosal surface of the foreskin accounting for half of all cases followed by glans (2 cases). This was in concordance with a study from France and Paraguay.<sup>(8,9)</sup> In our current study, there was an equal distribution of differentiated and undifferentiated PeIN and this is not in agreement with prevalent literature on the topic. This inconsistency can be attributed to the relatively small sample size understudy. Differentiated PeIN shows epithelial changes like hyperkeratosis, and hypergranulosis with acanthosis, elongated rete ridges, intraepithelial keratin pearls and intercellular bridges. Basally located cells shows cellular atypia and the superficial cells have abundant cytoplasm with a vesicular nucleus and occasional nucleolus.<sup>(6,8)</sup> The differentiated PeIN in the current study, showed the above findings and the undifferentiated PeIN was sub-categorized as Warty PeIN. The lesions displayed consistent histomorphological features of papillomatosis, spiky epithelial surface, and koilocytes. These findings are consistent with the criteria laid down by the recent WHO classifications and studies by Chau and Velazquez.<sup>(6,7,8)</sup>

**Penile squamous cell carcinoma (PSCC):** Penile carcinoma presents as a denovo lesion or may arise from a pre-malignant lesion. Presentation varies from small induration to a large ulcero-proliferative growth with metastasis.<sup>(10)</sup> Patients with PSCC in the current study population predominantly presented with a single focal lesion. Almost half the cases (49%) presented with a lesion over the glans and 31% had a lesion on the mucosal surface of the foreskin. A case of outer foreskin and shaft was also noted. This distribution is in concordance with a few studies conducted in

New Delhi in India, (5) Baltimore in the USA<sup>(11)</sup>, Tanzania<sup>(12)</sup>, and Brazil<sup>(13)</sup>. Interestingly, all cases received during the study period were that of PSCC and its histomorphological variants. This is in concordance with various literatures and recent WHO that states PSCC is the most common malignant lesion.<sup>(4,7,12,14-17)</sup> Partial penectomies were the most studied specimen followed by incisional and excisional biopsies, total penectomy, and circumcisions. The study conducted by Bezzera et al showed partial penectomy to be the most common specimen.<sup>(18)</sup> PSCC has been subcategorized into various distinct histomorphological variants based on clinical picture and HPV association.<sup>(19) (20)</sup> Lesions associated with HPV affect younger individuals and have a poor prognosis. In our study, we observed 7 PSCC variants. Similar studies in USA, Brazil, and Mexico, observed that Usual SCC was the most common variant regardless of the epidemiological barriers and the sample size of the study.<sup>(12) (17) (19) (21) (22)</sup> The discrepancies in representation of other variants with studies of Brazil and Mexico may be due to low sample size.<sup>(22, 23)</sup> 33 cases were diagnosed as usual SCC variant, and 17 cases showed well differentiated keratinization (Grade I), the cells were arranged in sheets and irregular nesting patterns with scant reactive stroma with abundant squamous keratin pearls. Twelve cases were categorized as moderately differentiated (Grade II) showing cellular atypia along with the irregular infiltrating border, small tumor cell nests, and a motley of other features. Poorly differentiated lesions (Grade III) accounted for 4 cases with minimal or absent keratinization, irregular growth (tumor invasion), cells were arranged in nests, solid and trabecular pattern and showed pleomorphism.<sup>(19, 21-23)</sup> Well differentiated lesions were most common in the present study which is contrary studies in the USA where moderately differentiated carcinoma was more common. Poorly differentiated was the most common lesion in Brazil and Mexico. The discrepancies in grading can be attributed to numerous factors like patient and consumer awareness, inter-observer variation from morphological assessment, and Quality of Health care. Verrucous carcinoma accounted for 7 cases with features of papillomatosis with hyperkeratosis and acanthosis without fibrovascular core (FVC). The tumor-stromal interface is broad-based and sharp delineation exists between the two. Based on the microscopic features, it is observed that the lesion is restricted to the lamina propria, no invasion was noted similar to other studies.<sup>(22,23)</sup>

Four cases of Warty carcinoma was diagnosed with malignant cells arranged in condylomatous papillae with a fibrovascular core and the presence of koilocytic cells. Tumor stroma interface is jagged in lesions with invasion and sharply demarcated in non-invasive lesions. Sarcomatoid carcinoma was observed in 2 cases in the study. They were papillomatous lesions with acanthosis having dysplastic cells with sub-epithelium replaced by sheets of spindle cells having high mitotic activity. One case of pseudoglandular carcinoma was reported which had the hallmark feature of pseudoglandular spaces resembling a honeycomb pattern.

One more case diagnosed as basaloid carcinoma had basaloid cells with the nested arrangement and keratin pearls in squamous areas along with frequent mitoses. A solitary case diagnosed as a mixed variant highlighted a combination of histological features of both basaloid and usual SCC.

**Non-malignant associated conditions of PSCC:** The conditions that are linked to the development of PSCC include squamous cell hyperplasia, Lichen sclerosis and Lichen planus of which lichen sclerosis shows the strongest PSCC association.<sup>(24)</sup> In our study, 5 cases of lichen sclerosis were seen associated with PSCC, of which 4 cases were of usual SCC and a solitary case of verrucous carcinoma. LVI is an independent morphological determinant of the aggressive nature of the lesion. In our study, 7 patients demonstrated LVI. The patients presented with deep-seated and multi-compartment involvement, which was appreciable, both macroscopically and in histopathological sections. The finding was similarly seen in the USA, Baltimore, 2015 which illustrated that LVI was an uncommon finding.<sup>(18)</sup> PNI was another morphological determinant studied by the researcher, where PNI was found to be the single most independent significant prognostic indicator and indicated poor outcomes.<sup>(25)</sup> In our study of 5 patients with perineural invasion, all additionally presented with lymphovascular invasion, which was as mentioned above linked to advanced disease. Regional lymph node metastasis is a major indicator of poor prognosis.<sup>(26-28)</sup> In the present study, lymph node metastasis was observed in 14.3% of cases. More deep-seated the tumor invasion into the erectile tissue, the greater the risk of lymph node metastases.<sup>(29)</sup> In our study, 11 cases presented with infiltration into the corpus cavernosum and corpus spongiosum out of which 7 cases were associated with nodal metastases (6 Usual SCC and 1 basaloid carcinoma). The finding of basaloid carcinoma with lymph node metastasis in agreement with the aggressive nature of the lesion.<sup>(30)</sup>

### Prognostic Index:

Histological grade, anatomical level of tumor infiltration, and PNI are considered among the chief prognostic parameters in penile cancer.<sup>(29,31)</sup> This Prognostic Index ranges scores from 2 to 7. It consists of grade, which is scored from 1 to 3, those are a) Grade I, PSCC with minimal atypia-scores 1, b) Grade III, tumors showing any proportion of anaplastic cells are scores 3, and c) Grade II scores 2 and includes lesions which can not be assigned either Grade I or Grade III; **Anatomic depth of Invasions** scored from 1 to 3, a) If Glans and foreskin show involvement of lamina propria, the lesion scores 1, b) If corpus spongiosum and/or dartos of the skin is involved the lesion scores 2, and c) A score of 3 was assigned to the lesion if it involved either one of the following corpus cavernosum, tunica albuginea or preputial skin.; the **Presence of PNI** was scored 1, and absence was scored 0. Based on the score as assigned by the prognostic index, cases were stratified into 3 groups.<sup>(29,31)</sup> They are 1) Low-risk group

Score 2 and 3, Intermediate risk group-Score 4, and high-risk group-Scores 5 to 7. The above groups quantify the risk of lymph node (LN) metastasis and also the need for inguinal dissection. Patients with low-risk groups do not undergo inguinal dissection while high-risk groups are suggested inguinal dissection. Patients in the intermediate group are treated on a case-by-case basis. In the current study, a majority of patients<sup>(16)</sup> received a prognostic index score of 2 or 3 (12) placing them in the low-risk group. 13 patients belonged to high-risk group. Ten patients with score 5, two with score 6 and one with score 7. Eight cases with score 4 belonged to intermediate risk. As study by Barreto et al was a multicentric study showed most cases were allotted to the high-risk groups.<sup>(29)</sup> In the current study, the perineural invasion (PNI) was seen in only the high-risk groups. PNI was seen in 4 out of 10 cases with score 5 and case with score 7. Current study and that by Barreto et al prove that high-risk groups demonstrated a relatively high rate of developing PNI, making it the standalone prognostic indicator.<sup>(29)</sup> The low-risk groups in the current study and study by Barreto et al showed no LN metastasis, intermediate and high-risk groups had nodal metastasis, which is in accordance with current literature as well as treatment guidelines.<sup>(29,31)</sup> Patients with a high risk underwent prophylactic inguinal lymph node dissection, while surveillance was done for low risk. LVI was seen in all high risk cases with LN metastasis. Additionally, 2 other cases with LN metastasis showed LVI but no PNI. The findings of LVI and PNI, and allocation of the case to the high-risk group are statistically significant in this study (p-value <0.001). Thus, the prognostic index was a strong predictor of nodal metastasis and survival in this study.

**The prognostic index was correlated with patient outcomes.** Patients in the intermediate groups generally had a favorable outcome compared to high-risk group. Of the 8 cases in the intermediate group, 2 patients had disease-free survival and another 2 required no additional interventions. 1 patient could only be followed for less than a year. On the flip side, 2 patients developed nodal metastasis and another one died because of illness not attributable to the disease. The study highlights the need for routine follow-up and monitoring of patients in the intermediate group, as the disease could advance and result in a poor prognosis. The data from the high-risk group is not representative of the 13 cases in the group, 6 were lost to follow-up. Another 2 cases were referred and had incomplete medical records. Of the remaining 5 cases, 2 showed disease-free survival, 2 died because of illness attributed to the lesion and 1 patient developed local recurrence. In comparison with the intermediate group, high-risk group did show worse patient outcomes, but these findings cannot be taken to be statistically significant, as the majority of cases could not be assessed accurately.

## CONCLUSION

Penile cancer is an uncommon malignancy. The substantial worldwide variation in penile cancer incidences has been attributed to varying socio-economic conditions and religious practices. With the advent of techniques such as IHC and HPV PCR has led to a better understanding of the pathogenesis of the tumor. This study has provided detailed analysis of the individual tumor determinants, such as histological grade, nodal metastasis, PNI, LVI and lastly, prognostic index. The scoring system was developed which is the prognostic index and has shown remarkable consistency in determining the risk of nodal metastasis in PSCC, which therein determines the treatment protocol for patients. The study calls for implementation of a pilot program to screen high-risk populations and provide them with HPV vaccinations and medical education to tackle the debilitating disease.

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**Conflict of interest:** The authors declare that they have no potential conflicts of interest to disclose.

**Data availability statement:** The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material. Raw data that support this study is available from the corresponding author upon reasonable request.

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