Original Article

Characterization of perineural invasion in different histological grades and variants of oral squamous cell carcinoma

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Abstract

Background: Oral squamous cell carcinoma (OSCC) accounts for 3% of all malignant neoplasms and is the fifth most frequent cancer in the world. They usually spread by hematogenous or lymphatic spread, and perineural invasion (PNI) is considered an alternate method of tumor spread where it is described as the tumor affinity toward a neural tissue.

Aim and Objectives: The present study aims to evaluate the biological behavior of OSCC with respect to PNI and to evaluate the importance of PNI with respect to different histopathological grades and variants, tumor stage and lymph node status of OSCC. PNI was also assessed with respect to its frequency, patterns, types and number in various grades of OSCC.

Materials and Methods: This retrospective, double-blind study was conducted on 148 histopathologically proven cases of different histopathological grades and variants of OSCC. The tissue sections were examined for PNI and its patterns and were further compared with habit history, site of the lesion, tumor staging, grading and lymph node status.

Results: A Chi-square test was performed. A percentage positivity of 45.27% (67 cases) among 148 cases was found. PNI positivity of 63.6% and 50% was observed in T4 and T3 tumor stages, respectively, with high significance. Seventy percent of cases belonging to poorly differentiated squamous cell carcinoma showed positivity for PNI, which was statistically significant. PNI positivity with respect to lymph node status is nonsignificant.

Conclusion: The present study showed that there is a direct proportionality between PNI and different grades and stages of OSCC. Given this context, a histopathologist ought to examine for PNI and make it mandatory to report the same to the clinician for better treatment and follow-up of the patient.

Keywords: Cancers, neurotropism, oral squamous cell carcinoma, perineural invasion

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INTRODUCTION

Head-and-neck cancers constitute a diverse group of epithelial malignancies that arise in the upper aerodigestive tract which includes paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx.[1] Oral cancers being the most common of head-and-neck cancers, accounts for 354,864

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new cases and 177,384 cancer-related deaths worldwide in 2018.[2] Cancers of lip and oral cavity are highly frequent in Southern Asia and also the leading cause of death in men of India and Sri Lanka.[2] The prime feature of malignant cells is their ability to dissociate and invade adjacent structures and distant sites. Increased locoregional recurrence and metastasis are attributed to its spread to the distant sites through lymphatic and hematogenous route.[1] The alternative mode of tumor spread with petite research consideration is through perineural invasion (PNI). The space between the axons of the nerve and the surrounding perineural layer is termed as perineural space; an accession into this space by the tumor cells is likely called as PNI.[2,3]

PNI is usually defined as a microscopic identification of small unnamed peripheral nerves within the vicinity of an invasive tumor.[4] The mere presence of tumor cells around the nerve does not contribute for PNI, keeping this in mind various definitions were proposed by different authors. Batsakis in 1985 proposed PNI as tumor cell invasion in, around and through the nerves.[5] However, in view of providing a broader definition, Liebig *et al.* in 2009 suggested that any tumor in close proximity to nerve and involving at least 33% of its circumference or tumor cells within any of the three layers (the epineurium, perineurium and endoneurium) of the nerve sheath is called PNI.[6]

PNI is a well-recognized factor associated with poor prognosis in tumors of prostate, melanoma, colorectal and pancreatic cancer and carcinoma of the salivary glands.[7] The purpose of the present study is to evaluate the biologic behavior of oral squamous cell carcinoma (OSCC) grades, histopathological variants, tumor stage and lymph node status with respect to PNI; to assess various patterns of PNI among different histological grades and variants of OSCC and to compare and correlate PNI between grades and variants of OSCC.

MATERIALS AND METHODS

A retrospective analysis of 148 histopathological sections of primary cases of OSCC patients from the archives of the Department of Oral and Maxillofacial Pathology, Government Dental College and Hospitals, Afzal Gunj, Hyderabad, Telangana, from January 1, 2017, till December 31, 2018, was carried out after obtaining institutional ethical committee clearance. The histopathological tissue sections stained with hematoxylin and eosin were evaluated by two observers independently to prevent interobserver bias, and the cases were divided into two categories depending on the presence or absence of PNI. The interobserver bias was calculated using intraclass coefficient analysis, which was 0.96 implying a good agreement between the two observers. The present study did not include recurrent cases of OSCC.

The case history and biopsy report files of these cases were retrieved, and the demographic data of age, sex, habit history and site of the lesion were recorded for all the patients. The data were compared with tumor stage, lymph node status, tumor grade and histopathological variants. The tissue sections were further evaluated for the predominant pattern of invasion of tumor cells and also at the tumor edge, which was based on the criteria given by Bryne *et al.* and Brandwein-Gensler *et al.* [Table 1].[8]

PNI was further assessed based on its size, extent, distance between the tumor edge and nerve and pattern of PNI. The size of the invaded nerve was categorized into two small nerve (diameter <1 mm) and large nerve (>1 mm). The extent of PNI, i.e., the number of nerves invaded by tumor cells in a tissue section, was evaluated based on the criteria used by Chinn *et al.* It is categorized as focal (1 focus of PNI), moderate (2–5 foci of PNI) and extensive (>5 foci of PNI).[9] The patterns of PNI are categorized as complete encirclement, incomplete "crescent-like" encirclement, sandwiching "onion skin," partial invasion and neural permeation [Figure 1].[10]

Statistical analysis

The obtained data of all the parameters were enlisted in Microsoft Excel sheet and further results were calculated in percentages and analyzed statistically through Chi-square test using the Statistical Package for the Social Sciences software, version 20.0 (IBM Corp. Released 2011, IBM SPSS Statistics for windows version 20.0, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The demographic and PNI data are illustrated in Table 2. In the present study, out of 148 histopathologically diagnosed cases of OSCC, 67 (45.27%) cases showed positive for PNI. The percentages of PNI with respect to site of the

Table 1: Various types of patterns of invasion

Type	POI
Type I	Tumor invasion in a broad pushing manner
Type II	Tumor invasion with broad pushing "fingers," or separate large tumor islands, with a stellate appearance
Type III	Invasive islands of tumor >15 cells per island
Type IV	Strands of tumor cells in a single-cell filing pattern, regardless of island size
Type V	Widely dispersed pattern of tumor infiltrate/tumor satellites of any size with 1 mm or greater distance of intervening normal tissue at the tumor/host interface

POI: Pattern of invasion

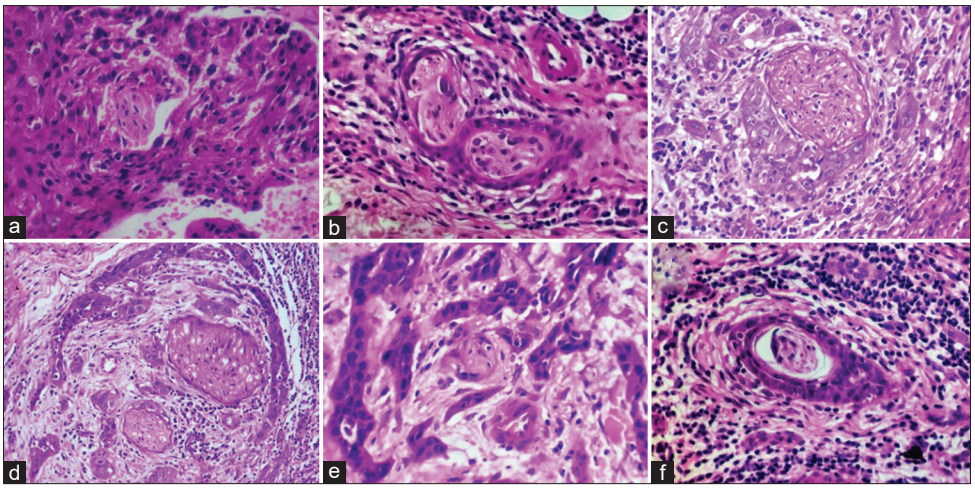

Figure 1: The patterns of perineural invasion: (a) Intratumoral encirclement, (b) complete encirclement, (c) incomplete "crescent-like" encirclement, (d) partial invasion, (e) "onion skin" and (f) neural permeation

Table 2: Demographic data and the percentages of perineural invasion with respect to tumor stage, grade and lymph node status

Characteristics	Number of total cases	Cases with PNI (%)
Gender		
Females	36	16 (44.45)
Males	112	51 (45.53)
Site		
Buccal mucosa	93	42 (45.16)
Floor of the mouth	3	2 (66.67)
Tongue	22	1 (4.5)
Alveolus	20	4 (20)
Palate	4	2 (50)
Gingiva	6	3 (50)
Lip	1	1 (100)
Retromolar area	1	0 (0)
Tumor		
T1	14	1 (7.14)
T2	75	35 (46.67)
T3	48	24 (50)
T4	11	7 (63.63)
Node		
N0	78	37 (47.43)
N1	67	30 (44.77)
N2	03	0 (0)
Grade		
WDSCC	47	13 (27.65)
MDSCC	70	34 (48.57)
PDSCC	20	14 (70)
Variants		
Basaloid	3	2 (66.66)
PIOC	6	2 (33.33)
Spindle-cell variant	1	1 (100)
Clear-cell OSCC	1	1 (100)

WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma, PIOC: Primary intraosseous carcinoma, PNI: Perineural invasion, OSCC: Oral squamous cell carcinoma

lesion are illustrated in Figure 2. OSCC in relation to the floor of the mouth and lip showed high positivity for PNI.

Habit history of paan and gutkha chewing, cigarette smoking and areca nut chewing was noticed in majority of the patients of OSCC. When habit history was compared with the presence or absence of PNI, of the 67 positive cases for PNI, 60 (89.5%) cases showed deleterious habits and the remaining 7 (10.5%) cases had no habit history.

All cases (148) of OSCC were evaluated for the size of the tumor (T), with 14 cases belonging to T1, 75 cases of T2, 48 cases of T3 and 11 cases of T4. PNI positivity was seen in 7.14% of cases of T1, 46.67% of T2, 50% of T3 and 63.63% of T4. Chi-square test showed a highly significant $P = 0.016908$ ($P < 0.05$) among various cases with respect to tumor size, with T4 tumors having high amount of PNI [Table 3].

In different grades of OSCC, out of 47 cases of well-differentiated squamous cell carcinoma, 27.65% of cases show PNI. Among 70 cases of moderately differentiated squamous cell carcinoma (MDSCC), 48.57% of cases show PNI, and among 20 cases of poorly differentiated squamous cell carcinoma (PDSCC), nearly 70% of cases showed PNI. Chi-square test showed highly significant difference with $P = 0.003827$ ($P < 0.05$) [Table 4].

Histopathological variants of OSCC included in the present study are basaloid-cell variant, PIOC, spindle-cell variant and clear-cell squamous cell carcinoma, where most of the cases showed PNI. The proportion of cases of PNI in different grades and variants of OSCC is illustrated in Figure 3.

Among the total of 148 OSCC cases, 70 cases showed lymph node involvement, of which only 30 (42.9%) cases showed PNI. The Chi-square test of these OSCC cases with or without PNI in relation to lymph node status

showed a nonsignificant $P = 0.576352$ ($P > 0.05$). The comparison of lymph node status with PNI involvement and calculations are illustrated in Figure 4 and Table 5.

In cases of OSCC with PNI, the predominant mode of invasion of tumor cells in the tissue section is Type II pattern (55.7%) and the predominant pattern of invasion of tumor cells at tumor edge is Type III (55.7%) [Table 6].

Further assessment of all cases with PNI in relation to the nerve size showed 119 small- and 104 large-sized nerves (total of 223 nerves) in all cases of PNI-positive OSCCs. In 67 cases, 37.3% of cases showed focal ($n = 1$) number of nerves, 46.2% of cases showed moderate ($n = 2–5$) amount of nerves and 16.4% of cases showed extensive ($n > 5$) amount of nerves in their respective tissue sections.

Chi-square test of density of PNI in different grades of OSCC showed $P = 0.1596$ ($P > 0.05$), which was statistically nonsignificant [Table 7].

Various patterns of PNI among different cases of PNI are as follows: 21 cases showed intratumoral encirclement, 13 cases showed complete encirclement, 20 cases showed incomplete "crescent-like" encirclement, 1 case showed sandwiching "onion skin," 27 cases showed partial invasion and 3 cases showed neural permeation.

A total of 223 small and large nerves in 67 cases showed various patterns of PNI. The details are as follows: 47 (21%) nerves showed intratumoral encirclement (a), 28 (12.5%) nerves showed complete encirclement (b), 26 (11.6%) nerves showed incomplete "crescent-like" encirclement (c), 2 (0.08%) nerves showed sandwiching

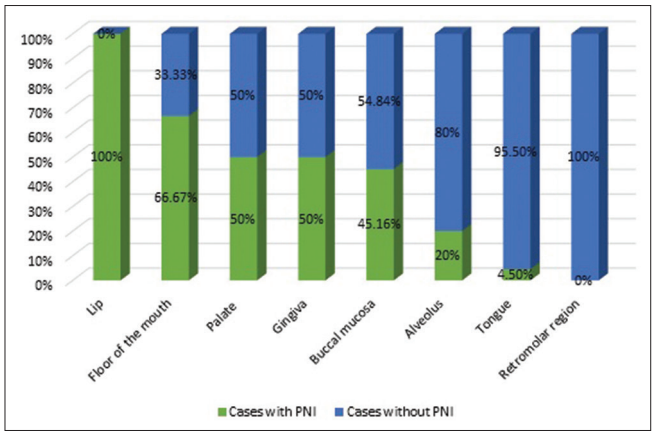

Figure 2: Percentage of cases with PNI based on the location

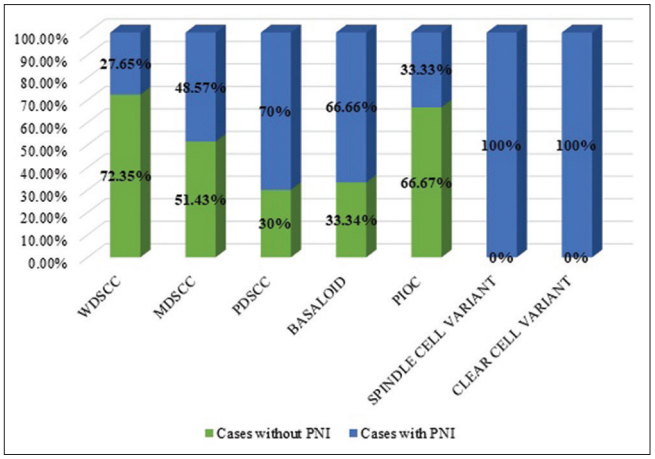

Figure 3: Percentages of PNI in different grades and variants of OSCC

Table 3: Presence of perineural invasion with respect to tumor thickness (T) using Chi-square test

Tumor stage	Number of cases without PNI (%)	Number of cases with PNI (%)	Chi-square value	*P*
T1	13 (92.85)	1 (7.15)	10.2042	0.016908*
T2	40 (53.33)	35 (46.67)		(<0.05)
T3	24 (50)	24 (50)		
T4	4 (36.36)	7 (63.64)		

*Significant. PNI: Perineural invasion

Table 4: Chi-square test of different grades of oral squamous cell carcinoma with respect to perineural invasion

Grade	Number of cases without PNI (*n*1)	Number of cases with PNI (*n*2)	Chi-square value	*P*
WDSCC	34	13	11.1312	0.003827*
MDSCC	36	34		(<0.05)
PDSCC	6	14		

*Significant. PNI: Perineural invasion, WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 5: Chi-square test of comparison of oral squamous cell carcinoma cases with lymph node status to perineural invasion involvement

	Cases without PNI	Cases with PNI	Chi-square statistic value	*P*
OSCC without lymph node involvement	41	37	0.3122	0.576352
OSCC with lymph node involvement	40	30		(>0.05) NS

NS: Nonsignificant, PNI: Perineural invasion, OSCC: Oral squamous cell carcinoma

"onion skin" (d), 112 (50.2%) nerves showed partial invasion (e) and 8 (3.58%) nerves showed neural permeation (f) [Table 8].

DISCUSSION

OSCC is usually diagnosed and graded histopathologically using various parameters such as resemblance to parent epithelium, degree of atypia and atypical mitosis. However, on a routine basis, grading of OSCC is subjective and variable due to high interobserver bias.

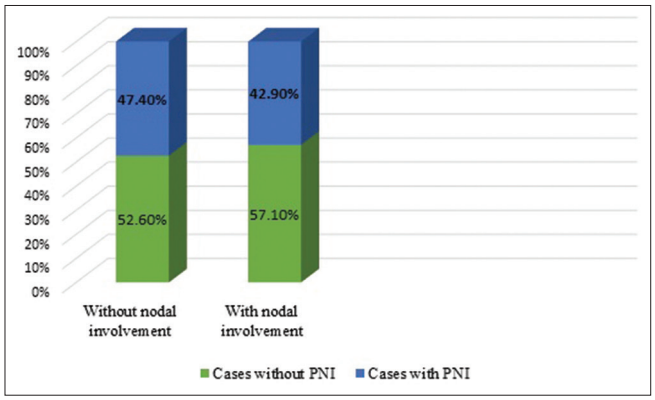

Figure 4: Lymph node status with relation to PNI

Table 6: Pattern of invasion of tumor cells in tissue section and at tumor edge of oral squamous cell carcinoma cases with respect to perineural invasion

POI of tumor cells	Predominant pattern in section (%)	At tumor edge (%)
Type I	1.49	0
Type II	55.7	11.4
Type III	37.7	55.7
Type IV	4.91	31.1
Type V	0	1.49

POI: Pattern of invasion

PNI is a parameter under consideration to provide the information related to aggressiveness of tumor. Although the Royal College of Pathologists in the United Kingdom and the College of American Pathologists recorded the existence of PNI in histopathological analysis, especially when occurring ahead of invasive tumor front, the accuracy of PNI is considered controversial and open to subjectivity.[11]

In 1835, Cruveilheir first described the perineural spread in relation to head and neck region.[12] PNI was studied extensively in different types of cancer and it is established with high recurrence rates and associated poorer prognosis.[7,13]

Various studies published in literature showed that PNI is associated with disease recurrence, probability for distant metastasis and decreased patient survival.[10,14] The pathogenesis behind PNI in cancers is because of the potentially weakened area formed due to the lack of perineural layer near the nerve ending. Production of proteases such as matrix metalloproteinases by tumor cells leads to direct invasion into the epineurium of the nerve. These tumor cells also undergo epithelial–mesenchymal interactions allowing individual cell invasion, which further release multiple chemical factors that modulate the risk of PNI. At first, to increase the physical contact between the nerve and tumor cells and for homing of tumor cells to nerve (neurotropism), they induce the proliferation of neurites via reciprocal signaling followed by changes in the tumor microenvironment to promote invasion of tumor cells.[15]

The neurotrophic factors that induce the neurotropism of tumor cells include brain-derived neurotrophic factor,

Table 7: Comparison of different grades of oral squamous cell carcinoma with the density of perineural invasion using Chi-square test

Grade	Focal (*n*=1 nerve)	Moderate (*n*=2-5 nerves)	Extensive (>5 nerves)	Chi-square statistic	*P*
WDSCC	8	3	2	6.5836	0.1596 (NS)
MDSCC	10	17	7		(>0.05)
PDSCC	4	9	1		

NS: Nonsignificant, WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 8: The total number of nerves showing different patterns of invasion in different grades and variants of oral squamous cell carcinoma

	WDSCC	MDSCC	PDSCC	Basaloid	Spindle	Clear cell	PIOC
a	6	26	13	1	1	-	-
b	2	12	13	-	-	-	1
c	4	12	9	-	-	-	1
d	-	1	1	-	-	-	
e	20	45	39	2	5	-	1
f	1	4	2	-	-	1	-
Total (%)	33 (14.79)	100 (44.84)	77 (34.52)	3 (0.13)	6 (0.26)	1 (0.04)	3 (0.13)

WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma, PIOC: Primary intraosseous carcinoma

glial cell line–derived neurotrophic factor), nerve growth factor, neurotrophins 3 and 4 (NT-3, NT-4), the neural cell adhesion molecule (N-CAM) and substance P.[4,15]

The incidence of PNI ranges from 2.5% to 5.0%.[16] PNI is observed in wide variety of head-and-neck malignancies, which includes salivary gland tumors such as adenoid cystic carcinoma and polymorphous adenocarcinoma.[15] A study conducted by Vural *et al.* showed 93% positive expression of N-CAM neuropeptide molecule in cases of head-and-neck squamous cell carcinoma.[17] Similarly, p75 neurotrophin receptor also helps in providing information of perineural spread of tumors.[15]

In the present study, the percentage of PNI observed was as high as 45.27% among 148 cases of OSCC. In a study conducted by Varsha *et al.*,[18] the percentage positivity of PNI observed was 40.5%, which was nearly similar to the current analysis. The present study also showed equal amount of positivity for PNI among females and males.

PNI was highly positive in OSCC occurring in relation to the floor of the mouth and lip followed by palate and gingiva, suggesting that these can be the sites of maximum invasion and spread.

Among different grades of OSCC, there is an increased PNI positivity observed from well differentiated to poorly differentiated OSCC with a high statistical significance. Manjula *et al.*[19] found positive association of PNI with PDSCC, whereas Varsha *et al.*[18] found PNI to be highly associated with MDSCC. The above-said results signify the importance of PNI relating to the belligerence of the tumor.

Spindle-cell and clear-cell variants of OSCC showed 100% of PNI. However, PIOC and basaloid variants showed 33.33% and 66.66% PNI, respectively. Among the above-said variants, the number of cases was limited, the percentage of PNI cannot be confirmed and an analysis on larger sample size is advised to presume the result. This study is the first of its kind to find the association of PNI with histopathological variants of OSCC.

Correlating the tumor stage with PNI exhibited a highly significant difference among different stages, with T3 and T4 showing the maximum amount of PNI. This brief correlation provides an insight into the proportionality of PNI with increase in the size of tumor. This observation was in concordance with the studies conducted by Varsha *et al.*[18] and Liao *et al.*[20]

Correlating with the lymph node status, it showed nonsignificance of PNI between the cases of OSCC with lymph node involvement and without involvement, suggesting PNI to be independent of lymph node status. These findings are in concordance with Wallwork *et al.*[21] who detected no significant association between PNI and nodal status. On the contrary, the studies conducted by Tarsitano *et al.*, Larsen *et al.*, Miller *et al.* and Varsha *et al.*[7,18,22,23] found a significant association between PNI and lymph node metastasis.

There is an involvement of 223 smaller and larger nerves among 67 cases of PNI-positive OSCC, of which 112 nerves showed PNI with partial invasion and 47 nerves showed PNI with intratumoral or complete encirclement**.** These two types of PNI are also associated with an increased tumor stage and grade of OSCC. Majority of the studies carried out to determine the clinical implications of PNI on the behavior of OSCC showed that PNI of different degrees is associated with disease recurrence, regional and distant metastasis and decrease in 5-year survival rate.[24] These variations indicating the prognostic importance of PNI might be due to the size of the nerves involved.[24,25] Binmadi and Basile, in their discussion related to significance of PNI found that, SCC of lip showed higher rate of recurrence when exhibiting PNI and were difficult to control, and also demonstrated intracranial spread through the regional nerves and subsequent invasion of the central nervous system, thereby severely limiting treatment options.[11] Woolgar *et al.*[24] and Barrett and Speight[25] in their studies concluded that both smaller and larger nerves exhibiting PNI can be allied with increased recurrence and reduced survival rates and the prognosis may worsen when major nerves are involved. However, the correlation between the recurrence and survival rates with relation to PNI was not done in the present study. Considering the density of nerves, a majority of cases, i.e., 32 (46.2%), showed moderate density of nerves (n = 2–5). The poorly differentiated tumors showed moderate density of nerves.

PNI with OSCC is associated with increased tumor stage and grade. This association suggests that tumor cells that invade the perineural space are more aggressive and also are more likely to recur.[14] The major limitation of the present study includes smaller sample size and lack of comparison between PNI with the treatment options, outcome, overall survival rate and prognosis.

CONCLUSION

Many of the treatment decisions in the current circumstances are based on TNM staging, imaging studies

and histopathological features. Given this, the present study showed the correlation and proportionality of PNI with the increasing tumor stage and grade of OSCC, which might affect the prognosis and outcome of the disease. Hence, histopathologists ought to examine for PNI in the tissue sections of head-and-neck cancers and report the same to the clinicians for unswerving treatment and follow-up of patient. Hence, PNI can also be included in the histopathological reporting pro forma, especially in OSCC cases.

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Conflicts of interest

There are no conflicts of interest.

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