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Peri-neural Invasion in Oral Squamous Cell Carcinoma (OSCC): A Clinico-pathological Marker of OSCC Prognosis and Risk Assessment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims And Objectives: To assess the incidence of Peri-Neural invasion in oral squamous cell carcinoma (OSCC), and to notify its significance as potent risk factor in OSCC recurrence and metastasis.

Study Design and Place of Study: A retrospective in vitro study was conducted at Indira Gandhi Institute of Medical Sciences, Patna, after approval of ethical committee

Material and Methods: Clinical, histopathological and follow-up details of 86 cases of oral squamaous cell carcinoma were collected from medical records as secondary data from December 2019 till April 2021. Peri-Neural invasion was assessed in all patients and was associated with, lymph node involvement and with the different histologic grades of OSCC. Location, density and

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patterns of Peri-Neural invasion was checked along with extracapsular spread and survival. Chisquare test was used for analyzing statistical data. P value of < .05 was considered as significant **Results:** On statistical analysis it was found that, out of total 86 cases of OSCC, 59 were primary and 27 were recurrent OSCC. Male to female ratio was 3:1 and primary cases were more in age group of 35-44 years where as recurrent OSCC were more in age group of 55-64 years. Out of 59 primary cases of OSCC, Peri-Neural invasion was seen in 27 cases and out of 27 recurrent OSCC 18 had Peri-Neural invasion with a total of 45 cases with Peri-Neural invasion out of 86. Intratumor location was assessed in 22 cases and density of 1-2 nerves per section was seen. "Crescent"

Conclusion: Our study affirmed that the incidence of Peri-Neural invasion is high in OSCC. It is present in both primary and recurrent tumors, irrespective of tumor's grading. PNI must be assessed in all cases of OSCC as it gives markable impression on recurrence, metastasis and prognosis, and modulates treatment protocols.

Keywords: Oral squamous cell carcinoma (OSCC); Peri-Neural invasion (PNI); Neurotropic carcinoma.

1. INTRODUCTION

Oral cancer contributes to 3% of all neoplasms [1] and particularly oral Squamous cell carcinoma (OSCC) encompasses 95% of all head and neck cancers and it is the 6th most frequently occurring cancer globally [2]. In spite of advanced treatment modalities, OSCC still for high recurrence, accounts disease complications, treatment morbidities and poor disease free survival [3]. Among all epithelial malignancies, OSCC is a heterogeneous group of neoplasm that initiates from the vicious cycle of genetic and epigenetic changes, mainly due to tobacco-associated carcinogens, which in turn activates oncogenes and inactivates tumor suppressors [4]. These genetic changes bestow proliferation and survival benefits to the altered cells, marked by growth factor individual cell division, resistance to apoptotic signaling and an increased capacity to degrade and pass through the tissues of the extracellular matrix and conquer structures in vicinity [5]. The capacity of cancer cells to break through the basal lamina, free themselves from the original lesion, avoid host defenses, gain passage to lymphatics or the circulation, and generate a new proliferating lesion at a distant site is the formula for metastasis and thus it's an enigma to even recent treatment techniques [6]. Interactions between epithelial tumor cells and the corresponding stroma may influence cancer initiation and disease progression. Treatment options in OSCC are mostly based on, TNM classification, site of tumor, pathologic features and patient's clinical conditions [7].

It is a well known fact that positive margins, nodal metastasis, extracapsular spread and perineural invasion (PNI) and lymphovascular invasion (LVI) are notable risk factors for the treatment outcomes of oral squamaous cell carcinoma (OSCC) patients [8]. Although earlier perineural invasion and lymphovascular invasion were not considered important but later many studies have reported it as significant risk marker of OSCC recurrence [9]. The perineural space provides an appropriate tumor microenvironment for the growth of cells from Neurotropic malignancies due to propensity of tumor cells for nerve fibers in the vicinity of the tumor and is a form of metastatic tumor spread unlike vascular or lymphatic invasion that stops the local control of a malignancy as tumor cells can travel along nerve tracts distant from the primary lesion [10]. As a result, these tumors can exhibit pain and persistent growth with a long clinical course and late onset of metastases, a pattern that has been observed in Neurotropic tumors like OSCC [11]. Clinical, histological, and biological features of PNI have been studied extensively in several types of head and neck cancers. Aim and objective of our study was also focused to check the incidence and risk of recurrence and morbidity bestowed by PNI in OSCC.

2. MATERIALS AND METHODS

2.1 Study Design, Place of Study & Ethical Clearance

A retrospective in vitro study was conducted at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India, after approval of ethical committee

2.2 Data Collection & Time of Study

Clinical, histopathological and follow-up details of 86 cases of oral squamaous cell carcinoma were

collected from medical records as secondary data. Data regarding the TNM staging were obtained retrospectively according to TNM staging proposed by the Union for International Cancer Control (*UICC*). Period of collection of data was from December 2019 till April 2021.

2.3 Inclusion and Exclusion Criteria

All patients from stage I to stage IV OSCC with clear margins were enrolled in this study. Exclusion criteria was cases with proven distant metastasis at presentation, previously treated/untreated primary head and neck cancer or malignancies outside the head and neck regions, the presence of simultaneous second primary cancer, or previous radiotherapy covering the head and neck region due to other diseases.

2.4 Materials and Methodologies of Study

Hematoxylin and eosin-stained sections cut from paraffin-embedded tumor specimens were assessed. Tumor grading was done as well, moderate and poor based on the degree of pleomorphism keratinization, nuclear and number of mitoses. The Clinico-pathologic features were associated and the cut sections were examined for the presence of PNI. Various parameters such as location of PNI, number of nerves involved per section (PNI density) and patterns of PNI were also assessed. PNI was confirmed when tumor cells were identified in the perineural space or epineurium. Tumor cells not within the perineural space, but present just abutting the nerve were not considered as PNI [12].

Density and location of PNI were assessed as per the the criteria specified by Miller *et al* [13]. For every foci of PNI identified, distance to tumor edge (in millimeters) was assessed. A positive value indicated extratumoral location and a negative value indicated an intratumoral location. Location was arbitrarily assigned as peripheral if the focus of PNI was located 0–0.2 mm from the tumor edge. The density of PNI was calculated by tallying the number of PNI foci per tissue section. They were broadly subcategorized as 1– 3 nerves/section and >3 nerves per section.

2.5 Statistical Analysis

Chi-square test was used for analyzing statistical data. P value of < .05 was considered as significant.

3. RESULTS

On data analysis it was found that, out of total 86 cases of OSCC, 59(68.6%) were primary and 27(31.3%) were recurrent OSCC (Fig. 1). Male to female ratio was 3:1(Fig. 2) and primary cases were more in age group of 35-44 years where as recurrent OSCC were more in age group of 55-64 years (Fig. 3). Summary of clinicopathologic characteristics of 86 patients is tabulated in Table 1.

Out of 59 primary cases of OSCC, Peri-Neural invasion was seen in 27(45.7%) cases and out of 27 recurrent cases of OSCC, 18(66.6%) had Peri-Neural invasion with a total of 45(52.3%) cases with Peri-Neural invasion out of total 86 cases of OSCC (Fig. 4).

Out of 47 well differentiated tumor 19(40.4%) had PNI (IMAGE 1), whereas 20(68.9%) out of 29 Moderately differentiated tumor (IMAGE 2) and 6(13.3%) out of 10 poorly differentiated OSCC had PNI (IMAGE 3) (Fig. 5).

Out of 17 T1 Stage cases 5(29.4%) showed PNI, 11(52.38%) out of 21 T2 stage cases, 14(63.6%) out of 22 T3 stage cases and 15(57.6%) out of 26 T4 stage cases had PNI involvement (Table 2). PNI was present in 19(48.71%) out of 39 cases of clinically negative nodes whereas PNI was present in 26(55.3%) out of 47 clinically positive nodes (Fig. 6). Intra tumor location was assessed in 22(48.8%) cases whereas 23(51.1%) cases had extratumoral location (Fig. 7). Density of 1-3 nerves per section was seen (Table 3). Distribution of perineural invasion in primary and recurrent cases of Squamous cell carcinoma using Chi-square test is depicted in Table 4. P value was not significant may be due to less sample size.

4. DISCUSSION

Histologic evidence of PNI is marker of a poor prognostic factor and indicative of the need for adjuvant therapy. PNI is an important pathologic entity that can even be seen in the absence of lymphatic or vascular invasion [14]. It can be main cause of distant tumor spread or may be the sole route of metastatic spread [15].

The perineural space provides an appropriate tumor microenvironment for the growth of cells from neurotropic malignancies, probably due to the secretion of cellular factors [such as brain derived neurotrophic factor (BDNF), the glial cell line derived neurotrophic factor (GDNF), the neural cell adhesion molecule (NCAM), the nerve growth factor (NGF), substance P (SP), and chemokines [16]. The presence of the respective receptors that attract cancer cells, stimulate their growth and proliferation along the nerves [17]. It is very likely that the prognosis worsens when major nerves are involved, which mainly occurs in advanced stage OSCC patients. For stages I and OSCC with PNI, tumors most often invaded "no-name" nerves. Thus, the survival of patients with stages I and II OSCC with PNI would not be significantly influenced [18].

Some of the drawbacks of the recent staging system is the lack of recognition of prognostic factors such as PNI, lymphatic and vascular



Fig. 1. Total No. Of OSCC Cases (86)

invasion, morphology (exophytic vs. endophytic), tumor host interface (infiltrative vs. pushing margins) under the "T" category in head and neck carcinomas [19]. To the best of our knowledge, there are no published studies focusing on specific characteristics of PNI, such as the type, extension, and quality in OSCC, especially as it associates with the clinical impact. In OSCC, only the assessment of presence or absence of invasion in the perineural space is a required component of pathologic analysis according to reporting protocols published [20]. Although perineural invasion (PNI) and lymphovascular invasion (LVI) were not regarded as significant risk factors in earlier studies, they were recognized as potent risk factors for local and regional control in other recent studies [21].



Fig. 2. Male: Female Ratio (3:1)

Table 1.	Clinicopat	hologic f	features
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Clinicopathologic Features	No. Of Cases	Percentage	
Primary Cases	59	68.6%	
Recurrent Cases	27	31.3%	
Histologic Differentiation			
Well	47	54.6%	
Moderate	29	33.7%	
Poor	10	11.6%	
T- Staging			
T1	17	19.7%	
T2	21	24.4%	
Т3	22	25.5%	
Τ4	26	30.2%	
Nodal involvement			
Node present	47	54.65%	
Node absent	39	45.3%	

Stage of Tumor	PNI Involved	PNI Not Involved	
T1	5	12	
T2	11	10	
Т3	14	8	
T4	15	11	

I	able	2.	Tumor	stage
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TADIE J. DEHSILY ULFINI	Table	3.	Density	of	PNI
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Density	No. of Cases
1-3 Nerves / Section	34(75.5%)
More than 3 Nerves /Section	11(24.4%)



Fig. 3. Recurrent and primary cases



Fig. 4. Present and absent of PNI

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Fig. 6. Absent and presence of nodes

Table 4.Chi square results

Type of tumor	PNI Present	PNI Absent	CHI-square Test	P value
Primary Tumor	27 (45.7%)	32 (54.2%)		
Recurrent Tumor	18 (66.6%)	9 (33.3%)	2.461	0.116

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Fig. 7. PNI location



Image 1. Well differentiated OSCC



Image 2. Moderately differentiated OSCC

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Image 3. Poorly differentiated OSCC

Prognosis and, therefore, treatment guidelines are mostly dependent on TNM staging, as determined by clinical examination, imaging and histopathologic characteristics in the biopsy which affect patient outcome. The presence of PNI is one such histopathologic feature. Most of the studies have shown that PNI is associated with disease recurrence, increased probability of regional and distant metastasis and an overall decreased 5-year survival rate in head and neck squamous cell carcinoma [22].

Our study may have some limitations considering its sample size and a statistical model applied as ours was a hospital based retrospective observational study with qualitative data. Another minor limitation could be the arbitrarily assigned location of PNI from the tumor edge which may have led to an observational bias. Well-designed randomized prospective studies with more patients are needed to accurately clarify the importance of PNI in prognosis of OSCC.

Clarifying the mechanism of its spread, the various molecular events that promote PNI in OSCC can bring paradigm shift in the development of therapeutic agents that target this form of tumor spread. Since PNI is present in both primary and recurrent tumors, irrespective of its histologic grade, it should be checked and uniformly reported in every OSCC case as it is of utmost importance to modulate the prognosis and treatment protocol.

5. CONCLUSION

Our study revealed that the incidence of Peri-Neural invasion is high in OSCC. It is present in both primary and recurrent tumors, irrespective of tumor's grading. PNI must be assessed in all cases of OSCC as it gives markable impression on recurrence, metastasis and prognosis, and modulates treatment protocols.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

A retrospective in vitro study was conducted at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India, after approval of ethical committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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