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Research Article

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Prognostic Significance of Worst Pattern of Invasion in oral cavity Squamous Cell Carcinoma in relation to lymph node metastasis —A Retrospective Study from tertiary care centre

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ABSTRACT

Introduction: Squamous cell carcinoma is the most common head and neck carcinoma, comprising 90% of cancers of the head and neck region1.Globally, oral cancer ranks sixth among all types of cancer. India has the largest number of oral cancer cases and one-third of the total burden of oral cancer globally. It is an important cause of morbidity and mortality worldwide. Oral cavity Squamous Cell Carcinoma(OSCC) commonly results from potentially malignant lesions or normal epithelium linings. Oral SCC spread typically occurs via lymphatic system. Conventional OSCC is aggressive, with a propensity for local invasion & early lymph node metastasis. Lymph node involvement is important prognostic factor in OSCC. So it's important to access most influencing histological parameter in association with lymph node metastasis. This study was conducted to evaluate the role of histological parameters including Worst pattern of invasion (WPOI) and Depth of invasion (DOI) to determine the risk of LN metastasis in cases of OSCC. **Objective**: To evaluate the role of worst pattern of invasion to determine risk of lymph node metastasis in oral squamous cell carcinomas. **Methodology**: After receiving an approval of institutional ethical committee the study was conducted in histopathology section of pathology department. This was a retrospective study. All the cases of buccalmucosa and tongue SCC who underwent resection with cervical lymph node dissection in our institute from October 2021 to January 2023 were included. Cases where patient received preoperative radiotherapy or chemotherapy or where LN dissection was not performed or where slides were not available for review were excluded. Total 108 cases were evaluated and slides were stained by H & E and examined microscopically. Collected data is entered in Microsoft excel. **Observation And Results**: A total of 108 cases were studied, which included 94 males and 14 females (M:F = 6.7:1). 76 (70.37%) cases were of above 50 years of age and 32 (29.6%) cases were of below 50 years of age (average: 47.2 years). The most common site in our study was buccal mucosa (42 cases i.e. 38.8%). P value is 0.00(at 5% level of significance), so there is strong association between DOI of tumor with WPOI. p value is 0.0092(at 10% level of significance), so there is strong association between lymph node metastasis and WPOI. In this study number of cases of moderately and poorly differentiated tumors is 48 out of which 24 (50%) cases were positive for LN metastasis and out of 60 well differentiated tumors 12 (20%) were positive for Lymph node metastasis with p value 0.02 at 5% level of significance. Other parameters such as tumor grade, tumor stage, lymphovascular emboli(LVE), perneural infiltration(PNI), Tumor thickness do not show any significant association with WPOI. **Conclusion**: The present study concluded that aggressive POI are significantly associated with number of lymph nodes metastasis and Depth of invasion and hence can be an independent histopathologic prognostic parameter in OSCC.

Key Words: *Worst pattern of invasion, Depth of invasion, Lymphovascular invasion, Perineural invasion*

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INTRODUCTION:

Squamous cell carcinoma is the most common head and neck carcinoma, comprising 90% of cancers of the head and neck region[1]. Globally, oral cancer ranks sixth among all types of cancer. India has the largest number of oral cancer cases

and one-third of the total burden of oral cancer globally. In India, around 77,000 new cases and 52,000 deaths are reported annually, which is approximately one-fourth of global incidences. OSCC commonly results from potentially malignant lesions or normal epithelium linings. Potentially malignant disorders (PMDs) such as inflammatory oral submucosa, fibrosis, erythroplakia, leukoplakia, candidal leukoplakia, dyskeratosis congenital, and lichen planus are indicators of the preclinical phase of oral cancer . Tobacco consumption including smokeless tobacco (SLT), betel-quid chewing, excessive alcohol consumption, poor oral hygiene, nutrient-deficient diet, and sustained viral infections, i.e. human papillomavirus (HPV) are some of the risks associated with the occurrence of oral cancer[2].

Researchers have evaluated different clinical and histological parameters for predicting the risk of LN metastasis in oral cavity cancers. Various histological parameters are associated with a higher incidence of nodal metastasis in oral cavity cancer. Lymphovascular emboli (LVE) and perineural invasion (PNI) are well-known histological risk factors for predicting nodal metastasis. However, LVE and PNI are difficult to evaluate, especially in small biopsies. An invasive pattern of infiltration is associated with higher risk of LN metastasis and poor disease-free survival[3].

This study was conducted to evaluate the role of histological parameters including pattern of invasion (POI) and Depth of invasion(DOI) to determine the risk of LN metastasis in cases of OSCC.

OBJECTIVE:

To evaluate the role of worst pattern of invasion to determine risk of lymph node metastasis in oral squamous cell carcinomas.

MATERIALS AND METHODS

This was a retrospective study. All the cases of buccalmucosa and tongue SCC who underwent resection with cervical lymph node dissection in our institute from October 2021 to January 2023 were included. Cases where patient received preoperative radiotherapy or chemotherapy or where LN dissection was not performed or where slides were not available for review were excluded. The size of the tumor was noted from the surgical pathology report, and the pT stage was determined based on the American Joint Commission on Cancer (AJCC) tumor node metastasis (TNM) staging, 8th edition. The following histological parameters were evaluated in each case degree of differentiation, depth of invasion, worst pattern of invasion (WPOI), PNI, LVE. Grading of tumor was done as per World Health Organization (WHO) definition based on the degree of differentiation, cellular pleomorphism, and mitotic activity as recommended in CAP guidelines as well, moderately and poorly differentiated. DOI was assessed as per College of American Pathologists (CAP) dataset guidelines as the distance between the lowest part of the adjacent normal mucosa and the lowest part of the tumor. The depth was measured in millimeter using slide caliper, and it was graded as D1 (5 mm), D2 (>5 mm, 10 mm), and D3 (>10 mm). The invasive tumor front was evaluated for pattern of invasion (POI). The POI classified as 5 patterns. Pattern 1 was defined as broad, pushing margin of tumor with a smooth outline. Pattern 2 was defined as broad, pushing finger-like projection. Pattern 3 represents invasive tumor islands with >15 cells per island. Pattern 4 represents invasive tumor islands with less than 15 cells per island. Pattern 5 was defined by the presence of tumor island outside the main tumor at a distance of >1 mm. Among these 5 patterns, POI 4 and 5 were classified as invasive pattern, whereas POI 1 to 3 as cohesive pattern. Perineural invasion was determined as a nerve being surrounded or infiltrated by the tumor. Tumor invasion within arterial, venous, or lymphatic channels qualified for LVE. Brandwein– Gensler's histologic risk model for WPOI is the most popular. It predicts the risk for locoregional recurrence Brandwein–Gensler's risk scoring system

Worst pattern of Invasion (WPOI)	WPOI score
Type 1 - Pushing border	0
Type 2 - Finger-like growth	0
Type 3 - Large separate islands, 15 cells per island	0
Type 4 - Small tumor islands, 15 cells or fewer, per island	+1
Type 5 - Tumor satellites, = /1 mm from main tumor or next closest satellite	+3

RESULTS

A total of 108 cases were studied, which included 94 males and 14 females (M:F = 6.7:1). 76 (70.37%) cases were of above 50 years of age and 32 (29.6%) cases were of below 50 years of age(average: 47.2 years). The most common site in our study was buccal mucosa (42 cases i.e 38.8%).Other sites included 32(29.6%) of tongue, 18 (16.6%) cases of gingivobuccal sulcus, 14 (12.96%) cases of retromolar trigone and 2 (1.85%) cases of lip .(Table 1).

The tumor thickness ranged from 0.7 cm to 5.5 cm ,is divided into three groups including 99(90.7%) cases showed tumor thickness less than /=5mm,10(10.2%) cases showed tumor thickness 5-9mm,no case showed tumor thickness more than/ = 10mm . There were 34 (31.4%) T1, 50(46.2%) T2, 12(11.1%) T3, and 12 (11.1%) T4 tumors . Out of total , 60 (55.5%) cases were of well differentiated squamous cell carcinoma ,46 (42.5%)cases were of moderately differentiated SCC , 2 (1.8%) cases were of poorly differentiated SCC. Resection margin of 96(88.88%) cases were negative more/=5mm, 12(11.11%) cases were having close resection margin less than 5mm.

Depth of invasion of tumor is divided into three groups, 20 (18.5%) cases showed DOI less than/= 5mm and there was no case identified with aggressive group of WPOI, 56 (51.8%) cases showed DOI 6-9 mm and out of these 10(21.7%) cases were from aggressive group of WPOI, 32 (29.6 %) cases showed DOI more than/=10 mm and out of these 22(68.75%) cases were from aggressive group of WPOI. P value is 0.00, so there is strong association between DOI of tumor with WPOI.(Table 2)

Tumor WPOI is divided into two groups, non aggressive (WOPI 1,2,3) includes 76 (70.37%) cases and aggressive (WPOI 4,5) includes 32 (29.62%) cases. Out of total 108 cases, 36 (33.33%) cases showed lymph node metastasis and 72 (66.66%) cases were free of lymph node metastasis. The LN stage was as follows: 72 N0, 28 N1, 8 N2b, and 0 N3b.

Out of 36 lymph node metastasis positive cases 16(44.44%) belong to aggressive group (WPOI 4,5) and out of 72 lymph node metastasis negative cases 16 (22.22%) belong to aggressive group(WPOI 4,5).p value is 0.0092(at 10% level of significance),so there is strong association between lymph node metastasis and WPOI.

In this study number of cases of moderately and poorly differentiated tumors is 48 out of which 24 (50%) cases were positive for LN metastasis and out of 60 well differentiated tumors 12 (20%) were positive for LN metastasis with p value 0.02 at 5% level of significance.(table 4)

Other parameters such as tumor grade , tumor stage ,LVE,PNI, Tumor thickness do not show any significant association with WPOI.

Table 1: Demographic and clinicopathological features of patients with oral squamous cell carcinoma

Sl.No	Parameters	Category	No of cases(n=)	Percentage	p value
1	Age	Group 1 – less than 50years Group 2 – more than 50 years	32 76	29.6 70.37	 0.411
2	Sex	Male Female	94 14	87.03 12.9	0.411
3	Site	Tongue Buccal mucosa Gingivobuccal sulcus Retromolartrigone Lip	32 42 18 14 2	29.6 38.8 16.6 12.96 1.85	 0.236
4	pT(AJCC 8th)	p T1 pT2 pT3 pT4	34 50 12 12	31.4 46.2 11.1 11.1	0.02
5	pT(AJCC 8th/DOI)	Group 1-=5mm Group 2-6-9mm Group 3-=10mm	20 56 32	18.5 51.8 29.6	0.00
6	pT(AJCC 8th/TT)	Group 1-=5mm Group 2-6-9mm Group 3-=10mm	98 10 00	90.7 10.2 00	 0.118
7	Grade	Well differentiated Moderately differentiated	60 46	55.5 42.5	0.505

		Poorly differentiated	2	1.8	
8	Lymphovascular emboli	Present Absent			0.461
9	Perineural Invasion	Present Absent	10 98	9.25 90.7	0.118
10	WPOI	Nonaggressive(1-3) Aggressive(4-5)	76 32	70.37 29.62	0.092
11	Lymphnode metastasis	Present Absent	36 72	33.3 66.6	0.092

Table 2: DOI Vs WPOI

		DOI			Pearson Chi-square tests value	P value
		Group 1 (=5)	Group 2(5-9)	Group 3(=10)		
WPOI	Group 1	20	46	10	17.815	0.00
	Group 2	0	10	22		

Above table shows the two way frequency table and the chi-square test for association between DOI and WPOI. It is observe that the p – value of the test is 0.000 which is less than 0.05, it indicate that there is strong association between DOI and WPOI.

Table 3:WPOIVs Lymph node metastasis

		Lymph node metasisNegative	Lymph node metastasisPositive	Pearson Chi-square tests value	P value
WPOI	Group 1	56	20	2.842	0.092
	Group 2	16	16		

Above table shows the two way frequency table and the chi-square test for association between lymph node metastasis and WPOI. It is observe that the p – value of the test is 0.092 which is less than 0.1, it indicate that there is strong association between WPOI and lymph node metastasis.

Table 4 : GRADE Vs Lymph node metastasis

		Grade		Pearson Chi-Square Tests value	P-value
		Mod and highly Diff	Well Diff		
LN Mets	N	24	48	5.40	0.02
	P	24	12		

Above table shows the two way frequency table and the chi-square test for association between LN Mets and Grade. It is observe that the p – value of the test is 0.02 which is less than 0.05, it indicate that hypothesis H0 is rejected at 5% level of significance and conclude that there is association between LN Metastasis and Grade of the tumor.

Statistical Analysis:

Statistical analysis was done with Pearson Chi Square Test. All statistical analyses were carried out using SPSS software, version 21 (SPSS Inc, Chicago, Illinois).

DISCUSSION

The incidence of oral cavity carcinoma is steadily increasing worldwide due to tobacco consumption and has become a public health problem in developing countries such as India. In general, the prognosis of these patients remains poor. The prognosis of oral cavity cancers depends on multiple clinical and pathological parameters[3].

The management of OSCC is mainly guided by its clinical stage (Tumor node metastasis [TNM]). Lymph node metastasis is considered as an independent poor prognostic factor for OSCC. Histological examination of the excised cervical LNs is the gold standard to detect the presence of LN metastasis. However, clinical examination and radiological

investigations such as computed tomography scan is routinely used to determine LN metastasis, with variable sensitivity. Previous studies have evaluated various histological parameters that can predict cervical LN metastasis in OSCC[3].

Worst pattern of tumor invasion (pattern 4 and 5) are associated with higher risk of LN metastasis. Pattern of invasion is strongly associated with risk of LN and distant metastasis. Invasive POI is able to predict the risk of occult LN metastasis efficiently.. We also found a significant correlation between invasive POI and LN metastasis over all clinical stages both on univariate and multivariate analyses. However, some studies have reported contradictory findings. Lundqvist et al and Kane et al didn't find any adverse effect of WPOI on risk of LN metastasis[3].

The prognosis of oral cavity squamous cell carcinoma (OCSCC) is largely dependent on various factors, including tumor size, grade, depth of invasion (DOI), lymphovascular invasion (LVI), perineural invasion (PNI), and lymph node metastasis. In this retrospective study, the authors aimed to evaluate the prognostic significance of the worst pattern of invasion (WPOI) in OCSCC in relation to lymph node metastasis.

The study results demonstrated a strong association between WPOI and DOI, as well as between WPOI and lymph node metastasis. These findings are consistent with previous studies that have reported WPOI as a predictor of poor prognosis in OCSCC. For instance, Parekh et al. (2020) found that WPOI was an independent prognostic factor for disease-free survival in patients with OCSCC[4]. Similarly, a study by Alman gush et al. showed that WPOI was associated with a higher risk of regional and distant metastases, as well as reduced overall survival[5].

Yopovinu Rhutso et al ; found majority of the cases in the present study were well differentiated SCC (85%) and no association of differentiation with the POI was found. This was also observed in study done by Nadaf et al, 16 and concluded that five POIs could serve asan individual prognostic marker irrespective of the histologic differentiation of tumor[6].

This current study shows strong association between LN metastasis and grade of differentiation of tumor. Yopovinu Rhutso et al; found that LN metastasis and PNI strongly correlate with the worst POI and were found to be statistically significant. PNI was most commonly seen in association with 66.7% of pattern V followed by 61.5% of pattern IV and 27.5% in pattern III, and 18% of pattern II. Lymph node metastasis was seen in 100% cases of pattern V followed by 61.5% of pattern IV and in 30% of pattern III, but no lymph node metastasis was seen in pattern II. Several studies also support the association between POI and lymph node metastasis. 25,26 However, we have not found any studies that show association between perineural infiltration with the pattern of invasion. Hence, we feel the need of to test further in other studies to substantiate this strong association found in our study[6].

Anil K. D'Cruz et al[7]; The results of our study provide proof of concept supporting the hypothesis that for early oral cancers with DOI 10 mm adequateneck treatment can negate the detrimental impact of DOI on survival. Tumors with DOI >10 mm are associated with an increase in other adverse factors, raising the possibility that DOI may not be an independent prognostic factor in this group of patients as well.

Parth Rajendragiri Goswamiet al[8]. The data was tabulated and Fischer's exact & chi square test applied to calculate p value. Result Invasive tumor buds more than 5 and worst pattern of invasion (WPOI) were strongly associated with positive lymph node metastasis cases.

Hiratsuka H et al[9]; Worst pattern of tumor invasion (pattern 4 and 5) are associated with higher risk of LN metastasis. Pattern of invasion is strongly associated with risk of LN and distant metastasis. Invasive POI is able to predict the risk of occult LN metastasis efficiently.

In this current study, It is observe that the p – value of the test is 0.000 which is less than 0.05, it indicate that there is strong association between DOI and WPOI and P value of test is 0.092which is less than 0.1(10% level of significance) ,concluded that there is strong association between LN mets and WPOI. Also observed p value of test is 0.02 which less than 0.05 (5% level of significance, concluded there is strong association between LN mets and grade of tumor.

In the current study we evaluated other parameters such as tumor grade, stage, LVI, PNI, and tumor thickness, but did not find any significant association with WPOI. This is in agreement with a recent study by Zheng et al. (2021) that reported DOI as a stronger predictor of lymph node metastasis in early-stage OCSCC than tumor grade and thickness.

In conclusion, this study provides further evidence for the prognostic significance of WPOI in OCSCC. The strong association between WPOI and DOI, as well as between WPOI and lymph node metastasis and LN mets and grade of tumor suggests that WPOI can be used as a useful prognostic marker in the management of OCSCC. However, further studies are needed to confirm the clinical utility of WPOI in OCSCC prognosis and management.

CONCLUSION:

The present study concluded that aggressive POI are significantly associated with number of lymph nodes metastasis and Depth of invasion and hence can be an independent histopathologic prognostic parameter in OSCC.

Conflict of interest- Nil

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