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ORIGINAL ARTICLE

Worst Pattern of Invasion as an Independent Predictor of Lymph node Metastasis and Prognosis in oral Cavity Squamous cell carcinoma – A Retrospective Cohort Study

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Abstract

Although Worst pattern of invasion (WPOI) is one of the histopathological (HP) markers that has been utilized in risk stratification of oral squamous cell carcinoma (OSCC) patients, its potential as an independent predictive factor for lymph node metastasis (LNM) and prognosis is least analyzed. Aim of the study is to analyze the relationship of various HP parameters to WPOI, their propensity for lymph node metastasis and prognostic value. This retrospective study included 140 patients diagnosed with resectable OSCC who underwent definitive surgery. Multiparametric HP risk assessment was done on the postoperative specimen and patients were categorized as low-risk WPOI (Type 1–3), and high-risk group (type 4 and 5). After categorization, 36.1% patients had low-risk WPOI and 63.9% had high-risk WPOI. Significant association was noted between WPOI and patient's age ($p = 0.001$), nodal stage ($p = 0.001$), lymphovascular invasion (LVI) ($p = 0.006$) and neural invasion ($p = 0.001$). 87% patients with nodal metastasis had high risk WPOI. LVI ($p = 0.014$) and WPOI ($p < 0.001$) had significant predictive role in LNM. High-risk WPOI and bone involvement were found to be predictive factors for overall survival, and only high risk WPOI had strong correlation with disease free survival having significant poor prognosis. Analyzing WPOI is essential in reporting HP specimens in OSCC. High-risk WPOI can act as an independent predictor for LNM, early recurrence and poor prognosis. Incorporation of WPOI into TNM staging is recommended to improve clinician's ability to prognosticate and individualize treatment strategies.

Keywords Worst Pattern of Invasion · Oral squamous cell carcinoma · prognosis · lymph node metastasis · overall survival · disease free survival

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Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 200,000 newly diagnosed cases of cancer worldwide annually. It is highly prevalent in developing countries like India, due to rampant use of tobacco products. It accounts for almost one-third of the cancer in our country [1]. OSCC has a poor prognosis due to high chance of locoregional recurrence. Neck node involvement in OSCC plays an important prognostic role in disease-free survival (DFS) and overall survival (OS) of the patient, wherein neck node involvement will reduce survival by 50% [2].

Although clinical TNM staging system forms the basis of categorizing patients to appropriate treatment strategies, it may not be adequate for prognostication, as some early-stage tumors may have unfavorable outcomes that cannot be explained by TNM staging alone. To overcome this limitation, many histopathological markers like lymphovascular invasion (LVI), perineural invasion (PNI), tumor thickness, grade and extranodal extension (ENE) have been utilized in predictive nomograms to allow risk-stratification of OSCC patients. Addition of molecular markers have been used to better determine outcomes, these expensive markers have conflicting results in various studies, thus limiting clinical utility [3, 4]. The need for easily available and commonly reported prognostic factors for risk-stratification to provide individualized therapy is therefore apparent [5].

The multiparametric risk assessment model proposed by Brandwein-Gensler et al. includes worst pattern of invasion (WPOI) at the tumor-host interface, used to predict lymph node metastasis (LNM), recurrence, and survival in OSCC [6, 7]. WPOI is classified into five types [8], and more aggressive tumors will have a more dispersed pattern of invasion [7].

In this study, we analyzed the predictive value of WPOI for detecting LNM and recurrent disease in our patients with OSCC.

Materials and Methods

Study Population

This retrospective cohort observational study included data from 140 patients diagnosed with OSCC in our hospital between February 2019 and March 2020. These patients had newly diagnosed, previously untreated, resectable OSCC of various oral cavity subsites, who underwent definitive surgery. Informed consent was obtained from all patients for access to their data for the study. All patients were periodically assessed every 6 months postoperatively for recurrence clinically and radiologically whenever necessitated. The mean follow-up period of patients in the present study is 26 months. Clinical and pathological data retrieved from the hospital information system were used after approval from the Institutional Research Board and Ethics committee.

Histopathological Analysis

Apart from routine reporting of the post-operative histopathological specimens, we included two pathologists blinded to the clinical details to independently assess specific histopathological parameters – WPOI, tumor size, depth of invasion (DOI), histological grading, LVI, PNI, margin status, ENE, adjacent dysplasia, and bone/skin involvement.

WPOI was classified into five types, as per the collaborative scoring system of Bryne et al. [9] and Brandwein-Gensler et al. [6]. Broad, pushing margin with smooth outline is classified as type 1, broad, finger-like pushing margins are defined as type 2, invasive tumor islands with more than 15 cells per island as type 3, less than 15 cells per island as type 4 and presence of tumor island outside the main tumor at more than 1 mm as type 5 (Fig. 1).

Statistical Methods

For this study, WPOI was categorized into low-risk group, which included types 1–3 and high-risk group, which included types 4 and 5. All histopathological parameters with propensity for LNM were analyzed by univariate analysis by Chi-square test and Fisher's extract test. Multivariate analysis was calculated using Cox Proportional hazards model and a p value of < 0.05 was concluded to be significant. We analyzed the DFS and OS rates for the study population using logistic regression ratio outcome analysis. All statistical analysis was performed using SPSS software version 23.0 (IBM, Chicago, IL).

Results:

Correlation of WPOI with Clinical Parameters:

Demographic distribution of the study population is displayed in Table 1. Of the 140 patients included in the study, majority were males (102, 72.9%; M:F ratio of 2.68:1) and ranged from 25 to 91 years (mean age 48.7 years). Among the oral cavity subsites, OSCC of the tongue, buccal mucosa and the lower gingivobuccal sulcus accounted for 50.7%, 26.4% and 10.7% respectively. Tobacco and/or alcohol were consumed by 75% of the study population. In analysis of WPOI, 2 (5%) patients had WPOI 2, 46 (32.9%) had WPOI 3, 67 (47.9%) had WPOI 4 and 22 (15.7%) had WPOI 5, with type 4 being the most common. After categorization,

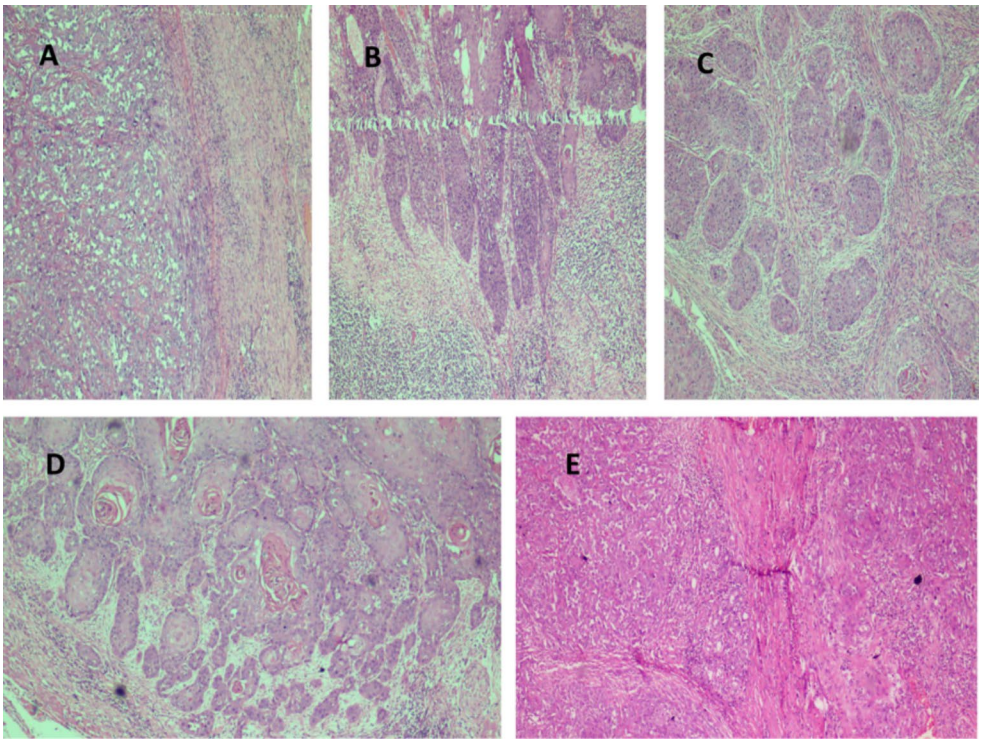

Fig. 1 Worst pattern of Invasion categories: **A** - Type 1: Broad, pushing margin with smooth outline. B - Type 2: Broad, finger like pushing margins. C - Type 3: Invasive tumor islands with more than 15 cells per island. D - Type 4: Invasive tumor islands with less than 15 cells per island. E - Type 5: Presence of tumor island outside the main tumor at a distance of more than 1 mm

51 (36.1%) patients showed low-risk WPOI (types 2–3) and 89 (63.9%) showed high-risk WPOI (types 4–5). No significant association was noted between WPOI either with oral cavity subsite or patient's habit in the present study. Also, it was seen that high risk WPOI was noted in 82.6% (38/46) in younger age group < 45 years when compared with older age group of 54.3% (51/94) which is the single clinical parameter showing significant correlation. ($p < 0.001$)

Correlation of WPOI with Other Histopathological Parameters:

On analysis of pathological tumour staging, 51.5% (72/140) belonged to early pT1/T2 stage and 48.6% (69/140) belonged to advanced pT3/T4 staging and no significant association was noted. No statistical association was noted between pathological tumour stage and WPOI. As shown in Table 1, significant correlation was noted between WPOI and nodal stage ($p = 0.001$), LVI ($p = 0.006$), PNI ($p = 0.001$). DOI of > 10 mm showed marginal correlation with presence of high-risk WPOI (p value = 0.019).

Prognostic Correlation of WPOI and Other Parameters with Lymph node Metastasis:

A detailed analysis of distribution of WPOI categorized as low risk and high-risk groups and their association with LNM is depicted in Table 2. 87% (54/62) of patients with pathologically positive nodes (pN+) nodes had high risk WPOI compared with only 44% (35/78) with negative nodes (pN0) showing significant correlation. Univariate analysis of the prognostic efficiency of various parameters in the detection of LNM is given in Table 3. DOI > 10 cm ($p = 0.003$, HR:4.35, CI: 1.65–11.4), presence of LVI ($p = 0.001$, HR: 5.20, CI: 2.03–13.3), PNI ($p = 0.001$, HR: 3.14, CI: 1.57–6.29) and WPOI ($p < 0.001$, HR: 8.29, CI: 3.49–19.72) had significant correlation with high-risk WPOI. Multivariate logistic regression analysis on significant parameters showed that only LVI ($p = 0.014$, HR: 3.78, CI: 1.31–10.92) and WPOI ($p < 0.001$, HR: 6.78, CI: 2.38–19.3) had significant association, of which the presence of high risk WPOI is almost 7 times more predictive of LNM, indicating strong correlation (Table 4). Although the presence of high-risk WPOI was a predictive factor of nodal metastasis, no significant association was noted between ENE and WPOI. ($p = 0.118$)

Survival Analysis of WPOI and Other Parameters:

We found that patients with low-risk WPOI had an overall survival of 90.2% (46/51) compared to 61.8% (55/89) in the high-risk category WPOI. The overall two-year survival rate of the cohort was 72.2%. Similarly, recurrence rates were 7.8% (4/51) and 32.6% (29/89) for low and high-risk categories respectively. The overall recurrence rate was 23.6% (33/140). On multivariate analysis, presence of high-risk WPOI ($p = 0.005$, HR: 6.28, CI: 1.74–22.62) and bone involvement ($p = 0.013$, HR: 5.70, CI: 1.44–22.62) were

Table 1 Table showing Worst Pattern of Invasion and its Association with the Clinicopathological Variables in Oral Squamous cell carcinoma

S. No	Parameter	Variable	Number of Patients (N = 140)	n (%)	Low-risk category WPOI 1–3 (n=%)	High-risk category WPOI 4–5 (n=%)	P value (Chi - Square test)
1	Age	< 45 years	46	32.9	8 (17.4)	38 (82.6)	**0.001**
		≥ 45 years	94	67.1	43 (45.7)	51 (54.3)	
2	Sex	Male	102	72.9	37 (36.3)	65 (63.7)	0.951
		Female	38	27.1	14 (36.8)	24 (63.2)	
3	Site	Tongue	71	50.7	24 (33.8)	47 (66.2)	0.153
		FOM	1	0.7	0 (0)	1 (100)	
		Alveolus	6	4.3	1 (16.7)	5 (83.3)	
		Gingivobuccal sulcus	15	10.7	8 (53.3)	7 (46.7)	
		Buccal mucosa	37	26.4	15 (40.5)	22 (59.5)	
		Lip	2	1.4	2 (100)	0 (0)	
		Retromolar trigone	8	5.7	1 (12.5)	7 (87.5)	
4	Tumor size	PT1: ≤2 cm	41	29.3	18 (43.9)	23 (56.1)	0.441
		PT2: >2 cm and < 4 cm	75	53.6	24 (32)	51 (68)	
		PT3: ≥4 cm	24	17.1	9 (37.5)	15 (62.5)	
5	Node Stage	0	78	55.7	43 (55.1)	35 (44.9)	**0.001**
		1	23	16.4	2 (8.7)	21 (91.3)	
		2	22	15.7	3 (13.6)	19 (86.4)	
		3	17	12.1	3 (17.6)	14 (82.4)	
6	Habit	Yes - Single	59	42.1	25 (42.4)	34 (57.6)	0.457
		Yes - Multiple	46	32.9	15 (32.6)	31 (67.4)	
		No	35	25.0	11 (31.4)	24 (68.6)	
7	DOI	< 5	28	20.0	16 (57.1)	12 (42.9)	0.019
		5–10	44	31.4	18 (40.9)	26 59.1)	
		10–20	63	45.0	15 (23.8)	48 (76.2)	
		> 20	5	3.6	2 (40)	3 (60)	
8	Histological grading	Well differentiated	24	17.1	13 (52.4)	11 (45.8)	0.136
		Moderately differentiated	109	77.9	36 (33)	73 (67)	
		Poorly differentiated	7	5.0	2 (28.6)	5 (71.4)	
9	LVI	Absent	112	80.0	47 (42)	65 (58)	**0.006**
		Present	28	20.0	4 (14.3)	24 (85.7)	
10	PNI	Absent	78	55.7	39 (50)	39 (50)	**0.001**
		Present	62	44.3	12 (19.4)	50 (80.6)	
11	Margin	Free	72	51.4	30 (41.7)	42 (58.3)	0.312
		Close	62	44.3	20 (32.3)	42 (67.7)	
		Involved	6	4.3	1 (16.7)	5 (83.3)	
12	ENE	No	124	88.6	48 (38.7)	76 (61.3)	0.118
		Yes	16	11.4	3 (18.8)	13 (81.3)	
13	Adjacent dysplasia	Yes	10	7.1	4 (40)	6 (60)	0.808
		No	130	92.9	47 (36.2)	83 (63.6)	
14	Bone Involvement	Yes	23	16.4	10(19.6)	13(14.6)	0.442
		No	117	83.6	41(80.4)	76(85.4)	
15	Skin Invasion	Yes	16	11.4	6(11.8)	10(11.2)	0.925
		No	124	88.6	45(88.2)	79(88.8)	

DOI: Depth of invasion, LVI: Lymphovascular invasion, PNI: Perineural invasion, ENE: Extranodal Extension

found to be independent predictive factors for overall survival, and only high-risk WPOI had strong correlation with DFS (p = 0.012, HR: 4.09, CI: 12.29), thus indicating prognostic efficacy of WPOI for both OS and DFS (Table 5). On Kaplan Meier analysis, patients who belonged to high-risk WPOI category had statistically significant reduction in both overall (p = 0.003) and disease-free survival (p = 0.001) when compared with patients who had low-risk WPOI. (Fig. 2)

Table 2 Correlation of Worst Pattern of Invasion with Lymph Node Metastasis in Oral squamous cell carcinoma

		LN Metastasis (− ve)	LN Metastasis (+ ve)
Low Intensity Tumour (WPOI 1–3)	Numbers	43	8
	% within WPOI	84.3%	15.7%
	% within Node Stage	55.1%	12.9%
High Intensity Tumour (WPOI 4,5)	Numbers	35	54
	% within WPOI	39.3%	60.7%
	% within Node Stage	44.9%	87.1%
Total	Numbers	78	62
	% within WPOI	55.7%	44.3%
	% within Node Stage	100.0%	100.0%

WPOI: Worst pattern of Invasion, LN: Lymph Node

Discussion:

Clinical and pathological TNM staging is the basis of risk stratification and prognostication for oral squamous cell carcinoma at present, dictating appropriate management protocols for these patients [5]. Nodal metastasis, the most important prognostic factor for OSCC, can be detected preoperatively with reasonable accuracy by appropriate imaging [10], aiding in pre-treatment risk stratification. Surgery with adequate margins with appropriate neck dissection is the standard of care resectable OSCC, followed by adjuvant therapy, dictated by the presence of histologic adverse factors. Despite good prognostic indicators guiding appropriate treatment strategies, the five-year survival rate is a dismal 50% in advanced OSCC [3].

The need for more precise prognostic factors remains of the utmost importance to improve outcomes of OSCC. Towards this end, inclusion of WPOI was considered in scoring systems to predict local recurrence and survival rates [6, 10, 11]. Although identified to have a prognostic value, WPOI does not have a well-defined role in treatment planning [4, 8, 12].

Almangush et al., in his study of 233 patients of early T1/T2 tongue squamous cell carcinoma, showed that WPOI in addition to tumor budding and DOI can be used as an independent marker for treatment planning and prognostication of the disease, significant both on univariate and multivariate analysis [4]. In our study, we found a significant correlation between high-risk WPOI and DFS, as well as overall survival rates. In another retrospective study done by Nadaf et al. analyzing inflammation in the connective tissue and WPOI of primary and secondary malignancies, it was shown that aggressive WPOI was seen in secondary tumors compared to their primary counterparts [11].

WPOI may also be predictive of occult nodal metastasis in oral cancer, especially oral tongue. Around 20–40% of patients with oral tongue cancer have occult nodal metastasis [13]. According to NCCN guidelines, although sentinel lymph node biopsy (SLNB) is recommended for detecting occult metastasis, many oncological centers prefer a "watch and wait" policy or perform elective neck dissection if DOI is more than or equal to 4 mm [8]. To add to the controversy, as per the Sentinel European trial, the sensitivity of SLNB is only 86% with false negativity rate of 14% [14]. Thus, the stratification of these early-stage candidates into low and high-risk categories for LNM is essential because a subset of them perform poorly despite apparently favorable histological parameters [10]. It has been shown that WPOI is associated with positive lymph nodes by Brandwein-Gensler in 2005 [6]. Hiratsuka et al., in his study also showed that WPOI 4 and 5 is associated with greater risk of nodal, and even distant metastasis [15]. In addition, in early invasive SCC, WPOI has been shown to be significantly associated with cervical LNM despite clinical N0 status [10, 16]. In our study, we found that only 15.7% patients had LNM when they had low-risk WPOI, compared to 60.7% in the high-risk category, which was found to be statistically significant. Inversely, we also found that of the patients who had high-risk WPOI were significantly more likely to have occult node positivity detected on final histopathology. Along with LVI, WPOI was the only factor showing significant correlation with LNM on multivariate analysis in our study, indicating the utility of WPOI as a predictor of nodal metastasis in OSCC.

The existence of PNI is considered as a crucial factor for categorization of high-risk patients for both predictor of LNM and prognosis of the disease in OSCC [17]. A study by Wu et al., analyzing high risk histological factors in early tongue carcinomas, showed that even though the presence of PNI is considered an adverse prognostic factor and a predictor for LNM in univariate analysis, on multivariate analysis a statistical significance was not achieved for PNI as an independent prognostic indicator [18]. Similarly, in the present study, although PNI was significantly associated with LNM and recurrence-free survival, a significant correlation was not achieved in multivariate analysis. Thus, according to our study, although PNI can be used as an adjuvant adverse HPE parameter in detecting metastasis and prognosis, its use as an independent factor might be questionable. Interestingly, a strong correlation was noted for PNI and LVI with WPOI indicating a more aggressive tumor front and more propensity for metastasis. The authors opine that the use of WPOI and PNI together might have more predictive and prognostic value than the use of PNI alone.

Byers et al., in their 1978 study on the significance of margin status in OSCC in 216 cases, revealed that patients with negative margin status have better local DFS and OS, stressing the importance of achieving negative surgical margins

Table 3 Clinicopathological Features and Their Association with Lymph Node Metastasis in Oral Squamous Cell Carcinoma

S. No	Parameter	Variable	Number of Patients (N = 140)	n (%)	LN Metastasis (– ve) N=, %	LN Metastasis (+ ve) N=, %	P value (Chi - Square test)
1	Age	< 45 years	46	32.9	21 (45.7)	25 (54.3)	0.095
		≥ 45 years	94	67.1	57 (60.6)	37 (39.4)	
2	Sex	Male	102	72.9	60 (58.8)	42 (41.2)	0.254
		Female	38	27.1	18 (47.4)	20 (52.6)	
3	Site	Tongue	71	50.7	38 (53.5)	33 (46.5)	0.654
		FOM	1	0.7	1 (100)	0 (0)	
		Alveolus	6	4.3	2 (33.3)	4 (66.7)	
		Gingivobuccal sulcus	15	10.7	9 (60)	6 (40)	
		Buccal mucosa	37	26.4	22 (59.5)	15 (40.5)	
		Lip	2	1.4	2 (100)	0 (0)	
		Retromolar trigone	8	5.7	4 (50)	4 (50)	
4	Habit	Yes - Single	59	42.1	37 (62.7)	22 (37.3)	0.307
		Yes - Multiple	46	32.9	22 (47.8)	24 (52.2)	
		No	35	25.0	19 (54.3)	16 (45.7)	
5	DOI	< 5	28	20.0	20 (71.4)	8 (28.6)	**0.003**
		5–10	44	31.4	32 (72.7)	12 (27.3)	
		10–20	63	45.0	23 (36.5)	40 (63.5)	
		> 20	5	3.6	3 (60)	2 (40)	
6	Histological grading	Well differentiated	24	17.1	17 (70.8)	7 (29.2)	0.253
		Moderately differentiated	109	77.9	57 (52.3)	52 (47.7)	
		Poorly differentiated	7	5.0	4 (57.1)	3 (42.9)	
7	LVI	Absent	112	80.0	71 (63.4)	41 (36.6)	**0.001**
		Present	28	20.0	7 (25)	21 (75)	
8	PNI	Absent	78	55.7	53 (67.9)	25 (32.1)	**0.001**
		Present	62	44.3	25 (40.3)	37 (59.7)	
9	Margin	Free	72	51.4	46 (63.9)	26 (36.1)	0.104
		Close	62	44.3	30 (48.4)	32 (51.4)	
		Involved	6	4.3	2 (33.3)	4 (66.7)	
10	Adjacent dysplasia	Yes	10	7.1	4 (40)	6 (60)	0.338
		No	130	92.9	74 (56.9)	56 (43.1)	
11	WPOI	1	0	0	0	0	**< 0.001**
		2	5	3.6	4 (80)	1(20)	
		3	46	32.9	39 (84.8)	7 (15.2)	
		4	67	47.9	28 (41.8)	39 (58.2)	
		5	22	15.7	7 (31.8)	15 (68.2)	
12	Bone Involvement	Yes	23	16.4	9(11.5)	14(22.6)	0.085
		No	117	83.6	69(88.5)	48(77.4)	
13	Skin Invasion	Yes	16	11.4	6(7.7)	10(16.1)	0.127
		No	124	88.6	72(92.3)	52(83.9)	

LN: Lymph node, WPOI: Worst Pattern of Invasion, DOI: Depth of invasion, LVI: Lymphovascular invasion, PNI: Perineural invasion

[19]. Many publications following this have illustrated the impact of negative margin status on improvement of recurrence-free and overall survival rates [19–21]. According to Loree and Strong, risk of recurrence is doubled when there is a compromised (positive/close) surgical margin, irrespective of radiotherapy status (36% vs. 18%) [21]. Although no significant correlation was noted for margin status for both LNM and prognosis in the present study, the role of clear surgical margins for better outcomes is undisputed in current literature.

Degree of differentiation is considered an important marker of prognostication, and it is extensively employed to prognosticate tumors, especially OSCC. Although many studies [22, 23] have emphasized the correlation between histological and adverse oncological outcomes in advanced grade tumors outcomes, no significant correlation was noted in the present study.

DOI is an important addition to the tumor staging in the latest revision of AJCC TNM staging, due to its prognostic value in OSCC [4, 7]. According to recent literature,

Table 4 Multivariate Analysis of the Clinicopathological Features and Their Predictive Potential for Lymph Node Metastasis in Oral squamous cell carcinoma

S. No	Parameter	Variable	Number of Patients (N = 140)	OR(95%CI)	P Value	aOR(95%CI)	P Value
1	Age	< 45 years	46	0.55(0.27,1.11)	0.095	0.91(0.37,2.28)	0.844
		≥ 45 years	94				
2	DOI	< 5	28				
		5–10	44	0.94(0.33,2.69)	0.905	0.35(0.09,1.34)	0.125
		10–20	63	4.35(1.65,11.4)	**0.003**	1.36(0.38,4.82)	0.639
		> 20	5	1.67(0.23,11.9)	0.611	0.96(0.08,10.60)	0.973
3	Histological grading	Well differentiated	24				
		Moderately differentiated	109	2.22(0.85,5.77)	0.103	1.78(0.52,6.07)	0355
		Poorly differentiated	7	1.82(0.32,10.34)	0.499	2.48(0.28,21.76)	0.412
4	LVI	Absent	112	5.20(2.03,13.3)	**0.001**	3.78(1.31,10.92)	**0.014**
		Present	28				
5	PNI	Absent	78	3.14(1.57,6.29)	**0.001**	1.86(0.72,4.84)	0.201
		Present	62				
6	WPOI	Low-Intensity Tumor	51	8.29(3.49,19.72)	**< 0.001**	6.78(2.38,19.30)	**< 0.0001**
		High-Intensity Tumor	89				
7	Bone Involvement	Yes	23	2.24(0.90,5.58)	0.085	3.47(0.96,12.55)	0.058
		No	117				
8	Skin Invasion	Yes	16	2.31(0.79,6.75)	0.127	0.99(0.22,4.48)	0.991
		No	124				

WPOI: Worst Pattern of Invasion, DOI: Depth of invasion, LVI: Lymphovascular invasion, PNI: Perineural invasion

5 mm is considered as a cut-off for prognostication especially in early OSCC [24]. In the present study, a cut-off of DOI > 10 mm has been shown to have a significant correlation for LNM in univariate analysis, and as an independent factor predictive of recurrence, metastasis, and overall survival in OSCC. Thus, it can be considered that DOI > 10 mm can indicate the propensity for nodal metastasis and poor prognosis, and prediction of early recurrence.

Multiple parametric studies done by Almangush to analyse the risk assessment of HPE factors, revealed that DOI more than 4 mm and WPOI are highly prognostic for overall survival in tongue SCC [7, 24]. However, neither DOI nor WPOI were suitable prognosticators for local recurrence in a recent report on 126 cases of lymph node-negative (pN0) oral tongue SCC. Tumor bed margin status (positive vs. negative) and other parameters (e.g., pattern and DOI) did not correlate with local recurrence [25]. Results of our study were like those of Almangush, in that DOI > 10 mm and WPOI can be used as prognostic markers irrespective of margin status.

The association of lymphocytic host response (LHR) with survival in tongue cancers has been proven to be significant in a few studies [26], but not always statistically significant [4]. A major drawback of LHR is inter–observer variability [7]. Since a wide range of inter – observer variability was present during analysis for LHR in our study, it was not included in the final analysis.

Bello et al. showed that high occurrence of cancer-associated fibroblasts, illustrated by smooth muscle actin on immunohistochemistry, is predictive of poor prognosis in tongue SCC [27]. Other factors such as hypoalbuminaemia and elevated C reactive protein are prognosticators in OSCC, which are potential field of future research [26].

To assess the prognostic efficacy of OSCC, predictive models including multiple histological parameters were proposed by Bryne et al. in 1989. He included degree of keratinization, nuclear polymorphism, number of mitoses, pattern of invasion and leukocyte infiltration to assess the prognosis of OSCC [9, 28]. This was the basis of the classic prognostic histological risk scoring assessment proposed by Brandwein – Gensler, validated as a constant outcome prognostic predictor for OSCC [29]. A study done by Li et al., [12] to assess the prognostic efficiency of Brandwein-Gensler model with 299 patients with early stage OCSCC revealed that the probability of developing locoregional recurrence is 42% in patients with WPOI type 5. This substantiates the model proposed by Brandwein et al. But none of the scoring systems are universally accepted because of variation of inter observer assessment and less reproducible parameters [30]. Our study supports the use of the Brandwein-Gensler model, as we found that patients with WPOI types 4 and 5 showed higher recurrence rates of 53.74% and 59.1% and OS of 62% and 54.4%, respectively compared to the lower risk WPOI group.

Table 5 Multivariate Analysis of the Pathological Features and their prognostic value in Oral squamous cell carcinoma

				Overall Survival		Recurrence free Survival	
S. No	**Parameter**	**Variable**	**Number of Patients (N = 140)**	**aOR (95%CI)**	**P Value**	**aOR (95%CI)**	**P Value**
1	Age	< 45 years	46	0.59(0.24,1.50)	0.272	0.46(0.19,1.15)	0.096
		≥ 45 years	94				
2	DOI	< 5	28				
		5–10	44	1.65(0.33,8.25)	0.545	1.01(0.24,4.28)	0.984
		10–20	63	2.61(0.56,12.12)	0.221	2.04(0.52,8.02)	0.305
		> 20	5	1.14(0.05,27.03)	0.937	0.60(0.03,12.29)	0.742
3	Histological grading	Well differentiated	24				
		Moderately differentiated	109	1.05(0.28,3.89)	0.944	1.50(0.42,5.37)	0.531
		Poorly differentiated	7	1.57(0.16,15.77)	0.699	1.52(0.16,14.21)	0.715
4	LVI	Absent	112	1.41(0.52,3.82)	0.502	0.69(0.25,1.85)	0.449
		Present	28				
5	PNI	Absent	78	1.29(0.45,3.72)	0.634	2.02(0.72,5.71)	0.183
		Present	62				
6	WPOI	Low-Intensity Tumor	51	6.28(1.74,22.62)	**0.005**	4.09(1.36,12.29)	**0.012**
		High-Intensity Tumor	89				
7	Bone Involvement	Yes	23	5.70(1.44,22.62)	**0.013**	3.40(0.91,12.76)	0.070
		No	117				
8	Skin Invasion	Yes	16	0.70(0.16,3.16)	0.644	0.69(0.16,3.04)	0.622
		No	124				
9	Margin	Free	72				
		Close	62	0.81(0.32,2.05)	0.651	1.19(0.49,2.88)	0.697
		Involved	6	0.38(0.05,3.11)	0.370	0.42(0.05,3.31)	0.408
10	Primary Site	Tongue	71	0.50(0.16,1.56)	0.234	0.38(0.14,1.15)	0.087
		Other Sites	69				
11	ENE	No	124				
		Yes	16	2.11(0.55,8.13)	0.275	3.05(0.81,11.53)	0.101

LVI: Lymphovascular Invasion, WPOI: Worst pattern of invasion, DOI: Depth of invasion, PNI: Perineural invasion, ENE: Extranodal extension

A meta-analysis performed by Abu-Ghanem et al. showed that even though elective neck dissection can significantly reduce the rate of regional recurrence and improve DFS in early (T1, T2) oral tongue SCC, the OS remains the same [31]. In patients with high grade of WPOI and DOI more than 4 mm, elective neck dissection is proposed to improve prognosis, [18, 32] thus illustrating the impact of inclusion of WPOI to individualize treatment strategies. In the present study, in early OSCC, a WPOI of either type 4,5 and/or presence of LVI were predictive of occult nodal metastasis. Therefore, WPOI can guide the decision to perform elective neck dissection in these patients.

The value of WPOI to predict nodal metastasis and prognosis in HNSCC has been studied in the western population, but robust data has been lacking from the South Asian subcontinent. The strength of our study is that this is one of the very few studies to our knowledge with comprehensive analysis of WPOI in relation to both LNM and prognosis in the Indian subset of population. Also, WPOI has been categorized based on the gold standard, final histopathology specimen rather than on preoperative biopsies in other studies [11], and analyzed by two pathologists, increasing the precision of our study. Our study is limited by the limited follow-up, and a longer follow-up might show greater predictive value of WPOI in OSCC.

Conclusion

Analysis of WPOI is mandatory for reporting of all resected histopathological specimens of OSCC. High-risk WPOI has high propensity and is an independent predictor for LNM, early recurrence and poor DFS and OS irrespective of margin status and other parameters. Incorporation of WPOI into TNM staging is warranted and can help the clinician to prognosticate and assess the need for adjuvant therapy.

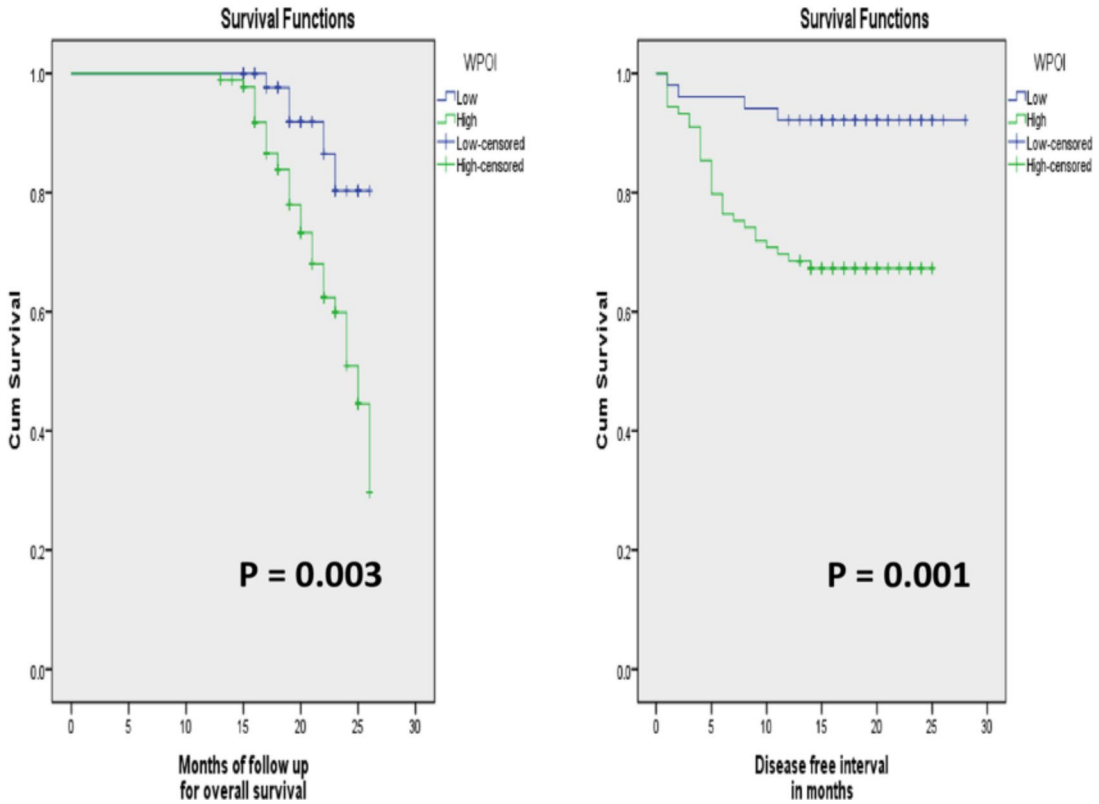

Fig. 2 Kaplan–Meier survival curves for overall and disease-free survival (DFS) in relation WPOI low and high-risk groups

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