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Original Research Article

The role of worst pattern of invasion in the prognosis of oral cavity malignancies

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ABSTRACT

Background: Our study aimed to assess the significance of worst pattern of invasion (WPOI) and its effect on survival in oral cavity squamous cell carcinoma (OCSCC).
Methods: This is a retrospective study of patients with OCSCC who underwent surgery. Univariate and bivariate analysis were used to analyze the association between WPOI and demographics, tumor characteristics and treatment. The association of WPOI with overall survival was evaluated.
Results: The 3-year OS was 77% for WPOI ≤4 and 70% for WPOI 5 (p=0.5). In the tongue subsite, the 3-year OS was 81% for WPOI ≤4 and 57% for WPOI 5 (p=0.08). WPOI-5 showed significant association with perineural invasion (p<0.01), lymphovascular invasion (p<0.01), lymph node involvement (p<0.03), and higher depth of invasion (p<0.01).
Conclusion: WPOI-5 may be considered a prognostic factor in deciding treatment in the post-surgical setting, and my become a mandatory parameter in pathology synoptic reports in the future.

Keywords: Worst pattern of invasion, Oral cavity, Malignancy, Tongue cancer, Head and neck cancer

INTRODUCTION

Oral cavity squamous cell carcinoma (OCSCC) is the most common malignancy among head and neck cancer.[1] There were 377,800 new oral cavity squamous cell carcinoma (OCSCC) cases and 177,700 OCSCC related deaths in 20202. These malignancies are staged according to TNM classification, which determines prognosis.[1] OCSCC is divided into early and advanced stages.

Advanced stages are treated by multimodality strategy like surgery followed by radiation therapy with or without chemotherapy, while the early stages are generally treated with single modality treatment.[3] Despite having better survival in the early stages, 25-37% of early-stage OCSCC with no nodal disease go on to develop locoregional recurrence or distant metastases.[4,5] This raises the question of whether adequate prognostic parameters are considered for the treatment of OCSCC in the adjuvant setting in high-risk early-stage malignancies.[5] In addition to tumor staging, histological factors also influence prognosis and the treatment strategy.

Specifically, depth of tumor invasion (DOI), degree of tumor differentiation, and the presence of perineural invasion, lymphovascular invasion, or extranodal extension are known to impact the locoregional recurrence, distant metastases and overall survival.[6] Worst pattern of invasion (WPOI) is one of the factors

which has not been discussed in literature extensively and remains under-researched.[7] Per the college of American pathologists' guidelines, WPOI is considered optional for reporting purposes.[7] This retrospective cohort study aimed to investigate the prognostic significance of WPOI.

METHODS

This is an Institutional review board (IRB) approved retrospective study. All OCSCC cases resected at our institution from 2010 to 2019 were identified using our pathology data management software (SoftPath®). Patients with recurrent tumors, or those who received preoperative radiation or chemotherapy, were excluded from the study.

Data pertaining to patient demographics, histological diagnosis, treatment, clinical status were collected by medical record review. Tumors were staged according to current AJCC guidelines.[8] Two board-certified pathologists reviewed cases with incomplete WPOI data (M. R and M.N) and assigned a WPOI grade per current guidelines (Table 1 and Figure 1).

Table 1: WPOI patterns.[7]

WPOI patterns	Definition	Images
I	Broad, pushing margin of the tumor with a smooth outline	A
II	Broad, pushing finger-like projection	B
III	Invasive tumor islands with >15 cells per island	C
IV	Invasive tumor islands with less than 15 cells per island	D (Low magnification) E (High magnification)
V	Presence of a tumor island outside the main tumor at a distance of >1 mm	F- The tumor satellites (identified in the dashed box) are located 1 mm or more away from the invasive front of the main tumor (identified by the dashed line). The Inset shows a higher magnification view of the tumor satellites in the boxed area.

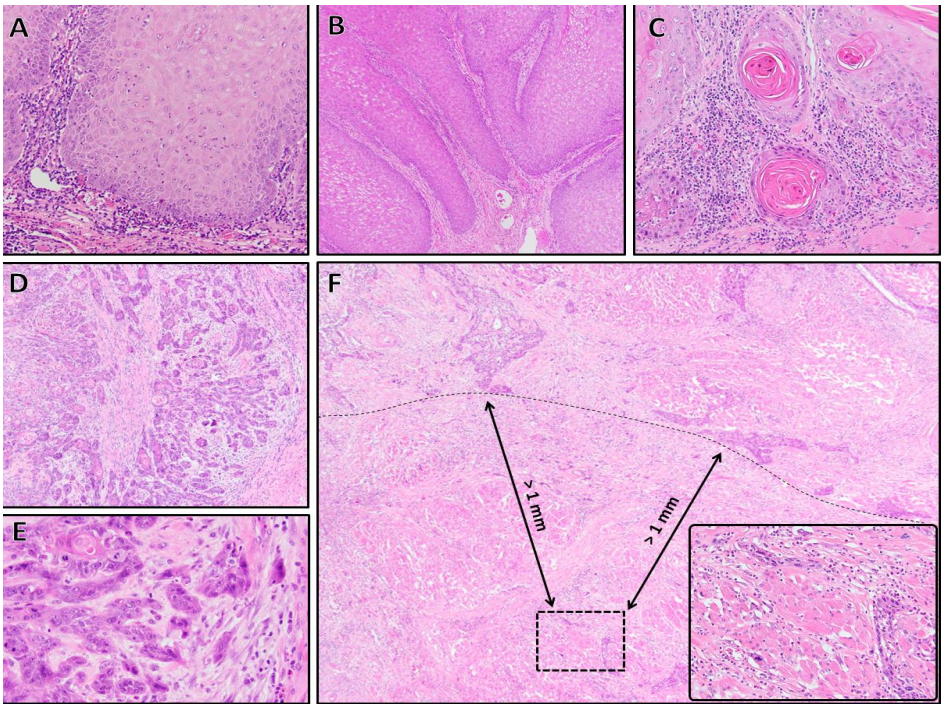

Figure 1: Representative examples of Worst Patterns of Invasion (WPOI) in oral squamous cell carcinoma, as described by Brandwein-Gensler et al. (A) Pattern 1, exhibiting broad, pushing borders. (B) Pattern 2, with finger-like invasive fronts. (C) Pattern 3, with large islands of invasive tumor (> 15 cells per island). (D) (low magnification) and (higher magnification). (E) Pattern 4, with small islands of invasive tumor (≤ 15 cells per island). (F) Pattern 5, with tumor satellites (dashed box) located 1 mm or more away from the invasive front (dashed line) of the main tumor. Inset shows a higher magnification view of the tumor satellites in the boxed area.

Tumor margins were classified as positive if tumor cells were present at the inked tumor resection margins or clear if no tumor cells were present within 5 mm of the inked resection margins. Tumor margins were classified as close if tumor cells were present within 5 mm of, but not touching, the inked resection margin nearest to the tumor. Early staged OCSCC included stage 1 and 2 diseases while advanced stage included stage 3 and 4 malignancies, per TNM criteria.

Statistical analysis

Baseline characteristics which included clinical, tumor and treatment information were summarized using medians and interquartile ranges (IQR) or frequency counts and percentages, and compared across treatment groups using the Wilcoxon rank sum, chi-square, and Fisher exact tests.

A similar subset analysis was done among patients with tongue malignancies. Distribution of WPOI and site of the tumor were described using histograms. We estimated overall survival (OS) and survival among patients with tongue malignancies using the Kaplan-Meier method, stratified by WPOI.

In addition, the association of WPOI with OS and survival amongst the subset cohort (tongue malignancy) was estimated using a Cox proportional hazards regression models.

Results are summarized using hazard ratios (HRs) with 95% confidence intervals (95% CI). We also used univariable logistic regression to evaluate the associations of baseline characteristics with WPOI=5. Results are summarized using odds ratios (ORs) with 95% confidence intervals (95% CI).

Statistical analyses were performed using R version 3.6.3 (R foundation for statistical computing, Vienna, Austria). All tests were two-sided, and p values <0.05 were considered statistically significant.

RESULTS

The clinicopathological and demographic features of the patients in the cohort are shown in Table 2. The cohort consisted of 41(60%) males and 27(40%) females. The median age at resection was 70 years (IQR 61-78) years.

The median follow-up for the cohort was 20.0 months (Range:13.0-72.0). 41(60%) OCSCC occurred in the tongue while the remainder (40%) occurred in other sites like buccal mucosa, alveolus, hard palate, retromolar trigone, and lip.

Histologically, 94% of cases were conventional squamous cell carcinoma, 3% were basaloid, 1.5% were verrucous squamous cell carcinoma, and 1.5% were acantholytic squamous cell carcinoma.

There were 2, 3, 17, 18, and 28 cases of WPOI 1, 2, 3, 4, and 5, respectively. Among the patients with WPOI 5, 46% were early-stage, and 54% were advanced-stage cancers.

Compared to the WPOI <= 4 group, the WPOI 5 group was statistically significantly more likely to display the presence of PNI (68% vs 25%, p<0.01), LVI (56% vs 12%, p=0.02) and LN involvement (50% vs 25%, p<0.03). The WPOI 5 group also showed an increased DOI compared to the two WPOI <=4 group (14 vs 4 mm, p<0.01). These findings are summarized in Table 4.

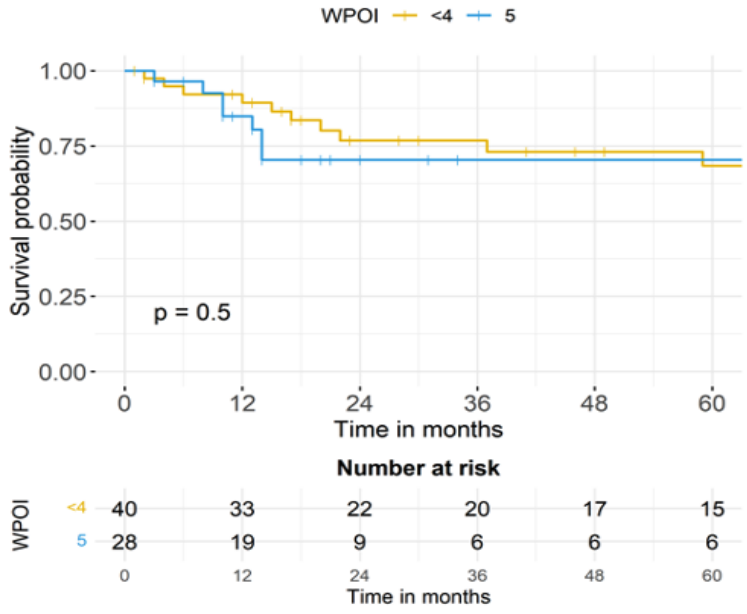

Figure 2: Kaplan-Meier plot of overall survival for WPOI group.

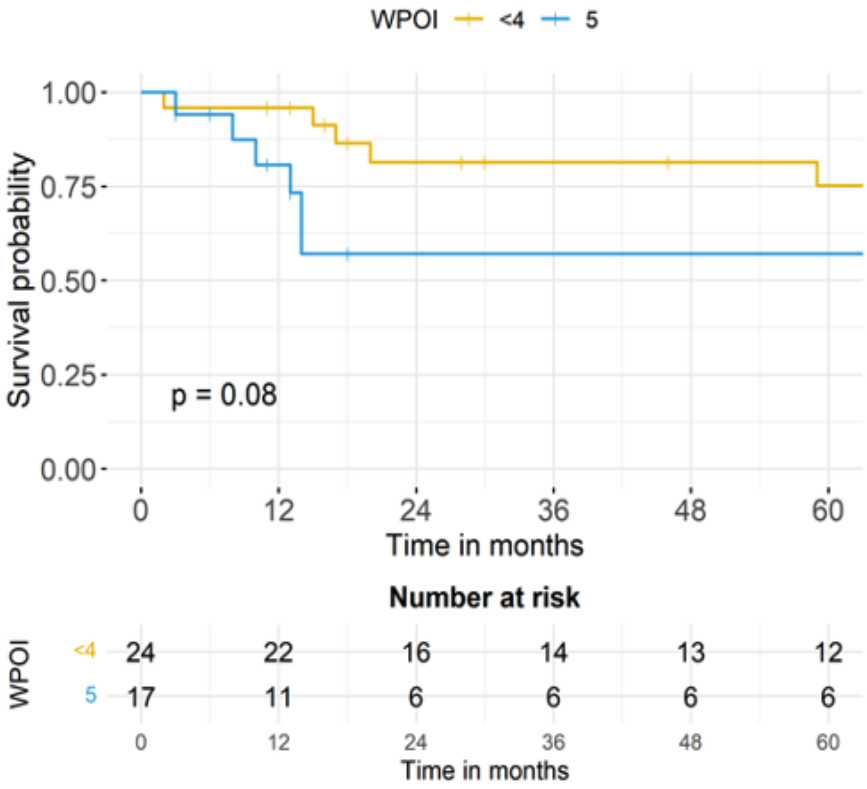

Figure 3: Kaplan-Meier plot of overall survival (Site=Tongue) for WPOI group.

Table 2: Baseline characteristics.

Characteristic	WPOI			P value[2]
	Total	≤4	5	
	68 (100%)[1]	40 (59%)[1]	28 (41%)[1]	
Clinical Information				
Age (in years)	70 (61, 78)	70 (63, 77)	70 (58, 78)	0.82
Sex				
Male	41 (60)	21 (52)	20 (71)	0.12
Female	27 (40)	19 (48)	8 (29)	
Smoking (packs/year)	0 (0, 26)	3 (0, 30)	0 (0, 11)	0.12
Immunocompromised disease				
No	58 (85)	31 (78)	27 (96)	0.04
Yes	10 (15)	9 (22)	1 (4)	
Tumor stage				
1	23 (35)	21 (55)	2 (7)	<0.01
2	14 (21)	5 (13)	9 (32)	
3	2 (3)	1 (3)	1 (4)	
4	27 (41)	11 (29)	16 (57)	
Missing	2	2	0	
Site				
Tongue	41 (60)	24 (60)	17 (61)	0.95
Others (Alveolus, BM, FOM, HP, Lip, RMT)	27 (40)	16 (40)	11 (39)	
Size	2.65 (1.00, 3.80)	1.45 (0.80, 2.92)	3.35 (2.70, 3.85)	<0.01
Grade				0.30
Well differentiated	24 (35)	17 (42)	7 (25)	
Moderately differentiated	30 (44)	15 (38)	15 (54)	

Continued.

Characteristic	WPOI			P value[2]
Poorly differentiated	14 (21)	8 (20)	6 (21)	
Depth of Invasion (in mm)	7 (3, 14)	4 (2, 7)	14 (10, 19)	<0.01
Perineural invasion				
Absent	39 (57)	30 (75)	9 (32)	<0.01
Present	29 (43)	10 (25)	19 (68)	
Lymphovascular invasion				
Absent	47 (70)	35 (88)	12 (44)	<0.01
Present	20 (30)	5 (12)	15 (56)	
Missing	1	0	1	
Lymph nodes involvement				
Negative nodes	44 (65)	30 (75)	14 (50)	0.03
Positive nodes	24 (35)	10 (25)	14 (50)	
Metastasis size (mm)	7 (2, 14)	2 (1, 15)	10 (4, 12)	0.31
Missing	45	30	15	
Extranodal extension				
Absent	12 (67)	6 (67)	6 (67)	0.99
Present	6 (33)	3 (33)	3 (33)	
Missing	50	31	19	
Treatment and follow-up				
Margins (Positive and close/clear)				
Close/clear margins	50 (75)	31 (78)	19 (70)	0.51
Positive margins	17 (25)	9 (22)	8 (30)	
Missing	1	0	1	
Margins (clear and positive/close)				
Clear margins	7 (10)	5 (12)	2 (7)	0.69
Positive/close margins	60 (90)	35 (88)	25 (93)	
Missing	1	0	1	
Recurrence				0.30
No	58 (85)	36 (90)	22 (79)	
Yes	10 (15)	4 (10)	6 (21)	
Follow up (months)	20 (13, 72)	34 (16, 88)	14 (11, 32)	0.03

[1]Median (IQR); n (%)[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 3: Baseline characteristics for tongue site.

Characteristic	WPOI			P value[2]
	Total 41 (100%)[1]	≤ 424 (59%)[1]	517 (41%)[1]	
Clinical information				
Age (in years)	68 (60, 78)	68 (62, 78)	68 (53, 78)	0.35
Sex				0.09
Male	25 (61)	12 (50)	13 (76)	
Female	16 (39)	12 (50)	4 (24)	
Smoking (packs/year)	0 (0, 20)	0 (0, 18)	0 (0, 20)	0.56
Immunocompromised disease				0.03
No	35 (85)	18 (75)	17 (100)	
Yes	6 (15)	6 (25)	0 (0)	
Tumor				
Size	2.60 (1.00, 3.30)	1.10 (0.80, 2.55)	3.00 (2.70, 3.50)	<0.01
Grade				0.04
Well differentiated	16 (39)	13 (54)	3 (18)	
Moderately differentiated	16 (39)	6 (25)	10 (59)	
Poorly differentiated	9 (22)	5 (21)	4 (24)	
Depth of Invasion (in mm)	6.0 (3.0, 14.0)	3.0 (1.8, 5.0)	14.0 (10.0, 15.0)	<0.01
Perineural invasion				<0.01
Absent	23 (56)	20 (83)	3 (18)	

Continued.

Characteristic	WPOI			P value[2]
Present	18 (44)	4 (17)	14 (82)	
Lymphovascular invasion				<0.01
Absent	29 (72)	23 (96)	6 (38)	
Present	11 (28)	1 (4)	10 (62)	
Missing	1	0	1	
Lymph nodes involvement				0.14
Negative nodes	27 (66)	18 (75)	9 (53)	
Positive nodes	14 (34)	6 (25)	8 (47)	
Metastasis size (mm)	3.2 (1.3, 7.8)	1.4 (0.9, 6.4)	5.0 (2.4, 8.2)	0.41
Missing	27	18	9	
Extranodal extension				0.99
Absent	9 (75)	4 (67)	5 (83)	
Present	3 (25)	2 (33)	1 (17)	
Missing	29	18	11	
Treatment and follow-up				
Margins (Positive and close/clear)				0.69
Close/clear margins	32 (80)	20 (83)	12 (75)	
Positive margins	8 (20)	4 (17)	4 (25)	
Missing	1	0	1	
Margins (clear and positive/close)				0.68
Clear margins	7 (18)	5 (21)	2 (12)	
Positive/close margins	33 (82)	19 (79)	14 (88)	
Missing	1	0	1	
Recurrence				0.99
No	36 (88)	21 (88)	15 (88)	
Yes	5 (12)	3 (12)	2 (12)	
Follow up (months)	30 (13, 90)	64 (18, 92)	14 (10, 70)	0.02

Table 4: Univariable logistic regression evaluating association of factors in Table 2 with WPOI=5.

Characteristic	OR (95% CI)[1]
Clinical information	
Age	0.99 (0.95, 1.03)
Sex	
Male	—
Female	0.44 (0.15, 1.21)
Smoking (packs/year)	0.99 (0.96, 1.01)
Immunocompromised disease	
No	—
Yes	0.13 (0.01, 0.74)
Tumor	
Site	
Tongue	—
Others (Alveolus, BM, FOM, HP, Lip, RMT)	1.03 (0.38, 2.80)
Size	1.45 (1.10, 2.05)*
Grade	
Well differentiated	—
Moderately differentiated	2.43 (0.80, 7.89)
Poorly differentiated	1.82 (0.45, 7.39)
Depth of invasion (in mm)	1.29 (1.16, 1.48) *
Lymph nodes involvement	
Negative nodes	—
Positive nodes	3.00 (1.09, 8.64)*

Continued.

Characteristic	OR (95% CI)[1]
Treatment and follow-up	
Margins (Positive vs close/clear)	
Close/clear margins	—
Positive margins	1.45 (0.47, 4.44)
Margins (positive/close vs clear)	
Clear margins	—
Positive/close margins	1.79 (0.35, 13.2)
Recurrence	
No	—
Yes	2.45 (0.63, 10.5)

1OR =Odds Ratio, CI =Confidence Interval, *=Significant

Compared to WPOI <=4, WPOI 5 was not associated with a statistically significant difference in OS (HR 1.36; 95% CI; p=0.5) when considering the whole cohort, nor when considering only patients with tongue malignancies (HR 2.58; 95% CI; p=0.09). There was a 60% recurrence rate in tumors with WPOI 5, and a 40 % recurrence rate in WPOI.[1-4]

DISCUSSION

OCSCC continue to pose a significant health burden worldwide.8. There have been few advances in oral cancer outcomes, and they frequently have a dismal prognosis9. Hence a detailed analysis of the prognostic factors is necessary for optimal treatment strategy. Brandwein-gensler proposed a histologic risk model, which describes WPOI as a five-category entity 4 (Table 1 and Figure 1). Currently, the treatment of OCSCC depends on TNM staging with advanced stage-managed by multimodality treatment. In our study of a cohort of 68 OCSCC, we observed that WPOI-5 had a strong association with presence of PNI, LVI, lymph-node metastases.

Lymph node metastasis impacts overall survival and confers poor prognosis. Notably, the N staging takes precedence over the T (tumor)-stage as a prognosticator.[10,11] Our study observed a significant association between WPOI-5 and lymph node metastases (p=0.03). Prior studies have had reported conflicting data regarding whether WPOI and LN involvement is strongly associated. Chatterjee et al. noted a strong correlation between WPOI 4-5 with lymph node involvement (p<0.001) and Manjula et al, show that the WPOI with strands or cellular dissociation has more tendency to spread to lymph nodes.[7,12]

However, studies by Lundqvist et al. and Kane et al did not show a significant association between WPOI and risk of lymph node metastases.[13,14] Since lymph node involvement is the single most important prognostic factor, WPOI may aid in identifying the risk of lymph node involvement and deciding the treatment strategies.[12] Our results suggest that WPOI is a valuable metric in this determination, albeit in the context of conflicting literature.

Very few studies have analyzed WPOI and its association with other independent histopathological characteristics like PNI and lymphovascular invasion that are used for risk stratification and adjuvant treatment decision making. PNI tracks the tumor along the nerves, resulting in poor locoregional control and increasing the risk of distant metastasis.[15,16] This makes it an important prognostic factor associated with aggressive disease and dismal prognosis.[16] Mishra et al, established a strong association between PNI and WPOI 4-5.[17] Our study corroborated the strong association between the histologic detection of PNI and WPOI-5. To our knowledge, our study is only the second study to establish this correlation.[17] Similarly, lymphovascular invasion (LVI) is a risk factor for overall survival and locoregional control in oral cavity malignancies. It has a negative impact on overall survival and recurrence-free survival.[18] While Mishra et al, did not find a significant relationship with LVI, our study showed a significant association between WPOI-5 and presence of LVI (p<0.01).[17] The association of PNI and LVI with WPOI-5 suggests WPOI is a significant histopathological factor that should be accounted for in pathologic assessment.

Not only was WPOI-5 associated with other aggressive histopathological factors, it also appears to have prognostic value for early and advanced stage oral cavity cancer patients in and of itself. On the Kaplan Meier plot, the overall survival rate was worse in tumors with WPOI-5 compared to WPOI 1-4. Our results validate the findings in Marinelli et al, which concluded that patients with tumors displaying WPOI-5 were more likely to have shorter overall survival than patients with WPOI 1-4.[19] WPOI 1-4 showed a trend towards better survival than WPOI-5 in KM survival curves. This finding resembles the study of the international cohort done by Almangush et al, suggesting that WPOI is a strong prognostic factor of death in OCSCC.[20]

Li et al, showed that in the risk model with WPOI-5, the probability of locoregional recurrence (LRR) was 42%, compared to 32 % in WPOI 1-421 There is a high risk of locoregional recurrence or distant metastases in OCSCC, and the prognostic value of WPOI-5 may be able to stratify which patients should undergo treatment intensification to reduce chances of treatment failure.

This is especially pertinent in patients that do not otherwise meet criteria for adjuvant therapy, but the tumor demonstrates WPOI-5. Prior studies have also begun to evaluate whether WPOI can help determine the extent of surgery and oncologic resection. Yue et al, found that WPOI-4,5 was associated with mandibular invasion and infiltrative invasion by the tumor.[22] They extrapolated their findings to suggest that WPOI on preoperative biopsy specimens can help in treatment strategy and operative planning for mandibulectomy (segmental vs marginal).

The histopathologic parameters can be assessed in the representative biopsy sample or intraoperative biopsy frozen section.[23] The above studies were preliminary investigation but may help clinicians for further studies to prove the relationship of bone invasion and type of surgery. Of very important note, WPOI preferably should be assessed in the post-operative samples as the advancing edge can be under-sampled in the biopsy samples.[21]

Limitations of this study include its retrospective nature and overall small sample size. The cohort has a heterogeneous group of patients with early and advanced stages of OCSCC.

CONCLUSION

Our study shows WPOI-5 may play a role as a prognostic factor in deciding the treatment strategies in the post-surgical setting. With larger datasets, it may possible to show a significant association of WPOI-5 with other prognostic factors like PNI, LVI, DOI. WPOI may become an important component of the mandatory reporting factors in CAP guidelines if a larger dataset establishes its importance. A randomized trial with larger sample size and homogenous population is needed to show the substantial impact of WPOI on overall survival.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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