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The prognostic significance of the 'Worst Pattern of Invasion' in oral cancers—an international collaborative multicentre analysis

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ABSTRACT

Worst pattern of invasion (WPOI) has been evaluated in many single-institute cohorts. Our goal was to perform a large multicentre evaluation of WPOI as a prognostic marker in oral squamous cell carcinoma (OSCC). Retrospective pathology data was collated from 14 institutions and compared with clinical outcome in 1374 OSCC patients with upfront curative resection. Most cases were of oral tongue (n = 645, 47%); T2 (33%) and N0 (59%). WPOI 1–3 frequency was 29.4%, WPOI 4 47% and WPOI 5 22%. On univariable analysis, the 3-year disease free survival (DFS) was 54.2% for WPOI 5 vs. 69.7% for WPOI 1–4 ($p < 0.001$). The locoregional control (LRC) was 68.9% vs 79.2% ($p = 0.001$), and overall survival (OS) 68.4% vs 83.8% ($p < 0.001$). On multivariable Cox-regression in the entire cohort, WPOI 4 or 5 was strongly correlated with other known poor prognostic factors and not an independent predictor of OS (HR 1.10, 95% CI 0.92–1.52), LRC or DFS. However, in early-stage (pT1-2 N0) patients treated with surgery alone without adjuvant radiotherapy, WPOI 5 was a robust independent predictor of DFS (HR 4.36, 95% CI 1.54–12.32, p = 0.006), OS (HR 3.69, 95% CI 1.23–11.1, p = 0.020) and LRC

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(HR 3.52, 95% CI 2.13–5.82, p <0.001) after applying inverse probability weighting to correct for selection bias. Furthermore, in the entire cohort of early-stage patients, interaction modeling showed that adjuvant radiotherapy significantly reduces the risk for both DFS and LRC for those with WPOI-5 (Interaction p = 0.002). Therefore, it may act as a predictive biomarker for the benefit of adjuvant radiotherapy. The prognostic and predictive role of WPOI-5 should be validated in prospective trials.

Introduction

Oral squamous cell carcinoma (OSCC) represents a significant global health challenge, especially in India. Apart from the tumour stage, nodal stage, and margin status, the clinical course and outcome in OSCC are determined by a multitude of histopathological prognostic markers. The worst pattern of invasion (WPOI) is one such important parameter that has long been recognized in OSCC. The patterns range from broad pushing (WPOI 1), finger-like (WPOI 2), large separate nests (WPOI 3), to small, dispersed nests of < 15 cells (WPOI 4), which represent worsening tumour biology [1]. In 2005, Brandwein et al defined WPOI 5 as the presence of tumour satellites with > 1 mm of dispersion from the main tumour bulk (irrespective of the size of the satellite) [2]. These satellites are said to represent extra-tumoral perineural invasion (PNI), extra-tumoral lymphovascular invasion (LVI), and/or tumour deposits (>1mm away). WPOI 5 was shown to indicate a significantly worse outcome compared to WPOI 1–4, resulting in its inclusion as a conditional data element in reporting OSCC by the College of American Pathologists (CAP) [3].

The International Collaboration on Cancer Reporting (ICCR) and Royal College of Pathologists (RCPath) minimum-dataset reporting guidelines have adopted a slightly different approach. They categorized patterns of invasion into 3 groups – cohesive, non-cohesive, and widely dispersed patterns, and included this parameter as a core data element. The widely dispersed pattern corresponds to WPOI 5 and was newly introduced in the dataset in 2021. WPOI 4 is the same as a non-cohesive pattern, while WPOI 1–3 correspond to cohesive patterns [4].

The prognostic significance of WPOI has been evaluated in multiple individual cohort studies, systematic reviews, and *meta*-analyses [5]. Some studies have evaluated WPOI 5 only, while others have explored both WPOI 4 and 5 as aggressive high-risk patterns. It is still controversial whether presence of WPOI 5 warrants adjuvant treatment, and if WPOI 4 and/or WPOI 5 need to be included as mandatory reporting criteria.

In this study, the primary objective was to determine the prognostic impact of WPOI on overall survival (OS), disease-free survival (DFS), and locoregional control (LRC) in a large multicentre international cohort, to validate its prognostic impact in a real-world setting and explore its potential role in guiding personalized adjuvant treatment. Secondary objectives were to determine the prevalence of WPOI 4 and 5 in OSCC and its relation to other known histopathological prognostic factors in OSCC.

Methods

Data was retrospectively collected from 14 large-volume academic institutes in India, the United States, and Australia. Eligible subjects were those with OSCC confined to the primary site and draining neck nodes undergoing curative intent primary surgical excision. Those who received any form of neoadjuvant chemotherapy or radiotherapy, had incomplete neck dissection, inadequate pathological evluation (with < 4 tumour sections or inadequate margin evaluation), prior history of neck surgery or radiation therapy (RT) due to any other malignancy, or with less than 1 year of follow-up at their primary institution in the absence of disease recurrence or death, were excluded.

The study was granted institutional review board approval. Details of patient demographics (age, sex) and pathological factors (tumour site, size, depth of invasion, grade, LVI, PNI, margin status, tumour, and nodal stage, extranodal extension (ENE), and WPOI types) were recorded in detail. Clinicopathological variables like T size and depth of invasion were modelled as continuous variables. Any nerve involved by the tumour (irrespective of the thickness of the nerve or the location – intra or extra-tumoral) was recorded as PNI. The extent of ENE was not recorded. Most of the prognostic parameters were predominantly captured from reports, while the hematoxylin-eosin-stained glass slides (at least 4 or more tumour sections, unless the tumour was submitted entirely in fewer sections for a smaller tumour) were reviewed for recording the exact WPOI category on the worst focus (even if focal) for each case. In some centers, re-staining of faded slides/ or fresh recuts from paraffin blocks was studied, especially in older archived cases, for better appreciation of WPOI.

The definition of WPOI adopted by participants in this study was that defined by Brandwein et al and accepted in the CAP minimum dataset guidelines [2,3,6]. For further clarity on the published definition of WPOI4 and 5, and uniformity in reporting in this study, the YouTube tutorial guide (https://www.youtube.com/watch?v=k2dMAgml1H8) was referred to. However, taking into cognisance the subjectivity in assessing and categorizing WPOI, before starting data collection, the group underwent a concordance evaluation exercise to ensure correct understanding of the definition of the categories of WPOI and improve uniformity of reporting. A set of 20 digitally scanned whole-slide images (1 slide per case) was shared for scoring. The interobserver concordance evaluation showed a Fleiss' kappa score of 0.23 (fair agreement). Cases with discordant scores and other difficulties in WPOI categorization were discussed over two virtual meetings, and a common approach to scoring was determined. Though currently there is no accepted published guideline on how small a focus was acceptable for determining the 'focal' worst pattern, the participants agreed that using a 1% cut-off as a rough guide was useful in WPOI 4 cases. For WPOI 5, even a single widely dispersed focus (>1mm away), which was clearly separate from the main tumour bulk (ensured by comparing with adjacent sections) was sufficient for the WPOI 5 category. The study of deeper levels or the use of immunohistochemistry for improving the accuracy of WPOI scoring was not mandated in this study. By definition, the discontinuous tumour satellite should be separated by normal tissue and not tumour-induced fibrosis. It is challenging to discern true dispersion (WPOI-4) in some tumours with feathery appearance at the tumour-stroma interface and can lead to discordance. (Fig. 1) We were able to discuss these cases and form a common approach to reporting with consensus.

The clinicopathologic, treatment and follow-up data were captured on a uniform template on REDCap. The outcome was coded as the occurrence of local, regional, or distant failure until the last follow-up. The database was divided into institutional data access groups (DAGs) for data security. Data analysis was exported in a de-identified format.

Statistical analysis

Data analysis was performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were summarized as frequencies and percentages, and continuous variables as medians with interquartile ranges (IQR) or means with standard deviations (SD). Associations between clinicopathological variables and WPOI status were evaluated using the Chi-squared test or Wilcoxon rank-sum test, as appropriate.

Outcomes were defined as follows: Disease-free survival (DFS) was defined as freedom from any relapse (locoregional or distant) or death

from any cause. Overall survival (OS) was defined as freedom from death from any cause. Locoregional control (LRC) was defined as freedom from relapse at the primary site or draining cervical lymph nodes. These were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable survival analyses were conducted using Cox proportional hazards models.

To account for the multicenter structure of the data and potential heterogeneity in practice across the 14 participating institutions, all multivariable models utilized robust variance estimates clustered by institution.

A subset analysis was performed for early-stage (pT1-2 N0) cancers. Sensitivity and interaction analyses were performed to rigorously evaluate the prognostic impact of WPOI 5 in early-stage disease while addressing potential selection bias in treatment allocation to adjuvant radiotherapy. Two complementary analyses were performed: a) Inverse Probability Weighting (IPW): A propensity score-weighted analysis was conducted to balance baseline covariates between treated (adjuvant RT) and untreated groups. Propensity scores were estimated using logistic regression based on relevant confounders (T-size, depth of invasion, margin status, LVI, and PNI). Inverse probability weights (IPW) were calculated to generate a pseudo-population in which treatment assignment was independent of measured covariates. Covariate balance was assessed using standardized mean differences (SMD), with an SMD < 0.1 considered indicative of adequate balance. A weighted Cox proportional hazards model was then used to estimate the hazard ratio of WPOI 5 in the subgroup of patients treated with surgery alone. b) Treatment Interaction Modeling: To formally test whether adjuvant radiotherapy modifies the prognostic effect of WPOI 5, a multivariable Cox regression model was fitted to the entire pT1-2 N0 cohort, including an interaction term between WPOI status and adjuvant RT.

We also performed a sensitivity analysis by reanalyzing the DFS impact, restricting it to 10 centers with the highest agreement.

Locoregional control (LRC) was analyzed using a competing risks framework, where death without prior recurrence was treated as a competing event. Multivariable analysis was performed using the Fine and Gray proportional subdistribution hazards model. To ensure robust estimation, this model was also weighted by propensity scores and clustered by institution to simultaneously account for selection bias, competing mortality, and institutional heterogeneity.

Given the potential for biological and treatment variation across oral subsites, an exploratory interaction analyses were conducted with a three-way interaction model (WPOI $\times$ Site $\times$ RT) to determine whether there were observed site-specific differences or differential responses to adjuvant radiotherapy. For all analyses, a two-sided p-value < 0.05 was considered statistically significant.

Results

WPOI data was initially collected from a total of 2166 patients from 14 centers. The cases with incomplete histopathology data/follow-up (<1 year) were excluded, and a total of 1374 cases were included for final analysis.

The clinical and pathological characteristics are shown in Table 1. There was a distinct male predominance (73:27 ratio). The commonest tumor location was the tongue (47%), followed by the buccal mucosa (33%). The majority of the tumors were distributed in T2(33%), T3 (25%) and T4a(26%) stages, with only 3.3% showing margin involvement. The median nodal yield was 31 nodes per case. Thirty-eight percent of patients had at least one positive lymph node. ENE was noted in 27% of the node-positive cases.

A total of 309 cases (22%) had WPOI 5. The WPOI distribution in this cohort is provided in Table 2, with WPOI 4 being the most prevalent pattern (49%). The presence of WPOI 5 correlated significantly with many of the other known histological poor prognostic markers (T size, depth of invasion, margin status, LVI, PNI, nodal status, and ENE) (Table 3). A similar significant correlation with all the above prognostic parameters was also seen in cases with aggressive patterns – WPOI 4 or 5 (Appendix Table 3b).

Adjuvant external beam radiotherapy (2 Gy per fraction dose equivalent of 60–66 Gy over 6–6.5 weeks) was advised for all stage III-IVB patients, with the addition of concurrent weekly or 3-weekly platinum-based chemotherapy for patients with involved surgical margins or extranodal extension in all centers. For stage I/II patients, the policies across institutions were variable and have evolved over the time period of the data collection. While all institutions advised adjuvant radiotherapy for involved margins, several other factors alone or in combination were also used. These factors included close surgical margins, PNI, LVI, DOI (with variable cut-offs ranging from 3 mm to 8 mm), WPOI5, poor differentiation, and the subsite of the primary (tongue/floor of mouth).

Outcome analysis in the entire cohort

With a median follow-up of 29 months by the reverse Kaplan Meier

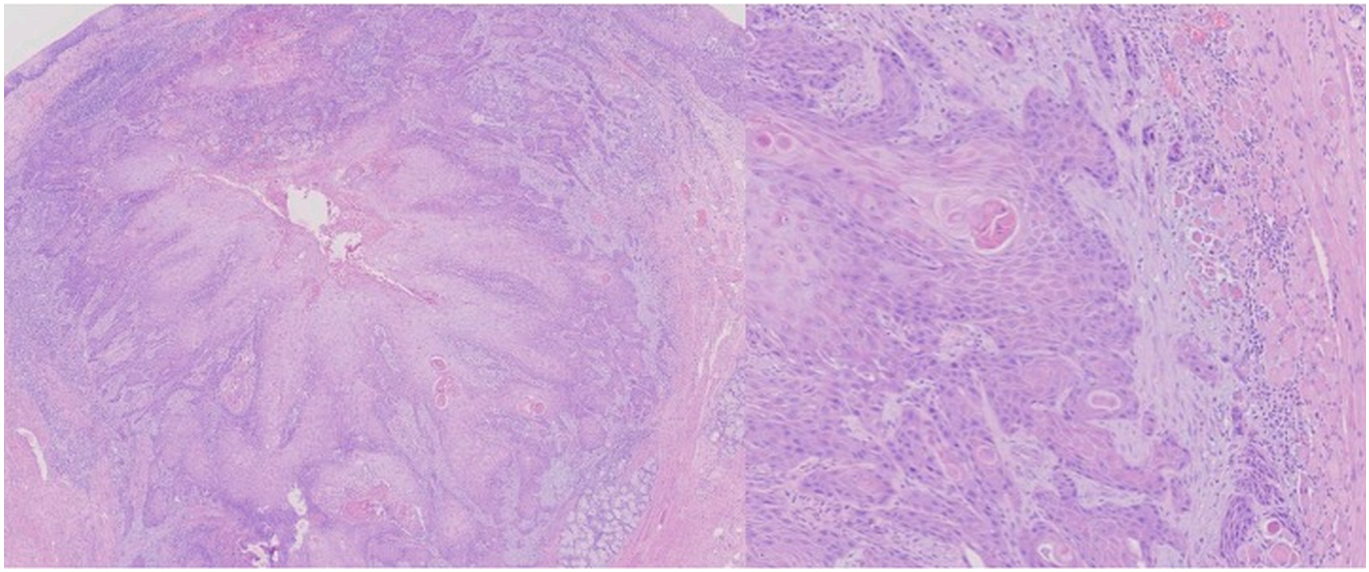

Fig. 1. Difficulty in assessing WPOI4 in cases with feathery appearance at the tumour-host interface.

Table 1
Patient and tumour characteristics.

Characteristic		N = 1,374[a]
Age (median; interquartile range)		52 (43, 61)
Sex		
Male		1,006 (73%)
Female		368 (27%)
Site	Oral Tongue	645 (47%)
	Buccal Mucosa	457 (33%)
	Lower Alveolus	126 (9.2%)
	Upper Alveolus	40 (2.9%)
	Lip	18 (1.3%)
	Retromolar trigone	34 (2.5%)
	Floor of Mouth	20 (1.5%)
	Overlapping	34 (2.5%)
T Size (mean (SD))		2.94 (1.43)
Depth (mean (SD))		1.10 (0.86)
Resection margin	Clear	1,065 (78%)
	Close (< 5 mm)	264 (19%)
	Involved	45 (3.3%)
Lymphovascular invasion	Absent	1,065 (78%)
	Present	309 (22%)
Perineural invasion	Absent	779 (57%)
	Present	595 (43%)
Bone invasion	Absent	632 (46%)
	Erosion	24 (1.7%)
	Cortical invasion	182 (13%)
	Bone not resected	536 (39%)
pT stage (AJCC 8th ed)	pT0	0 (0%)
	pT1	205 (15%)
	pT2	449 (33%)
	pT3	350 (25%)
	pT4a	357 (26%)
	pT4b	13 (0.9%)
pN stage (AJCC 8th ed)	pNx	30 (2.2%)
	pN0	816 (59%)
	pN1	189 (14%)
	pN2a	30 (2.2%)
	pN2b	155 (11%)
	pN2c	20 (1.5%)
	pN3a	7 (0.5%)
	pN3b	127 (9.2%)
Extranodal extension (ENE) present		144 (27% of node positive cases)
Adjuvant radiation therapy		968 (70%)
Concurrent chemotherapy		375 (29%)

[a] Mean (SD); n (%).

Table 2
Distribution of worst pattern of invasion.

Worst pattern of invasion (WPOI)	Number (proportion)
WPOI 1	23 (1.7%)
WPOI 2	40 (2.9%)
WPOI 3	334 (24.3%)
WPOI 4	668 (48.6%)
WPOI 5	309 (22.4%)

estimate, 446 (32.5%) patients had either disease recurrence and/or death. The overall survival (OS) for the whole group at 2 years was 81.9%, while at 3 years it was 80.5%. The disease-free survival (DFS) rates at 2 and 3 years were 70.7% and 66.3%, respectively. The overall median DFS was 95 months. The locoregional control (LRC) at 2 years was 80.5%, while at 3 years it was 77%.

There was a strong association of outcomes with WPOI on univariable analysis. The 3-year DFS was 54.2% for those with WPOI 5 vs. 69.7% for those without ($p < 0.001$), the corresponding 3-year LRC was 68.9% vs 79.2% ($p = 0.001$) and 3-year OS was 68.4% vs 83.8% ($p < 0.001$) as shown in Fig. 2.

When expanded into 3 groups, the 3-year DFS was 74.2%, 66.9%, 54.2% for WPOI 1–3, WPOI 4 and WPOI 5 patients ($p < 0.001$). The 3-year LRC was 80.6%, 78.4%, and 68.9% for these subgroups ($p = 0.005$); and the 3-year OS was 87.2%, 81.7% and 68.4% respectively ($p < 0.001$).

Table 3
Association of WPOI 5 with other prognostic variables.

Characteristic	Overall, N = 1,374[a]	WPOI 5 absent, N = 1,065[a]	WPOI-5 present, N = 309[a]	p-value[b]
T Size (max; in cm)	2.94 (1.43)	2.86 (1.43)	3.22 (1.41)	<0.001
Depth (max; in cm)	1.10 (0.86)	1.03 (0.86)	1.34 (0.81)	<0.001
Resection margin				<0.001
Clear	1,065 (78%)	856 (80%)	209 (68%)	
Close (< 5 mm)	264 (19%)	182 (17%)	82 (27%)	
Involved	45 (3.3%)	27 (2.5%)	18 (5.8%)	
Lymphovascular invasion				<0.001
Absent	1,065 (78%)	879 (83%)	186 (60%)	
Present	309 (22%)	186 (17%)	123 (40%)	
Perineural invasion				<0.001
Absent	779 (57%)	675 (63%)	104 (34%)	
Present	595 (43%)	390 (37%)	205 (66%)	
Nodal metastasis				<0.001
Node negative	909 (66%)	751 (71%)	158 (51%)	
Node positive	465 (34%)	314 (29%)	151 (49%)	
Extranodal extension (ENE) present	144 (10%)	83 (7.8%)	61 (20%)	<0.001

[a] Mean (SD); n (%).
[b] Wilcoxon rank sum test; Pearson's Chi-squared test.

The results of multivariable analyses are shown in Table 4. The presence of WPOI 5 was not found to be an independent prognostic factor for LRC, DFS, and OS. The independent prognostic markers were the maximum tumour dimension (DFS and OS), depth of invasion (DFS and OS), PNI (LRC and DFS), margin status, pathological nodal involvement, and ENE (LRC, DFS, and OS). Multivariate analysis with cases showing any aggressive pattern – ie. WPOI 4 or 5, did not yield any different results. (Appendix Table 4b).

Outcome analysis in stage I and II only

We performed a subgroup analysis on 430 early-stage oral cancers (pT1-2 N0). Recognizing that there is considerable heterogeneity in the practice of adjuvant radiotherapy based on the presence or combination of risk factors in this group, initially, the cohort of patients was divided into those treated with and without adjuvant RT.

Patients with pT1-2 N0 cancer, who received adjuvant radiotherapy ($n = 181$), had larger tumors, greater depth, and a greater incidence of positive or close margins, lymphovascular and perineural invasion (See Appendix Table 6). The incidence of WPOI 5 was 32 (18%). The 2 and 3-year DFS was 74.8% and 66.7%. WPOI 5 was not a significant predictor of DFS, LRC or OS in this group.

However, in the cohort of patients in whom adjuvant radiotherapy was not offered ($n = 249$), WPOI 5 was present in 22 (8.8%) cases. The 2- and 3-year DFS was 94.1% and 93.3%. In univariate analysis, WPOI 5 was a significant predictor for DFS (3-year 94.6% vs 80%, $p < 0.001$) and LRC (3-year 95.6% vs 86.1%, $p < 0.001$). It was also an independent prognostic factor in multivariable analysis for DFS (HR 3.56, 95% CI 1.37–9.25, $p = 0.009$) and for LRC (HR 4.63, 95% CI 1.59–13.5, $p = 0.005$). It was not prognostic for OS in univariate or multivariable analysis. Further details are shown in Table 5.

This result was maintained after applying inverse probability

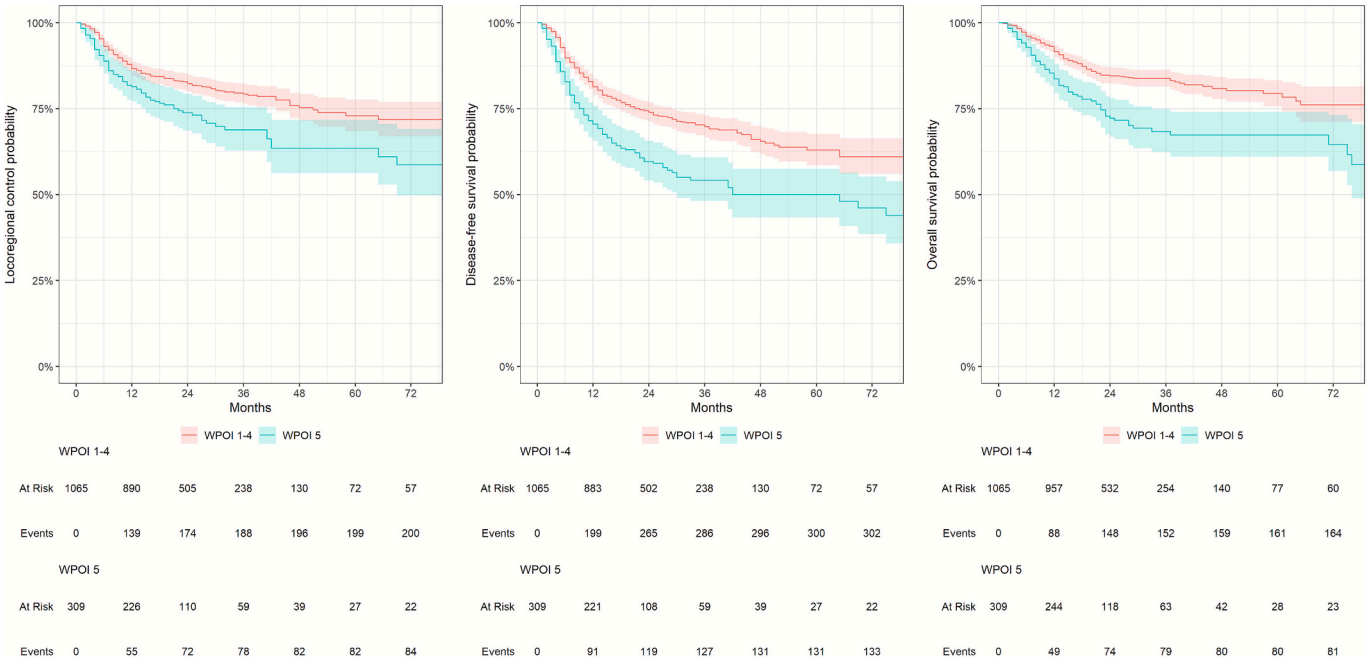

Fig. 2. Correlation of the Worst pattern of invasion 5 with outcomes in the entire cohort.

Table 4
Multivariable analysis of outcomes for the entire cohort.

	Locoregional control			Disease-free survival			Overall Survival		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
T Size (maximum dimension) in cm	1.02	0.92, 1.13	0.7	1.11	1.03, 1.21	0.011	1.24	1.11, 1.37	<0.001
Depth (maximum) in cm	1.13	0.95, 1.34	0.2	1.17	1.03, 1.33	0.016	1.21	1.03, 1.41	0.019
Close margins (< 5 mm vs. clear margins)	1.57	1.19, 2.07	0.001	1.41	1.12, 1.76	0.003	2.07	1.56, 2.74	<0.001
Involved margins (vs. clear margins)	2.08	1.26, 3.45	0.004	2.16	1.48, 3.17	<0.001	3.54	2.28, 5.49	<0.001
Lymphovascular invasion present (vs. absent)	1.08	0.81, 1.44	0.6	1.23	0.98, 1.54	0.075	1.29	0.97, 1.73	0.082
Perineural invasion present (vs. absent)	1.25	0.97, 1.62	0.085	1.28	1.04, 1.57	0.019	1.04	0.79, 1.37	0.8
Worst Pattern of Invasion 5 Present (vs. absent)	1.08	0.80, 1.28	0.18	1.07	0.83, 1.18	0.16	1.09	0.82, 1.34	0.10
Node positive (vs. negative)	1.45	1.10, 1.91	0.008	1.78	1.43, 2.22	<0.001	2.04	1.52, 2.73	<0.001
Extranodal extension present (vs. absent)	1.95	1.41, 2.72	<0.001	1.78	1.38, 2.30	<0.001	1.90	1.39, 2.60	<0.001

Table 5
Multivariable analysis of outcomes in pT1-2 N0 patients who were not offered radiotherapy (n = 249).

	Locoregional control			Disease-free survival			Overall survival		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
T Size (maximum dimension) in cm	0.89	0.46, 1.72	0.7	0.88	0.48, 1.60	0.7	1.22	0.43, 3.47	0.7
Depth (maximum) in cm	0.44	0.05, 4.05	0.5	0.61	0.09, 4.11	0.6	0.97	0.05, 17.4	>0.9
Close Margins (< 5 mm vs. clear margins)	1.67	0.36, 7.78	0.5	3.25	1.03, 10.2	0.044	14.7	2.67, 81.5	0.002
Perineural invasion present (vs. absent)	1.86	0.53, 6.51	0.3	1.79	0.59, 5.45	0.4	2.27	0.34, 15.2	0.4
Worst Pattern of Invasion 5 Present (vs. absent)	4.63	1.59, 13.5	0.005	3.56	1.37, 9.25	0.009	1.81	0.32, 10.2	0.5

weighting to correct for selection bias. WPOI 5 remained a robust independent predictor in multivariable analysis of DFS (HR 4.36, 95% CI 1.54–12.32, p = 0.006), OS (HR 3.69, 95% CI 1.23–11.1, p = 0.020) and LRC (HR 3.52, 95% CI 2.13–5.82, p <0.001) in patients who did not receive adjuvant RT.

To determine the impact of adjuvant radiotherapy in patients with WPOI-5, an interaction analysis was performed on the cohort of early-stage patients. For DFS, we found that in the absence of adjuvant RT, WPOI 5 was a significant predictor of poor outcomes with (HR 3.94, 95% CI 1.61–9.65, p = 0.003). The interaction term was highly statistically significant (HR 0.16, 95% CI 0.05–0.51, p = 0.002), indicating that the administration of radiotherapy significantly reduced the risk of relapse or death associated with WPOI 5. For LRC (using death as a competing risk), we again found that in the absence of adjuvant RT, WPOI 5 was a significant predictor of poor LRC (HR 3.46, 95% CI 1.89–6.34, p <0.001). The interaction term was again highly statistically significant (HR 0.09, 95% CI 0.02–0.42, p = 0.002), indicating that the administration of adjuvant radiotherapy significantly reduced the locoregional recurrence risk associated with WPOI 5. For OS, in the absence of adjuvant RT, WPOI 5 was a potentially important but not a significant predictor of poor OS (HR 2.49, 95% CI 0.73–8.47, p = 0.15). The interaction term was also not statistically significant (HR 0.40, 95% CI 0.05–3.55, p = 0.4).

The sensitivity analysis restricted to 10 centers with the highest agreement (n = 276, number of events = 57) showed consistent results with WPOI 5 remaining a significant predictor with a Hazard Ratio (HR)

of 4.60 (95% CI 2.14–9.90, p <001). The interaction term testing the effect of radiotherapy on cases with WPOI-5 also remained highly statistically significant (HR 0.14, 95% CI 0.04–0.52, p = 0.003). Therefore, the findings are not affected by centers with lower agreement.

As an exploratory analysis, a 3-way interaction model for DFS was implemented using the site-group of tongue vs gingivobuccal added to WPOI-5 and adjuvant RT. The interaction between WPOI 5 and adjuvant RT was not significant in gingivobuccal cancer (p = 0.92) but was significant for tongue cancer (p = 0.036). This leads to a hypothesis that adjuvant RT may be more useful in mitigating the risk of relapse or death in tongue cancers over gingivobuccal cancers (see discussion).

Discussion

This study represents the largest multicentre effort with a large sample size to critically evaluate the prognostic significance of WPOI in OSCC. We attempted to replicate a real-world scenario of clinical reporting and the use of this prognostic parameter by including a mixed group of highly experienced head and neck pathologists and general oncopathologists, who evaluated their own cases as would be done in routine reporting. The group met online multiple times to discuss and minimise subjectivity in interpreting WPOI score groups.

WPOI 4 was the most prevalent pattern in our series (48.6%), while WPOI 5 comprised 22%. Many studies have shown similar proportions, though the distribution is extremely variable in the literature [5]. Prior large single-institute Indian data showed high prevalence of WPOI 4 (64%) and 5 (13.5%) [7,8]. Prevalence of WPOI 4 and 5 in early-stage cancers is reported to be lower: 29% and 4.6%, respectively [9]. Xu et al reported a high prevalence of WPOI 4 (57.8%) in tongue cancers (of < 4 cm size), while Kohler et al, who have the largest published series to date, report a much lower prevalence of 28.5% for WPOI 4 and 16.1% for WPOI 5, in a mixed cohort of all stages [10,11].

Multicentre validation of the prognostic significance of WPOI was the main intent of this study. Like many other reported studies, we too found WPOI 4 or 5 to correlate significantly with DFS, LRC, and OS on univariate analysis [5,10]. However, the independent prognostic significance was lost on the multivariable analysis, both for WPOI 5 and for the presence of any aggressive pattern (i.e. WPOI 4 or 5), when the whole cohort was analyzed.

Several studies have reported the prognostic significance of WPOI 5 or any aggressive WPOI (WPOI 4 or 5) in relation to multiple clinical outcomes. These have mostly been univariate analyses [5]. However, when looking at WPOI as an independent predictor, we find considerable heterogeneity in the approach taken by other researchers. In most studies, only a subset of known prognostic factors have been included in the Cox regression analysis [12,13]. One of the more recent larger series by Xu et al has shown WPOI 5 to have an independent correlation with OS (p = 0.010), but not with local or regional recurrence-free survival, or distant metastasis-free survival, when adjusted for T stage, LVI and PNI and compared with tumor budding [10]. Mohamed et al also showed WPOI 5 (satellite nodules) to be significantly correlating with OS on multivariable analysis (OS OR 6.61 (95% CI 2.83 – 15.44), but there were only 9 cases of WPOI 5 in their series, and they did not correlate with locoregional recurrence. [14] We included all of the known prognostic factors in the multivariable analysis (size, depth, margins, LVI, PNI, nodal involvement, and extranodal extension). We believe this approach is more robust and allows us to more clearly evaluate the true implications of higher WPOI scores.

In our cohort, the lack of independent prognostic significance in the entire cohort could be attributed to the correlation of WPOI with other poor prognostic parameters (T size, depth, grade, LVI, PNI, margin status, nodal metastasis, and ENE). This correlation has been selectively reported previously in other studies [10,12]. WPOI scores have also been reported to correlate with increasing tumour and nodal stages (along with stage determinants – tumour size, depth of invasion, nodal status, and ENE) [15–17]. The clinical impact of WPOI on margin status has been further explored by Kohler et al. They proposed the need for a higher margin cut-off (7.8 mm) in patients with aggressive WPOI (4 or 5), compared to 1.7 mm for the low-risk WPOI patterns (1–3) [11].

When we analyzed the early-stage cancers, we discovered a potentially important prognostic and predictive role for WPOI. We found that in patients who were not advised RT due to the absence or paucity of the currently known high-risk factors (tumour size, depth, perineural invasion, close margins), the presence of WPOI 5 emerged as the only independent factor for DFS and LRC. This association was lost in those who received RT. Propensity score weighting was performed to mitigate potential bias in adjuvant treatment selection, and results remained robust. This establishes the prognostic importance of WPOI-5 in early-stage patients treated with surgery alone.

To determine the impact of adjuvant radiotherapy in early-stage cancers with WPOI-5, we performed an interaction analysis in the entire early-stage cohort, which confirmed that the presence of WPOI-5 significantly increases risk in both DFS and LRC in patients treated with surgery alone in multivariable analysis, and that adjuvant radiotherapy results in a large and significant reduction of risk in both DFS and LRC. This establishes WPOI-5 as a predictive biomarker in treatment selection for adjuvant therapy.

To identify signals on whether the predictive impact of radiotherapy was more prominent in a particular anatomical subsite, we performed a 3-way interaction analysis with tongue and gingivobuccal sites, which showed that the impact of adjuvant treatment may be more prominent on oral tongue. In view of the relatively smaller cohort of early-stage cancers tested, we believe this result should be considered exploratory and should be confirmed by future prospective studies with an appropriate sample size and site-based stratification.

Many of the reported studies on WPOI have focused on early-stage tongue cancers, which is where WPOI is likely to have the highest impact on treatment selection [5,14,18]. In our institutional reported series of 95 cases of early-stage OSCC (sub-cohort of the current study), we similarly found WPOI 4 and 5 correlated with poor DFS on univariate analysis (p = 0.033) [19]. Brandwein et al added WPOI to the histological risk model and validated its prognostic potential in 305 early-stage OSCC [6]. Thakur et al. further validated this model on AJCC8-staged OSCC and showed its prognostic significance in both early as well as advanced-stage tumors [7]. This larger multicenter cohort provides further robust confirmation of the impact of WPOI-5 in the early-stage setting.

While these results are illuminating, they mandate cautious interpretation and prospective validation before treatment guidelines incorporate WPOI5 as a standalone high-risk criterion.

The importance of WPOI-5 and other known prognostic and predictive histopathological biomarkers for oral cancer suggests that future research should focus on the integration of these biomarkers into statistical and/or machine learning/ artificial intelligence-based modelling for outcome prediction and adjuvant treatment selection, as well as using more advanced histopathological slide-imaging-based prediction tools.

Our study has three main limitations. The first is a relatively short follow-up. Despite this limitation, we believe that a 29-month follow-up captures the most important window of locoregional recurrence. Secondly, as this study involved 14 centers across 3 continents, there was a lack of uniformity in the adjuvant treatment protocols and margin evaluation in this cohort. We have taken several statistical measures to correct for the effects and improve the reliability of our results. The other limitation is the large number of observers with an initial suboptimal interobserver concordance in categorizing WPOI. We had over 28 reviewers of the slides for the data collected in the study, which could introduce some subjectivity. This was addressed in the consensus meeting and its corresponding guidance. Further standardization of reporting will be beneficial. Nevertheless, this method also brings out the prognostic importance of real-world reporting of WPOI.

Conclusion

Based on this large multi-institutional analysis of OSCC, the presence of WPOI 5 is established as a significant prognostic factor for DFS, LRC, and OS on univariate analysis. While not an independent prognostic factor in the entire cohort of patients, the presence of WPOI 5 is an important independent prognostic factor in the cohort of early-stage OSCC without adjuvant treatment. Adjuvant radiotherapy improves DFS and LRC in patients with WPOI-5 in early-stage cancers, and therefore, WPOI-5 can potentially be considered as a predictive biomarker for adjuvant treatment selection. Prospective studies in the early-stage cancers will be required to validate these findings and define the precise role of WPOI-5 in adjuvant therapy decisions in early-stage oral cancers.

Précis: In a large multinstitutional cohort of patients with oral cancer treated with curative intent, the worst pattern of invasion is indicative of poorer outcomes. It is an independent prognostic factor in early-stage cancers that do not receive adjuvant radiotherapy after surgery.

Statement related to ethics—

- data availability statement − The data is not available for sharing
- funding statement − There was no external funding for this study
- patient consent statement − Patient consent waiver was approved for this study as this is an anonymized retrospective assessment.
- permission to reproduce material from other sources − not applicable
- clinical trial registration − not applicable

Ethics approval statement

This study received IRB approval at TMC Kolkata (2022/TMC/236/IRB41) and all the participating institutes.

CRediT authorship contribution statement

Paromita Roy: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Margaret Brandwein Weber:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Ruta Gupta:** Writing – review & editing, Data curation. **Aanchal Kakkar:** Writing – review & editing, Data curation. **Daphne Fonseca:** Writing – review & editing, Data curation. **Munita Bal:** Writing – review & editing, Data curation. **Meenakshi Kamboj:** Writing – review & editing, Data curation. **Nidhi Anand:** Writing – review & editing, Data curation. **K.R. Anila:** Writing – review & editing, Data curation. **Shanthi Velusamy:** Writing – review & editing, Data curation. **Megha Shantveer Uppin:** Writing – review & editing, Data curation. **Suvradeep Mitra:** Writing – review & editing, Data curation. **Meera Thomas:** Writing – review & editing, Data curation. **Poonam Abhay Elhence:** Writing – review & editing, Data curation. **Indu Arun:** Writing – review & editing, Data curation. **Sunil Pasricha:** Writing – review & editing, Data curation. **Nuzhat Husain:** Writing – review & editing, Data curation. **Rekha V. Kumar:** Writing – review & editing, Data curation. **Amanjit Bal:** Writing – review & editing, Data curation. **Asawari Patil:** Writing – review & editing, Data curation. **Shubhada V. Kane:** Writing – review & editing, Data curation. **Shantveer G. Uppin:** Writing – review & editing, Data curation. **Anand Bardia:** Writing – review & editing, Data curation. **Shivani Sarkar:** Writing – review & editing, Data curation. **Sahithi Shilpa Arya:** Writing – review & editing, Data curation. **Reshma Kurian:** Writing – review & editing, Data curation. **R. Chitra:** Writing – review & editing, Data curation. **Pramod Kumar Pamu:** Writing – review & editing, Data curation. **Christina Wiedmer:** Writing – review & editing, Data curation. **Jenny Tung Hiong Lee:** Writing – review & editing, Data curation. **Ritu Srivastava:** Writing – review & editing, Data curation. **Akhila Gopakumar:** Writing – review & editing, Data curation. **Tsu-Hui Hubert Low:** Writing – review & editing, Data curation. **Mark Urken:** Writing – review & editing, Data curation. **Jerry Liu:** Writing – review & editing, Data curation. **Deepa Nair:** Writing – review & editing, Data curation. **Rajsekhar Shantappa:** Writing – review & editing, Data curation. **Sarthak Tandon:** Writing – review & editing, Data curation. **Shaji Thomas:** Writing – review & editing, Data curation. **Cessal Thomas:** Writing – review & editing, Data curation. **Jeevan Ram Vishnoi:** Writing – review & editing, Data curation. **Kapila Manikantan:** Writing – review & editing. **Pattatheyil Arun:** Writing – review & editing. **Sanjoy Chatterjee:** Writing – review & editing. **Indranil Mallick:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

Table 3b
Association of WPOI 4 or 5 with other prognostic variables.

Characteristic	Overall N = 1,374[1]	WPOI 1–3N = 397[1]	WPOI 4–5N = 977[1]	p-value[2]
T size (max, in cm)	2.94 (1.43)	2.71 (1.49)	3.03 (1.40)	<0.001
Depth	1.10 (0.86)	0.94 (0.90)	1.17 (0.84)	<0.001
Resection margin				<0.001
Clear	1,065 (78%)	335 (84%)	730 (75%)	
Close (< 5 mm)	264 (19%)	59 (15%)	205 (21%)	
Involved	45 (3.3%)	3 (0.8%)	42 (4.3%)	
Lymphovascular invasion				<0.001
Absent	1,065 (78%)	358 (90%)	707 (72%)	
Present	309 (22%)	39 (9.8%)	270 (28%)	
Perineural invasion				<0.001
Absent	779 (57%)	314 (79%)	465 (48%)	
Present	595 (43%)	83 (21%)	512 (52%)	
Nodal metastasis				<0.001
Node negative	909 (66%)	328 (83%)	581 (59%)	
Node positive	465 (34%)	69 (17%)	396 (41%)	
Extranodal extension	144 (10%)	9 (2.3%)	135 (14%)	<0.001

[1]Mean (SD); n (%)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test

Table 4b
Multivariable analysis of outcomes compared to presence of WPOI 4 or 5.

	Locoregional control			Disease-free survival			Overall Survival		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
T Size (maximum dimension) in cm	1.02	0.92, 1.13	0.7	1.11	1.03, 1.21	0.011	1.24	1.11, 1.37	<0.001
Depth (maximum) in cm	1.13	0.95, 1.34	0.2	1.17	1.03, 1.33	0.017	1.20	1.03, 1.41	0.019
Margins close (< 5 mm) vs. clear	1.59	1.21, 2.10	<0.001	1.42	1.13, 1.78	0.002	2.08	1.57, 2.76	<0.001
Margins Involved (vs. clear)	2.14	1.29, 3.56	0.003	2.21	1.51, 3.25	<0.001	3.64	2.34, 5.66	<0.001
LVI Present (vs. absent)	1.10	0.82, 1.46	0.5	1.25	1.00, 1.56	0.055	1.32	0.99, 1.77	0.058
PNI Present (vs. absent)	1.31	1.01, 1.69	0.044	1.32	1.07, 1.62	0.009	1.08	0.82, 1.42	0.6
WPOI 4–5 (vs. WPOI 1–3)	1.10	0.85, 1.31	0.13	1.06	0.72, 1.38	0.20	1.10	0.92, 1.52	0.07
Node positive (vs. negative)	1.48	1.13, 1.96	0.005	1.82	1.45, 2.27	<0.001	2.08	1.55, 2.80	<0.001
Extranodal extension present (vs. absent)	1.99	1.43, 2.78	<0.001	1.81	1.40, 2.35	<0.001	1.94	1.41, 2.67	<0.001

Table 6
Differences in the prevalence of prognostic factors in patients treated with or without adjuvant radiotherapy.

Characteristic	**Overall** N = 430[1]	**No Adjuvant radiotherapy** N = 249[1]	**Adjuvant radiotherapy** N = 181[1]	**p-value**[2]
T size (cm)	2.04 (0.92)	1.77 (0.80)	2.40 (0.95)	<0.001
Depth of invasion (cm)	0.57 (0.37)	0.47 (0.33)	0.71 (0.37)	<0.001
Resection margin				0.011
Clear	381 (89%)	229 (92%)	152 (84%)	
Close (< 5 mm)	47 (11%)	20 (8.0%)	27 (15%)	
Involved	2 (0.5%)	0 (0%)	2 (1.1%)	
Lymphovascular invasion				0.095
Absent	412 (96%)	242 (97%)	170 (94%)	
Present	18 (4.2%)	7 (2.8%)	11 (6.1%)	
Perineural invasion				<0.001
Absent	328 (76%)	211 (85%)	117 (65%)	
Present	102 (24%)	38 (15%)	64 (35%)	
WPOI 5				0.006
Present	54 (13%)	22 (8.8%)	32 (18%)	
Absent	376 (87%)	227 (91%)	149 (82%)	

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

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