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Original Article

Pathology Section

Comparison of Worst Pattern of Invasion with Other Histopathological Prognostic Indicators in Oral Cavity Squamous Cell Carcinoma: A Cohort Study from Regional Cancer Centre, Thiruvananthapuram, Kerala, India

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ABSTRACT

Introduction: Oral Cavity Squamous Cell Carcinoma (OCSCC) is one of the most common cancers worldwide and a leading cause of morbidity and mortality in certain parts of the world like South-Central Asia. In the year 2005, the histologic risk assessment model was introduced by Brandwein Gensler for OCSCC to predict disease outcome and included risk factors like Perineural Invasion (PNI), Worst Pattern Of Invasion (WPOI), and Lymphocyte Host Response (LHR), which have a strong association with Local Recurrence (LR), Disease-Free Survival (DFS) and Overall Survival (OS).

Aim: To evaluate WPOI in OCSCC and analyse its association with other histopathological prognostic indicators in patients who have undergone primary surgery.

Materials and Methods: This cohort study was conducted in Department of Pathology at Regional Cancer Centre, Thiruvananthapuram, Kerala, India, from January 2023 to December 2023. A total of 100 cases of OCSCC diagnosed and treated between January 2018 and December 2021 were reviewed and clinical, histopathological and treatment data were analysed. The histopathological features analysed included grade, Lymphovascular Invasion (LVI), PNI, WPOI, LHR, tumour size, Depth of Invasion (DOI), margin status, bone invasion and lymph node status. The follow-up details of patients with respect to recurrences or terminal event was recorded from the medical records as of December 2023. Statistical Package for the Social Sciences (SPSS) version 28.0 was used for analysis. Chi-square tests and Fisher's exact test were used to analyse association between WPOI in OCSCC and other histopathologic prognostic indicators. A p-value of <0.05 was considered significant.

Results: Most common pattern of invasion was WPOI 4, comprising 61 patients. WPOI 3 was present in 38 patients and only one case with WPOI 5. A statistical significance between WPOI 4 and the presence of PNI and LVI, with p-values of 0.017 and 0.012, was observed. There was no statistical significance between cancer stage and POI (p-value=0.885), LHR and POI (p-value=0.686), or tumour differentiation/grade and POI (p-value=0.298). The OS for POI 3 was 97.1%, while OS for POI 4 was only 86%.

Conclusion: This outcome demonstrates that the existence of WPOI 4 may be a predictive factor of the presence of LVI and PNI, which are established risk factors of aggressive tumour behaviour and poor prognosis in OCSCC.

Keywords: Local recurrence, Lymphocyte host response, Perineural invasion

INTRODUCTION

The OCSCC is a worrying public health problem and is among the leading cancer cases across the globe [1]. Recent recorded data of Taiwan, India and Southeast Asia shows that buccal mucosa is the predominant subsite involved in OCSCC; this may be mainly due to the high rates of betel nut chewing in these areas [2]. Few parameters have gained importance to predict the outcome of OCSCC, including LVI, PNI, WPOI, surgical margin, DOI, bone involvement, and extracapsular extension of lymph nodal metastasis, which are widely used as indicators of adverse outcome [3,4]. These adverse prognostic factors in OCSCC are associated with the risk of LR and lymph node metastasis [5,6]. A model for histologic risk assessment was proposed by Brandwein-Gensler in 2005, incorporating three parameters, namely WPOI, PNI, and LHR and this model shows high prediction power for LR, DFS and OS [7]. Numerous researches have confirmed the prognostic validity of this risk rating method [8-12]. Recognising that WPOI is a critical determinant of disease progression and mortality in OCSCC, it has been classified into five groups, with increasing loss of cohesion of tumour cells from Group 1 to Group 5. Group 1 is characterised by a pushing border; Group 2 by finger-like growth; Group 3 by large separate islands of more than 15 cells per island; Group 4 by small tumour islands of 15 cells or fewer per island; and Group 5 by tumour satellites that are more than or equal to 1 mm from the main tumour or next closest satellite [7].

Among these, the American Joint Committee on Cancer (AJCC) has recently included reporting of WPOI 5 as an optional parameter in the dataset for reporting of OCSCC [13]. There are studies highlighting the prognostic implication of not only WPOI 5 but also WPOI 4 in OCSCC [14,15]. The present study aimed to determine the prognostic significance of WPOI in OCSCC. The objective of the study was to assess the prognostic significance of WPOI in the context of other known histopathological prognostic indicators. Although there are similar studies in the literature, authors believe that this study can be an addendum to the existing literature.

MATERIALS AND METHODS

The cohort study was conducted in Department of Pathology in patients with OCSCC diagnosed and treated in our tertiary cancer care centre, Regional Cancer Centre, Thiruvananthapuram, Kerala, India, over a four-year period from January 2018 to December 2021

in the Department of Pathology were studied. Study period was from January 2023 to December 2023. This study received approval from the Ethics Committee of our institute (HEC No: 42/23).

Inclusion criteria: All cases of OCSCC that underwent primary resection surgery and were diagnosed in the centre, with a follow-up of at least two years, were included in the study.

Exclusion criteria: Patients who had received any form of neoadjuvant chemotherapy or radiotherapy prior to curative intent surgical excision were excluded. Small biopsies from oral lesions were also excluded from the study.

After application of inclusion and exclusion criteria, a total of 100 cases were included in the study.

Study Procedure

Histomorphological features of individual cases of OCSCC were analysed by the authors. The Haematoxylin and Eosin (H&E)-stained slides were reviewed for features such as grade/differentiation, PNI, LVI, LHR, pattern of invasion, tumour size, DOI, margin status, bone invasion and lymph node metastasis. Features such as PNI, LVI, and bone invasion were assessed as either present or absent. In this study, we did not score the PNI based on size of nerve bundle involved. Bone invasion was considered positive when there was involvement of medullary bone; cortical erosion alone was not sufficient to be considered as bone invasion. Differentiation was characterised into well, moderate, or poorly differentiated. Pattern of invasion was recorded and categorised into one of the five groups. DOI and margin status were recorded in mm. For margin status, a clearance of 5 mm or more was considered a negative margin, while less than 5 mm clearance was considered as close margin. Clinical data, including age, sex, tumour site and stage, were recorded, and follow-up data with respect to recurrence or terminal event was updated till 2023.

STATISTICAL ANALYSIS

SPSS version 28.0 was used for the analysis. Chi-square tests and Fisher's exact test were used to analyse the association between WPOI in OCSCC and other histopathological features such as PNI and LVI. The p-value <0.05 was considered significant.

RESULTS

During the four-year period from January 2018 to December 2021, 100 cases of OCSCC who had undergone primary surgery were included in the study. Patients included 63 males and 37 females. Age ranged from 32 years to 91 years, with a mean age of 57 years. The maximum number of patients, 36, was in the sixth decade of life. The most common primary subsite in the oral cavity was oral tongue, with 61 cases, followed by 21 cases involving alveolus, 17 cases involving buccal mucosa, and one case in retromolar trigone. The demographic characteristics of patients are presented in [Table/Fig-1].

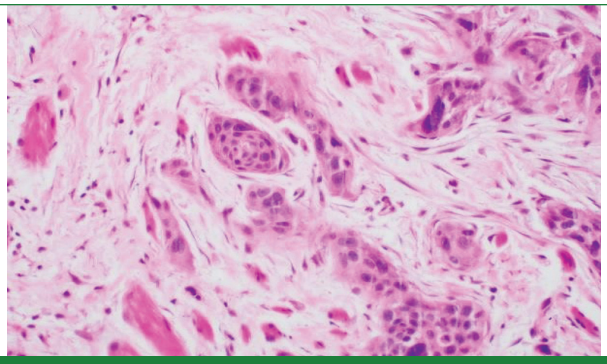
Variables		n
Sex	Female	37
	Male	63
Age (in years)	Less than 50	21
	More than and equal to 50	79
Tumour site	Tongue	61
	Alveolus	21
	Buccal mucosa	17
	Retromolar trigone	1

[Table/Fig-1]: Demographic data.

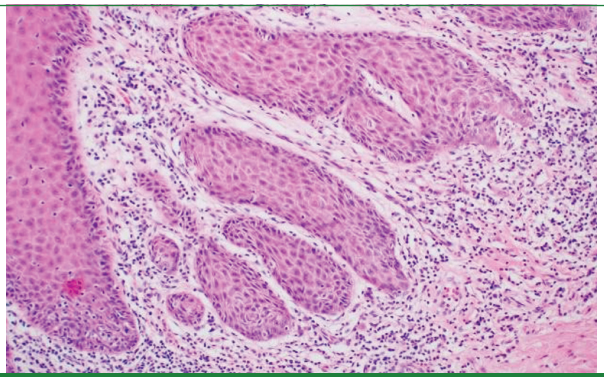
All patients had undergone neck dissection along with resection of primary tumour. Ninety patients underwent unilateral neck dissection, while ten patients had to undergo bilateral neck dissection. Majority of cases were moderately differentiated, LVI was identified in 10 cases, while intratumoural PNI was identified in 37 cases. Bone invasion was identified in seven cases. Nine cases had close margins with clearance of less than 5 mm, and two cases had positive margins. In rest of cases, margins were free. Forty-three patients had metastasis to lymph nodes, of which eight patients had extranodal extension of metastasis. The histopathological characteristics of the study group are presented in [Table/Fig-2]. Pattern of invasion four was seen in 61 patients [Table/Fig-3], POI 3 was noted in 38 patients [Table/Fig-4], and one case had POI 5 [Table/Fig-5]. LHR score 1 was present in 17 cases, score 2 in 51 cases, and score 3 in 32 cases.

Variables		n
POI	3	38
	4	61
	5	1
LVI	0	90
	1	10
Differentiation	Well	33
	Moderate	67
LHR	1	17
	2	51
	3	32
PNI	0	63
	1	37
pTNM stage	1	21
	2	28
	3	28
	4	23

[Table/Fig-2]: Histopathological parameters.
POI: Pattern of invasion; LVI: Lymphovascular invasion; LHR: Lymphocyte host response; PNI: Perineural invasion

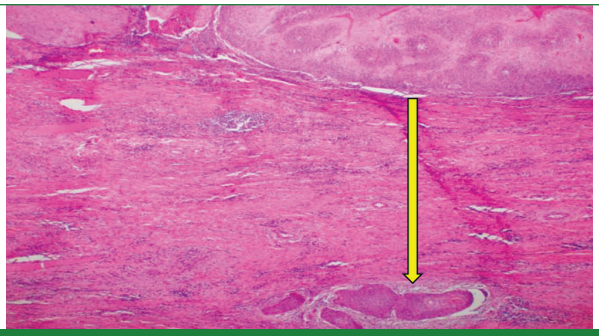


[Table/Fig-3]: Pattern of invasion 4 showing tumour cell nests with less than 15 cells (H&E X400).



[Table/Fig-4]: Pattern of invasion 3 showing tumour cell nests with more than 15 cells (H&E X200).

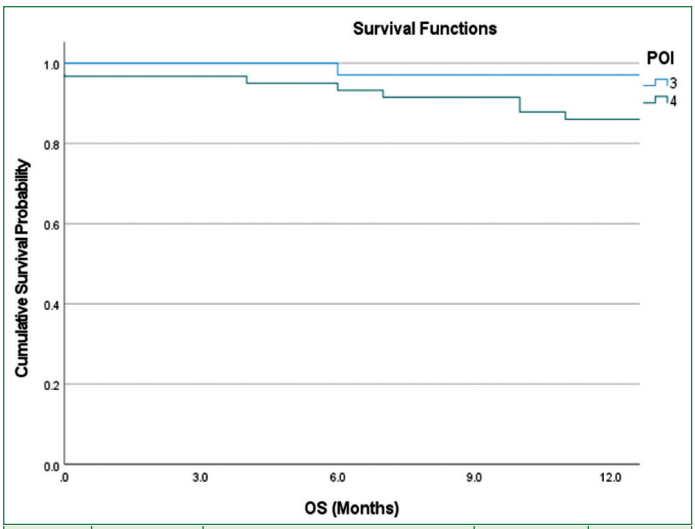
Most of the histopathological features assessed did not show any statistical significance with POI. However, there was statistical



[Table/Fig-5]: Pattern of invasion 5 showing tumour cell nests separated by more than one millimeter (H&E X100).

significance of POI 4 with PNI and LVI. Out of the 61 cases with POI 4, ten cases showed LVI, with a significant p-value of 0.012. None of the 38 cases with POI 3 showed LVI. Also, out of the 61 cases with POI 4, 29 cases showed PNI, with a significant p-value of 0.017. Out of the 38 cases with POI 3, PNI was observed in eight cases. There was no statistical significance of POI with other histopathological parameters like differentiation, LHR, stage (tumour size, DOI, lymph node status, and bone invasion). There was no discernible significance found between WPOI and either the LHR (p-value=0.686) or tumour differentiation grade (p-value=0.298). There was no statistical significance between cancer stage and WPOI (p-value=0.885).

Forty-two patients required radiotherapy following surgery. Nineteen patients required combined radiotherapy and chemotherapy following surgery, while five patients underwent chemotherapy alone after surgery. Sixteen patients had LR, out of which ten patients had POI 4 and six patients had POI 3. Fifteen patients died due to disease, of which nine patients died within one year of diagnosis. Of these nine patients, eight patients had pattern of invasion 4, while one patient had POI 3. The OS for POI 3 was 97.1%, while OS for POI 4 was only 86% [Table/Fig-6].



Year	POI	Survival probability (%)	SE (%)	p-value
1	3	97.1	2.9	0.094
	4	86.0	4.6	

[Table/Fig-6]: Overall Survival (OS) of Pattern of invasion 3 and 4.
POI: Pattern of invasion; OS: Overall survival

DISCUSSION

OCSCC is a common cancer, constituting more than 90% of malignancies in the oral cavity [16]. The global prevalence of oral cancer cases is estimated to range from 1-5%; however, the prevalence in Southeast Asia is reported to be much higher [17]. Although no definite aetiology has been proposed for OCSCC, it has been hypothesised that genetic factors and environmental exposures serve as risk factors [18,19]. Most common subsites of OCSCC reported in the literature are oral tongue and buccal mucosa [20]. In the present study, also the most common subsite in the oral cavity involved by OCSCC was oral tongue, constituting 61% of the cases. Most of the studies have shown a male preponderance [21]. In the present study also male patients predominated, 63 numbers versus 37 female patients. Studies have shown a prevalence of OCSCC from fifth decade onwards [22]. In the present study maximum number of patients was in sixth decade, 36 cases, followed by 25 cases in fifth decade.

Many histopathological grading systems have been proposed over the years for prognostication of OCSCC. The earliest of these is the Broders grading system, which was proposed as early as 1920 [23]. However, it is a subjective assessment based on the degree of differentiation, cellular pleomorphism and mitotic activity, wherein OCSCC is graded as well, moderately, or poorly differentiated. Its usefulness in prognostication is doubtful, as up to 90% of OCSCC may be moderately differentiated. In the present study, also majority of cases, 67 was moderately differentiated. Annoreth et al., proposed multifactorial grading system based on the tumour cell population and tumour-host relationship [24]. The grading system proposed by Bryne et al., is based on Invasive Front Grading (IFG) with 5 histological features, including host response [25].

Brandwein Gensler introduced a risk scoring system for OCSCC based on three variables, namely WPOI, LHR and PNI. WPOI was categorised into five types: type 1, showing pushing border; type 2, characterised by finger-like growth; type 3, with large separate islands containing more than 15 cells per island; type 4, consisting of small tumour islands with less than or equal to 15 cells per island; and type 5, which includes tumour satellites that are more than or equal to 1 mm from the main tumour or next closest satellite. LHR was also categorised into type 1 to 3 based on density of lymphocytes at the tumour interphase. Type 1 includes dense complete host response, with dense lymphocytic infiltrate rimming the tumour; type 2 includes lymphoid nodules present in some but not all 4x fields; and type 3 includes little or no host response. PNI was scored based on the size of the nerve involved: none (PNI score 0) indicates no PNI; PNI involving nerve bundles less than 1 mm in diameter is assigned a PNI score of +1; and PNI involving nerve bundles more than or equal to 1 mm in diameter is assigned a PNI score of +3 [7].

Many studies in the literature have validated the Brandwein Gensler risk scoring system and confirmed its usefulness in predicting Locoregional Recurrence (LRR) [26,27]. The AJCC has incorporated only WPOI type 5 as optional data in the dataset for reporting OCSCC; however, studies have shown that not only WPOI type 5 but even POI 4 is an important prognosticator for OCSCC [27].

In present study, 61 cases with POI 4, 38 cases with POI 3, and one case with POI 5 was observed. When correlating these with other histopathological prognostic indicators, significant association of POI 4 with high-risk factors like PNI and LVI was found. This observation is important as it highlights the need to include POI 4 in the dataset for reporting OCSCC. Since one case of POI 5 was found in the present series, significance of POI 5 was not analysed in the present study.

Previous studies in the literature on significance of WPOI based on meta-analysis and systematic review of 18 articles involving 3,954 patients, showed that higher WPOI types, namely four and five, are associated with reduced OS, DFS and Local Disease-Free Survival (LRFS) rates, as well as more mortality and LRR in comparison to the lower WPOI types, one, two, and three [27]. Present study also observed a significant difference in OS for POI 3 and 4, namely 97.1% and 86%, respectively.

The observations from other studies in the literature regarding strong association of WPOI with survival, and observations from present study and other studies in the literature of strong association of

WPOI 4 and 5 with high-risk histopathological prognosticators like PNI and LVI emphasis the need to include WPOI 4 also into prognostic assessment models.

Limitation(s)

This study was limited with respect to WPOI 5, since only one case of POI 5 was there in the study.

CONCLUSION(S)

Present study included 100 patients with oral squamous cell cancer contributes to the existing evidence that WPOI is a poor histopathologic prognostic indicator for OCSCC. The data showed a significant association of WPOI 4 with poor histopathological prognosticators like PNI and LVI. It is recommended that pattern of invasion, specifically WPOI 4, should be incorporated as essential or core histopathological data in the dataset for reporting OCSCC.

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