RESEARCH ARTICLE

ASSOCIATION OF WORST PATTERN OF INVASION WITH CLINICOPATHOLOGICAL CHARACTERISTICS IN ORAL SQUAMOUS CELL CARCINOMA: A RETROSPECTIVE STUDY

Kanwal Iqbal, Fizza Abidi, Zofeen Hashim Bhurgri, Sana Fatima

Department of Oral Pathology, Ziauddin University, Karachi Pakistan

ABSTRACT

Objective: *Over the past few decades, research on a variety of prognostic histopathological indicators has been captivated by the biological aggressiveness of OSCC (Oral Squamous Cell Carcinoma). The association between the worst pattern of invasion (WPOI) with various clinicopathological characteristics is not well documented in the literature. The purpose of the present research was to assess the association of WPOI with clinicopathological factors in oral squamous cell carcinoma.*

Study design: *Retrospective study*

Place and duration of study: *Ziauddin University Hospital, Karachi, Pakistan from March 2023 to December 2024.*

Patients and methods: *The histological reports of forty-two OSCC patients who received primary surgery were reviewed in this retrospective study. The cases were assessed for the WPOI, perineural invasion (PNI), lympho-vascular invasion (LVI), depth of invasion (DOI), nodal status, histological grade and tumor staging. To assess the association between WPOI and clinicopathological characteristics, the Fisher's exact/Chi-square test was employed. To find significant risk factors for WPO-V, univariate logistic regression was employed. The data were analyzed using the Statistical Package for Social Sciences (SPSS) software, version 25.*

Results: *Of the 42 patients, 33.33% (n=14) and 66.66% (n=28) had WPOI I-IV and V respectively. There was a significant association between WPOI and site of tumor (0.005), histological grade (0.009), PNI (0.000), and tumor staging (0.000). However, there was no association seen with LVI, DOI or nodal status.*

Conclusion: *We have found significant association between WPOI and clinipathological characteristics in patients of OSCC. It is imperative to include the easily identifiable histological characteristic of the pattern of invasion when reporting oral SCCs. However, more detailed studies with a larger cohort are required for composing a definitive risk stratification module based on WPOI for OSCC.*

Keywords: *Oral squamous cell carcinoma, worst pattern of invasion, histopathological features*

INTRODUCTION

The sixth most frequent malignancy worldwide is oral cancer.[1] The burden of oral cancer is far higher in less developed Asian nations, at about 40% than in the West, where the overall prevalence is between 2 and 5%. Additionally, squamous cell carcinoma (SCC) accounts for 90% of all cancers of the mouth that originate from the oral mucosa.[2] The mortality rate and 5-year survival rate for those who have OSCC have not substantially improved over the past few decades, despite several diagnostic and treatment advancements. OSCC patients have a poor 5-year survival rate, and those who experience recurrence in particular have poor results.[3]

The biological aggressiveness of this tumor has led to the development of numerous prognosticating markers in recent decades, which further facilitate adjuvant therapy. T stage and nodal status are the two key variables that affect the course of treatment and its result.[4] Perineural and lymphovascular invasion are

Correspondence:
Dr. Kanwal Iqbal
Department of Oral Pathology
Ziauddin University, Karachi Pakistan
Email: kanwal.iqbal@zu.edu.pk
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additional histological markers that predict nodal metastasis and a poor prognosis. In addition to this stromal response, the prognosis for OSCC is predicted by histological grade, host lymphocytic response (HLR), and invasive tumor front.[5] Of them, a new development in the invasive tumor front has resulted in various POIs (patterns of invasion), which have been outlined in earlier research. The term "invasive tumor front" refers to the tumor stroma interface at the lowest part of the tumor.[6] The idea of POI was broadened by Brandwein-Genslar et al., and POI types were later included and given more attention in the eighth staging edition of the AJCC (American Joint Committee of Cancer).[7] Prior research has demonstrated that POI-V, which is considered a WPOI, is linked to nodal metastasis and locoregional recurrence.[8]

Microscopic tumor islands that are more than 1 mm from the advancing tumor end are referred to as WPOI.[9] As suggested by Cancer Protocol Templates (CAP), the assessment of different POIs is a straightforward, low-cost process that may be integrated into routine reporting with little interobserver disagreement. Additionally, in 2018, the International Collaboration of Cancer Reporting (ICCR) made WPOI a required reporting component for OSCC.[10] The cornerstone of treatment for OSCC is still surgery, either with or without adjuvant therapy. Cancers of the buccal mucosa and tongue are the most prevalent sites in the oral cavity, which have been demonstrated to exhibit varying degrees of biological aggression. The survival rate for these cancers has not increased much despite recent therapy advancements. The tumor node metastasis (TNM) system is a commonly used clinical evaluation tool for determining the level of tumor load and, consequently, therapy alternatives for OSCC patients.

Histological prognostic factors have been rarely evaluated in Pakistani patients. The association between numerous clinicopathological characteristics and the different invasion patterns, including the WPOI, is, nevertheless, little documented throughout the literature. This research aimed to evaluate the association between POI and several clinicopathological characteristics.

PATIENTS AND METHODS

A retrospective analysis of individuals who had OSCC treated with curative or resection surgery between March 2023 and December 2024 was carried out at the Ziauddin University Hospital in Karachi, Pakistan. The histological reports were collected from the department of Histopathology, Ziauddin Hospital North Campus, Karachi. The Institute Ethics Committee granted ethical clearance from Dr. Ziauddin University Hospital (Reference code: 6520123ZHOM, Dated: 25/2/2023). From the medical records, all pertinent clinical and demographic information was gathered, as well as the histological sections were examined for the worst pattern of invasion. Additionally, extra-nodal extension, perineural invasion, lymphovascular invasion, depth of invasion, and histological grade were examined on Hematoxylin and Eosin-stained slides.

Inclusion criteria:

This study included all patients who had surgical resection of the original tumor, whether or not they received radiation therapy or chemoradiotherapy. Age, gender, tumor site, stage, and histological parameters were all ascertained by reviewing the reports of the patients.

Exclusion criteria:

The study did not include patients who underwent neo-adjuvant treatment.

Histopathological evaluation:

Tumor resections with the most aggressive tumor front and hotspot were chosen after a thorough histological analysis. Analysis was done by the verified histopathologist. WPOI was classified in accordance with the CAP procedure.[11] The following is how the POI was defined:

i) WPOI-I: broad pushing tumor front

ii) WPOI-II: finger-like pushing pattern of tumor invasion

iii) WPOI-III: tumor islands having > 15 cells (large tumor islands)

iv) WPOI-IV: tumor islands having < 15 cells (small tumor islands)

v) WPOI-V: tumor satellites which are away from the main tumor by 1 mm.

The number of mitotic figures, the degree of pleomorphism, and the intracellular or extracellular keratin pearl production were the basis for histological grading. Well-differentiated tumors with a low degree of nuclear pleomorphism, keratinization or keratin pearl production, and intercellular desmosome connections in more than 75% of the tumor, with just sporadic mitotic figures. In tumors that are moderately differentiated, about 25% of the cells exhibit keratin pearl production

and intercellular connections, with sporadic mitotic figures/10 hpf. Tumor cells were classified as poorly differentiated SCC if they lacked keratinization, intercellular desmosome connections, and 10/10hpf mitotic patterns combined with noticeable pleomorphism.[12]

DOI was another histological parameter that was divided into two categories: a) up to 4 mm and b) >4 mm.[13]

To analyze and correlate WPOI with several clinicopathological characteristics, such as histological grade, tumor staging, PNI, LVI, nodal metastases, and DOI, all the information was tabulated.

The samples were divided into two groups for analysis. Of the 42 patients, group A comprised of patients with WPOI I-IV (n=14) and group B, had patients with WPOI-V only (n=28). The results were analyzed between the groups. The data were analyzed using the Statistical Package for Social Sciences (SPSS) software, version 25. It was manufactured by IBM in Chicago, USA. A p-value was determined to be statistically significant as one that was less than 0.05.

Numbers and percentages were used to display the category variables. However, the mean and standard deviation were employed to display the quantitative data. The results were subjected to the following statistical tests:

1. The qualitative variables were compared using the Chi-square test, and if any of the cells had an expected value less than 5 then Fisher's exact test was employed.
2. To find significant risk factors for WPO-V, univariate logistic regression was employed.

RESULTS

The research comprised 42 patients, in total of which 36 (85.7%) were males and 6 (14.3%) were females. The ratio of males to females was 6:1 as well as the mean age was 39.52±12.05 years (range: 23–70 years). With 30 cases (71.4%), buccal mucosa was the most frequent site, compared to the tongue (23.8%). In Table I, the specific histological features are displayed. The distribution of T stage showed T1-2 (4.8%), T2-10 (23.8%), T3-8 (19%) and T4-22 (52.4%). According to the histopathological differentiation of SCC, moderately differentiated was the most reported type (85.7%) followed by well-differentiated (9.5%) and poorly differentiated (4.8%) is the least reported type. Regarding the DOI, 85.7% were >4mm in depth and 14.3% were up to 4mm in depth. LVI and PNI were noted at 14.3% (n=6) and 57.1% (n=24) respectively. Concerning lymph node staging, a high proportion of the patients (47.6%, n=20) had N3 disease .

Table I: Descriptive characteristics of the patients

Variables	
Categories	
Age	**Mean±SD**
	39.52±12.05
Gender	**N (%)**
Male	36(85.7%)
Female	6(14.3%)
Histological grade	
Well differentiated	4 (9.5%)
Moderately differentiated	36 (85.7%)
Poorly differentiated	2 (4.8%)
Tumor site	
Buccal mucosa	30 (71.4%)
Tongue	10 (23.8%)
Maxillary alveolar process	2 (4.8%)
Depth of invasion	
Upto 4 mm	6 (14.3%)
>4mm	36 (85.7%)
Worst pattern of invasion	
I-IV	14 (33.3%)
V	28 (66.7%)
Lymphovascular invasion	
Present	6 (14.3%)
Absent	36 (85.7%)
Perineural invasion	
Present	24 (57.1%)
Absent	18 (42.9%)
Staging	
T1	2 (4.8%)
T2	10 (23.8%)
T3	8 (19%)
T4	22 (52.4%)
Nodal status	
N0	12 (28.6%)
N1	4 (9.5%)
N2a	4 (9.5%)
N2b	2 (4.8%)
N2c	0
N3	20 (47.6%)

The association between WPOI and demographic characteristics has been shown in Table II and a significant association has been found between WPOI with age (0.000) and WPOI with tumor site (0.005).

Histopathological features and WPOI:

Table II: Association between WPOI with demographic characteristics

Demographic characteristics	WPOI (I -IV)	WPOI (V)	Total	*p*-value
Age	14	28	42	
Mean±SD				0.000 *
39.52±12.05				
Gender				
Male	12	24	36	1.000
Female	2	4	6	
Site of tumor				
Buccal mucosa	10	20	30	
Maxillar y alveol ar process	1	1	2	0.005 *
Tongue	4	6	10	

Fisher's exact test, p-value <0.05

Table III: Association between WPOI with histopathological characteristics

Pathological parameters	WPOI (I -IV)	WPOI (V)	Total	*p*-value
Histological grade #				
Well differentiated	1	3	4	
Moderately differentiated	12	24	36	0.009*
Poorly differentiated	1	1	2	
Depth of invasion #				
Upto 4mm	2	4	6	0.155
> 4mm	12	24	36	
Lymphovascular invasion#				
Identified	2	4	6	0.083
Not identified	12	24	36	
Perineural invasion				
Identified	8	16	24	0.000 *
Not identified	6	12	18	
Tumor staging#				
T1	1	1	2	
T2	4	6	10	0.000 *
T3	3	5	8	
T4	8	14	22	
Nodal status #				
N0	4	8	12	
N1	1	3	4	
N2a	1	3	4	0.348
N2b	1	1	2	
N2c	0	0	0	
N3	6	14	20	

Fisher's exact test, °Chi-square test, p-value <0.05 significant

POI was divided into two groups: non-infiltrative (POI-I to IV) and infiltrative (POI-V) and there was a correlation between the two groups using several histopathological criteria. 33.3% of patients (n=14) had WPOI I-IV whereas pattern V was found in 66.7% of the patients (n=28). Histological grade, PNI, and tumor stage were the histological factors that were significantly associated with WPOI, with p-values of 0.009, 0.000, and 0.000, respectively. However, for DOI, LVI and nodal status, the results were not significant (p- 0.155, 0.083 and 0.348 respectively) with WPOI (Table III).

In univariate analysis, a significant association of tumor staging (p=0.002) and PNI (P=0.001) has been found

Table IV: Univariate logistic regression to find out significant risk factors of WPOI-V

Variable	Beta coefficient	Standard error of mean	*p*-value	Odds ratio
Age (years)	0.049	0.032	0.126	1.050
Gender	0.000	0.935	1.000	1.000
Histologic grading	-20.247	28420.75	0.999	0.000
Depth of invasion	-1.649	0.943	0.080	0.192
Perineural invasion	3.091	0.892	0.001*	22.000
Lymphovascular invasion	20.751	16408.711	0.999	1028029459
Tumor staging	-3.401	1.103	0.002*	0.033
Lymph nodes	-0.847	1.113	0.446	0.429

(Table IV). No significant association was detected with age, gender, histologic grading, DOI, LVI and lymph nodes.

DISCUSSION

A primary critique of the TNM system is its disregard for the unique histological characteristics of tumors.[14] To help with this, several histological characteristics have been investigated and taken into account when making decisions on adjuvant treatment. There are several prognostic factors that could impact survival. One of these factors is the invasion pattern. It is defined as the invasive front of the tumor at the interface between the tumor and the host.[15]

In the past, numerous histological prognostic models and grading systems have been created to forecast the biological behavior of OSCC. POI continues to play a significant role in each of these systems of grading. Jakobsson et al. created a multifactorial grading system in 1973 that scored tumor-host interactions and tumor features, however, it ultimately only worked well for tongue tumors. A revision of Jakobsson's approach was later suggested by Anneroth et al., who did so by evaluating six histomorphological characteristics.[16] Anneroth's grading system was amended by Bryne, who created a malignancy grading system that solely considered the tumor's invasive front.[17] Brandwein has developed a risk assessment score that predicts survival and local recurrence by including PNI, invasion pattern, and lymphocyte response.[18]

The pattern of invasion is indicative of biological mechanisms of malignancy, including enhanced tumor cell motility, lack of contact inhibition, and proteolytic enzyme output. A straightforward indicator of tumor behavior is provided by its findings in standard histological preparations. According to molecular analysis of the invasion pattern, deep invasive tumor fronts exhibit more cyclin-B1 and Ki-67 markers while expressing less E-cadherin. Consequently, there is a greater chance that cancerous cells may spread.[19]

The most frequent location of primary tumor in our study was the buccal mucosa, which was followed by the tongue. De Silva et al. discovered that the tongue was the most often affected region in their retrospective analysis of 623 individuals with oral and tongue malignancies. They also discovered that the rate of occult nodal positivity was significantly greater in the tongue than in the buccal mucosa.[20] Nodal spread happens early and quickly because the tongue's anatomical location near the floor of the mouth provides it with a strong supply of lymphatics. The standard histological reporting format requires the use of several histological markers, including tumor stage, different histological grades, DOI, LVI, and PNI, which are well-known prognostic variables for OSCC in all stages. Lundqvist et al.[21] and Kane et al.[22] were among the few earlier studies that did not demonstrate a significant correlation between WPOI and nodal involvement, similar to our research which showed a *p*-value of 0.348. A reduced sample size could be the cause of the non-significant association.

By univariate analysis, the several histological characteristics that demonstrated a strong association with WPOI in our study included the presence of PNI (0.001) and tumor staging (0.002). Almangush et al. reported similar results, indicating that early stages of oral SCC were substantially correlated with WPOI IV-V.[23] Furthermore, Adil et al. reported a significant

association between WPOI and tumor stage, nodal involvement, histological grade, LVI, PNI, DOI and tumor budding.[24] Marzouki et al. emphasized the worst prognosis of oral SCC by comparing WPOI V to other histological markers and determining that it was an independent predictive element for local recurrences.[25] WPOI IV and V were identified by Binmadi et al. in a meta-analysis they conducted as predictors of local recurrence and nodal metastasis, as well as markers of poor outcomes such as lower overall and disease-free survival.[26]

There were drawbacks to the study in relation to follow-up with patients, hence a disease-free survival was not evaluated. Second, because the study was retrospective, the data interpretation was heavily reliant on what was recorded at the time of surgery and finally the research was performed in a single place, therefore, the findings need to be externally validated to justify broad practice adjustments.

CONCLUSION

We have found a significant association between WPOI and clinipathological characteristics in patients of OSCC. This study is among the few that have assessed the function of WPOI as a separate indicator of prognosis. In conclusion, the invasion pattern is a readily identifiable histological characteristic that has to be reported with oral SCCs regularly.

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Authors' Contribution

Kanwal Iqbal: Conception of study / Designing / Planning, Analysis / Interpretation / Discussion, Manuscript Writing

Fizza Abidi: Conception of study / Designing / Planning, Critical Review

Zofeen Hashim Bhurgri: Experimentation / Study Conduction

Sana Fatima: Critical Review

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