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RESEARCH ARTICLE

Worst Pattern of Invasion in Oral Squamous Cell Carcinoma - An Independent Prognostic Predictor

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Abstract

Introduction: Oral Cavity Squamous Cell Carcinoma (OCSCC) shows an increasing trend in their incidence and some of them are aggressive and present with recurrence. Identification of pathologic prognosticators in early-stage OCSCC is prudent to aid selection of patients who may benefit from adjuvant chemotherapy. The objective of this study was to evaluate the prognostic ability of Worst Pattern of Invasion I-V (WPOI I-V) in early stage OCSCC. Many studies have reported WPOI I-V as an adverse prognostic factor associated with poor prognosis. However, these factors are not considered while planning for treatment protocols and disease-free survival rates. **Case Details:** 30 patients with early stage OCSCC who underwent treatment, from January 2024 – June 2024 was analysed. **Materials and Methods**: This is a prospective study of 30 patients. Clinicodemographic and histopathological details was extracted from the records. Univariate and multivariate analysis was done for the parameters. WPOI I-V was correlated with all histopathological prognostic factors. **Results:** We analyzed the results. WPOI I-V showed a significant association with T-stage (p = 0.025), N-stage (p = 0.002), Depth of Invasion (DOI) (p = 0.004), Perineural Invasion (PNI) (p=0.002), LymphoVascular Invasion (LVI) (P= 0.000), Tumor Grade (p = 0.001), Margin (p=0.013) and Lymphocyte Host Response (LHR) (p=0.000). **Discussion and Conclusion:** Presence of invasive WPOI is associated with advanced T stage, poor differentiation, PNI, greater DOI, and higher chances of nodal metastasis. Adjuvant chemotherapy in early-stage disease with WPOI type IV and V may improve survival rate and prevent recurrence.

Keywords: Depth of invasion, Oral squamous cell carcinoma, Prognostic predictor, Perineural invasion, Worst pattern of invasion.

1. Introduction

Oral Cavity Squamous Cell Carcinoma (OCSCC) is a group of malignancies, involving oral cavity. It is the seventh most common cancer worldwide, accounting 4.5% of all cancer diagnoses[1]. Incidence rate is higher in south and southeast Asia, particularly India. Oral Cavity cancers in India accounts for 30% of all cancers[1]. High incidence rate is due to chewing tobacco, areca nut, smoking, consumption of alcohol and recently due to high prevalence of human papilloma virus[2]. OCSCC is more common in men than in women, male to female ratio is 2:1. Most commonly presents at 5th - 6th decade[1]. Due to lack of clinical symptoms in early period, patient often presents at advanced stages of tumor. OCSCC are aggressive tumors having high invasive capacity which is due to phenotypic alterations between neoplastic cells and surrounding environment. Invadopodia are actin rich protusions on the surface of invasive neoplastic cells that promote degradation of extracellular matrix[3]. Despite the advancement of cancer management, the overall 5 year survival rate remains lowest among all 2 malignancies and has poor prognosis.

2. Aim and Objectives

The aim and objective of this study was to evaluate the prognostic ability of Worst Pattern of Invasion I-V (WPOI I-V) in early stage OCSCC. Many studies have

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reported WPOI I-V as an adverse prognostic factor associated with poor prognosis.

3. Review of Literature

Oral cavity is divided into outer smaller portion, the vestibule and inner larger part, the oral cavity proper[4]. Vestibule is bounded externally by lips and cheeks, and internally by teeth and gums (Figure 1).

Oral cavity proper, bounded by

1. Above - Roof of hard palate and soft palate
2. Below - Floor of mouth
3. Lateral – Buccal mucosa
4. Posterior – Retromolar trigone and glossopalatine fold. The oral cavity is divided into the following regions:

- Lip – having the vermilion surface and the upper and lower lip joins at the commissures of the mouth.
- Floor of the mouth - bounded by the lower gingiva and the oral tongue.
- Oral tongue - the portion of the tongue anterior to the circumvallate papillae.
- Base of the tongue - bound anteriorly by the circumvallate papillae, laterally by the glossotonsillar sulci, and posteriorly by the valleculae.
- Buccal mucosa - covers the inner surface of the cheeks and lips.

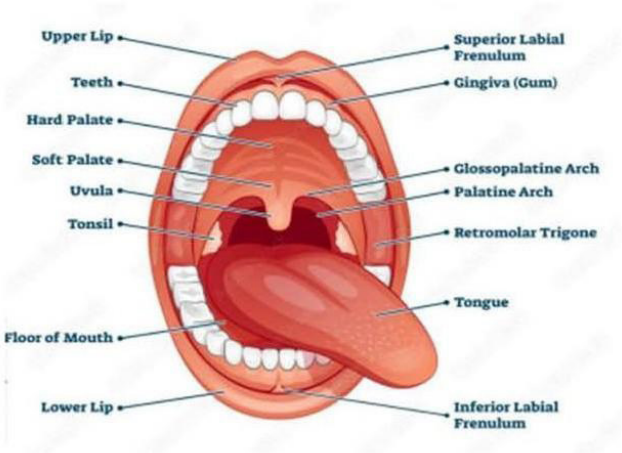

Fig 1. Anatomy of oral cavity

Figure 1. Anatomy of oral cavity.

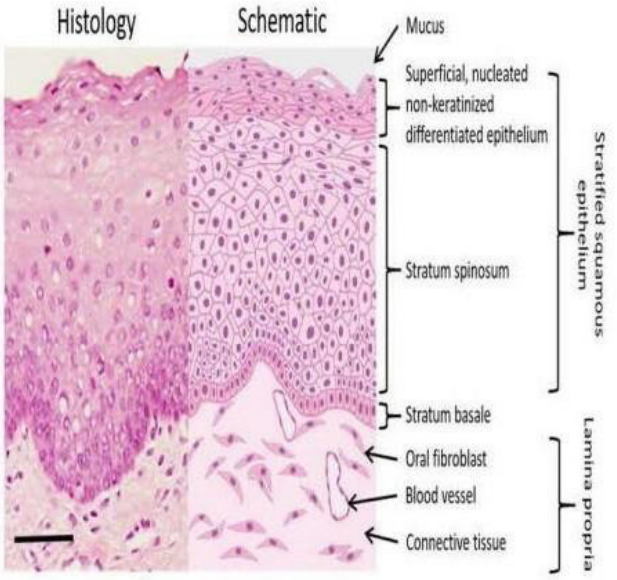

Figure 2. Histology of oral cavity.

- Alveolar ridge - the mucosa covering the mandible or maxilla from the gingivobuccal gutter to the origin of the mobile mucosa.
- Retromolar trigone - a small triangular surface behind the third molar covering the ascending ramus of the mandible.
- Hard palate - area located between the upper alveolar ridge and the mucous membrane covering the palatine process of the maxillary bones.
- Tonsillar area - the anterior and posterior tonsillar pillars histology of oral mucosa (Figure 2).

The oral mucosa is divided into three types based on differences in the epithelial covering, organization of connective tissue and its associated functions: lining, masticatory and specialized mucosa[4]. Lining mucosa is covered by non-keratinized stratified squamous epithelium, lamina propria containing elastic fibers, submucosa containing minor salivary glands and attached to underlying muscle. It includes inner surface of lip, cheeks, floor of the mouth and ventral surface of the tongue. Masticatory mucosa covered by keratinized stratified squamous epithelium with thick lamina propria and no submucosa attached to underlying bone. It includes gingiva and hard palate. Specialized mucosa covers anterior two thirds of tongue and consists of keratinized and nonkeratinized stratified squamous epithelium and numerous papillae.

3.1 Etiopathogenesis

Smoking is the most important cause of oral cancer. In India, betel quid, paan which contains areca nut, slaked lime and tobacco contains carcinogens and are the predisposing factors to squamous cell carcinoma[5]. Actinic radiation and pipe smoking are predisposing factors for cancers of lower lip. In recent times, infections with the high-risk Human Papillomavirus (HPV 16) are one of the most common causes of squamous cell carcinoma of oropharynx[6].

3.2 Clinical Features

Squamous cell carcinomas in the oral cavity clinically presents as white or erythematous ulcer with raised margins. On palpation, it typically has induration. Unilateral or bilateral cervical lymph node enlargement (Level I to Level V) is seen indicating the lymphatic spread of cancer[7].

3.3 Histologic Subtypes of Squamous Cell Carcinoma

1. Squamous cell carcinoma, conventional (keratinizing)
2. Squamous cell carcinoma, non-keratinizing
3. Adenosqumaous carcinoma
4. Basaloid squamous cell carcinoma
5. Papillary squamous cell carcinoma
6. Spindle cell squamous cell carcinoma
7. Verrucous carcinoma
8. Carcinoma cuniculatum
9. Lymphoepithelial carcinoma (non - nasopharyngeal).

3.4 Histologic Grade

The main histological features of squamous cell carcinoma are invasion and squamous differentiation[7]. Invasion manifests as interruption of the basement membrane of the surface epithelium and the downwards growth of tumor islands, cords or isolated tumor cells in the underlying tissue. Invasion is always accompanied by desmoplastic stromal reaction, which consists of proliferation of myofibroblasts, excessive deposition of extracellular matrix and neovascularisation. Three histologic grades are suggested based on 14 squamous differentiations. Squamous differentiation is characterised by keratinization and intercellular bridges[7].

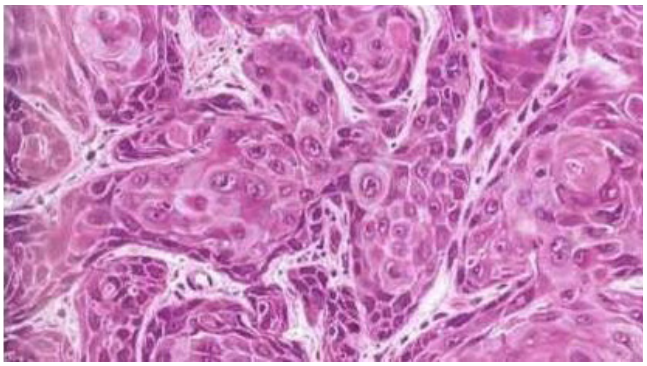

Figure 3. Well differentiated squamous cell carcinoma.

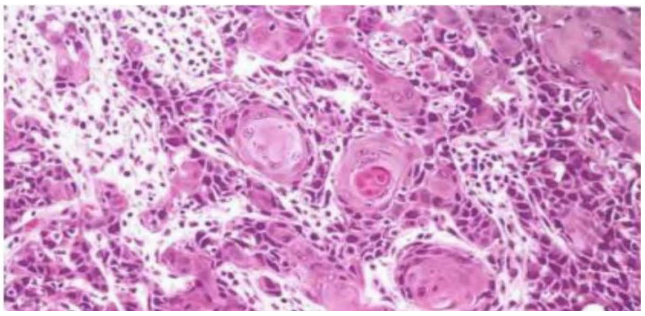

Figure 4. Moderately differentiated squamous cell carcinoma.

3.5 Well Differentiated Squamous Cell Carcinoma

It resembles normal squamous epithelium and contains large, differentiated, keratinocyte like squamous cells and small basal type cells at the periphery of tumor islands[7]. Intercellular bridges, individual cell keratinization and keratin pearls are present (Figure 3).

3.6 Moderately Differentiated Squamous Cell Carcinoma

It exhibits more nuclear pleomorphism, more mitoses including abnormal mitoses and less keratinization[7] (Figure 4).

3.7 Poorly Differentiated Squamous Cell Carcinoma

Basal type cells predominate, with frequent mitoses including abnormal mitoses, barely seen intercellular bridges with minimal or no keratinization[7] (Figure 5).

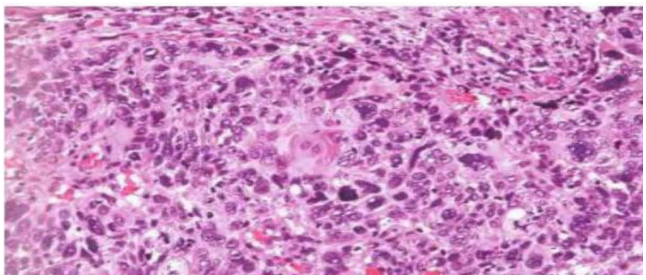

Figure 5. Poorly differentiated squamous cell carcinoma.

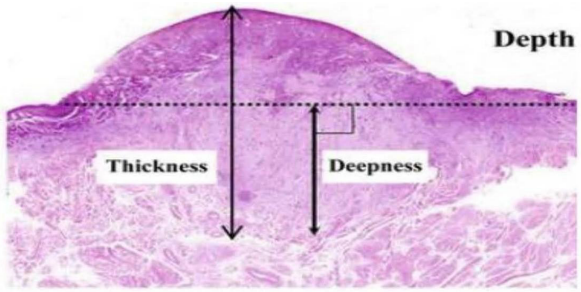

Figure 6. Depth of invasion and thickness.

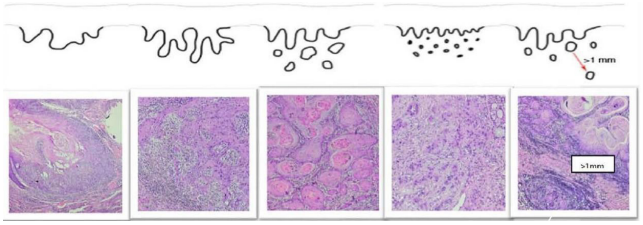

Figure 7. Worst pattern of invasion WPOI-I WPOI-II WPOI-III WPOI-IV WPOI-V.

3.8 Tumor Thickness/ Depth of Invasion (Figure 6)

The microscopic measurement of tumor thickness or depth of invasion has been a valuable parameter for predicting regional nodal involvement and survival in squamous cell carcinoma since long time.

Thickness is measured from the mucosal surface of the tumor to the deepest point of invasion in a perpendicular fashion. Depth of invasion is measured from the basement membrane of adjacent normal mucosa of the tumor to the deepest point of invasion[8]

3.9 Worst Pattern of Invasion (Figure 7)

Worst pattern of invasion is a prognosticator for oral cavity squamous cell carcinoma. It is the infiltration of the tissue by the tumor cells at the tumor host interface. There are 5 patterns, distinction between WPOI I-V and other patterns is most relevant[9].

WPOI-I: Low invasiveness, broad pushing borders and cohesive

WPOI-II: Broad pushing finger like growths or separate large tumor islands.

WPOI-III: Invasive tumor islands containing more than 15 cells per island

WPOI-IV: High invasiveness, invasive tumor islands containing fewer than 15 cells per island that are separated by main tumor mass.

WPOI-V: Tumor satellites of any size that are 1mm or further distant from the main tumor or next closest satellite with intervening normal tissue.

3.10 Perineural Invasion

Presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer. It is associated with poor local disease control and poor regional control and decreased disease survival rate[8].

pTNM Classification

pT category

pTis: carcinoma *in situ*

pT1: Tumor less than or equal to 2 cm with Depth of Invasion (DOI) less than or equal to 5 mm.

pT2: Tumor less than or equal to 2 cm with DOI greater than 5 mm or tumor greater than 2 cm and less than or equal to 4 cm with DOI less than or equal to 10 mm.

pT3: Tumor greater than 2 cm and less than or equal to 4 cm with DOI greater than 10 mm or tumor greater than 4 cm with DOI less than or equal to 10 mm.

pT4: Moderately advanced or very advanced local disease.

pT4a: Moderately advanced local disease. Tumor greater than 4 cm with DOI greater than 10 mm or tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face)

pT4b: Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base, and / or encases internal carotid artery.

pN category

pN1: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-) pN2

pN2a: Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE (+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-) pN2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)

pN2c: Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE (-)

pN3

pN3a: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE (-)

pN3b: Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE (+); or multiple ipsilateral, contralateral or 21 bilateral nodes any with ENE (+); or a single contralateral node of any size and ENE (+)

pM Category

pM1: Distant metastasis

4. Materials and Methods

Study Design

- Clinico-demographic and pathologic findings were recorded.
- Age, gender, primary site of disease.
- Standardized synoptic reporting is followed at our center to ensure the adequacy of pathology reporting.
- Sections were taken such that the slides included the deepest portion in terms of tumor-host interface or invasive front.
- Clinical history like habits, clinical staging and pathologic tumor staging; and histopathology parameters, such as margin status, depth of invasion, lymphovascular invasion, perineural invasion, nodal involvement was recorded.

Study Period

6 months (Jan-2024 to June-2024)

Study Group

Biopsies and resected specimens of head and neck squamous cell carcinomas

Selection Criteria

Inclusion Criteria

Patients with early stage OCSCC who underwent treatment. Adult more than 18 years. Both genders.

Exclusion Criteria

Histology other than squamous carcinoma.

Recurrent disease or second primary tumor were excluded. Study population

Biopsies and resected specimens of histopathogically proven

Oral cavity squamous cell carcinomas in department of Pathology of Tirunelveli medical college during the study period.

Technique

- WPOI I-V was correlated with all histopathological prognostic factors.
- Univariate and multivariate analysis was done for the parameters

Study Setting

This study was done at Histopathology lab of Tirunelveli medical college and approved by the Institutional Ethics Committee of Tirunelveli medical college.

Statistical Tests Used

Datas were entered in Microsoft Excel (Windows 10, version 2010) and analysis were done using the statistical package for social sciences (SPSS) for windows software (version 25; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation for continuous variables & frequencies and percentages for categoricalvariable were used.

Bar charts and pie charts were used for visualre presentation of the data. To find association between two categorical variables.

Pearson chi square test was used. Level of significance was set at the value of 0.05.

5. Results (Including Observations)

This study included 30 patients with early-stage oral cavity squamous cell carcinoma (OCSCC). The demographic characteristics are shown in Table 1. The mean age was 52.2 ± 12.7 years (range: 30–75 years), with a male predominance (M:F = 1.7:1).

The clinicopathological features of the cohort are summarized in Table 2. The buccal mucosa (26.7%) and tongue (26.7%) were the most frequent tumor sites. T-stage distribution was 9 cases (30%) T1 and 21 cases (70%) T2. On histopathology, most tumors

Table 1. Demographic and habit profile of the study population (n=30)

Variable	Category	n(%)
Age(years)	Mean±SD(Range)	52.2±12.7(30-75years)
sex	Male	19(63.3)
	Female	11(36.7)
Habits	Betel nut chewing	15(50.0)
	Alcohol	9(30.0)
	Smoking	6(20.0)

Table 2. Clinicopathological features of the study population (n=30)

Variable	Category	n(%)
Primary site	Buccal mucosa	8(26.7)
	Tongue	8(26.7)
	Floor of mouth	4(13.33)
	Retro molar trigone	4(13.33)
	others	6(20)
T-stage	T1	9(30.0)
	T2	21(70.0)
Histological grade	Well differentiated	11(36.7)
	Moderately differentiated	19(63.3)
Margin status	Free	28(93.3)
	Involved	2(6.7)
Nodal status	N0	24(80.0)
	N1	6(20.0)
Perineural invasion (PNI)	Present	12(40.0)
	Absent	18(60.0)
Lymphovascular invasion (LVI)	Present	7(23.3)
	Absent	23(76.7)
Depth of invasion (DOI)	≤ 5 mm	10(33.3)
	> 5 mm	20(66.7)
Lymphocyte host response (LHR)	Strong	2(6.7)
	Moderate	13(43.3)
	Weak	15(50.0)

were moderately differentiated (63.3%), while 36.7% were well differentiated. Surgical margins were free in 28 cases (93.3%) and involved in 2 cases (6.7%). Twenty-four patients (80%) had no nodal involvement (N0), while 6 (20%) showed positive nodes. Perineural invasion was present in 12 cases (40%), lymphovascular invasion in 7 (23.3%), and depth of invasion >5 mm in 20 cases (66.7%). The lymphocyte host response (LHR) was strong in 2 patients (6.7%), moderate in 13 (43.3%), and weak in 15 (50%).

Table 3. Distribution of worst pattern of invasion (WPOI) (n=30)

WPOI Category	n(%)
WPOI I–III (Cohesive) Type I - 2(6.67) Type II - 6(20) Type III - 15(50)	23(76.7)
WPOI IV–V (Non-cohesive) Type IV - 4(13.33) Type V - 3(10)	7(23.3)

The distribution of the worst pattern of invasion (WPOI) is summarized in Table 3. Cohesive patterns (WPOI I–III) were seen in 23 patients (76.7%), while non-cohesive invasion (WPOI IV–V) was present in 7 patients (23.3%).

The correlation of WPOI with prognostic factors is presented in Table 4. Non-cohesive WPOI (IV–V) was consistently associated with aggressive features and demonstrated statistically significant or highly significant associations across nearly all parameters.

- Tumor stage (T-stage): All WPOI IV–V tumors presented at advanced T2 stage (100%), compared with 60.9% of WPOI I–III tumors. This association was statistically significant (p=0.025).
- Nodal status: Nodal metastasis was observed in 57.1% of WPOI IV–V patients versus only 8.7% in WPOI I–III. This was highly significant (p=0.002).
- Depth of Invasion (DOI): DOI >5 mm was seen in 85.7% of WPOI IV–V versus 60.9% of WPOI I–III, a statistically significant finding (p=0.004).
- Perineural Invasion (PNI): Present in 100% of WPOI IV–V compared with 21.7% of WPOI I–III. This difference was significant (p=0.002).
- Lymphovascular invasion (LVI): More frequent in WPOI IV–V (57.1% vs. 13.0% in I–III), with a highly significant association (p<0.001).
- Histological grade: All WPOI IV–V tumors were moderately differentiated, while nearly half (47.8%) of WPOI I–III tumors were well differentiated. The association was significant (p=0.001).

Table 4. Correlation of WPOI with clinicopathological prognostic parameters (P-values calculated using Pearson's chi-square test.)

Prognostic parameter	WPOI I–III(n=23)	WPOI IV–V(n=7)	p-valve	Significance
T-stage (T2 vs T1)	14/9	7/0	0.025	Significant
Nodal status (N+ vs N0)	2/21	4/3	0.002	Highly significant
Depth of invasion (> 5 mm vs ≤ 5 mm)	14/9	6/1	0.004	Significant
Perineural invasion (Present vs Absent)	5/18	7/0	0.002	Significant
Lymphovascular invasion (Present vs Absent)	3/20	4/3	<0.001	Highly significant
Tumor grade (Well vs Moderate)	4/19	7/0	0.001	Significant
Margin status (Involved vs Free)	1/22	1/6	0.013	Significant
Lymphocyte host response (Weak vs Strong–Moderate)	8/15	7/0	<0.001	Highly significant

- Margin status: Involved margins were observed more often in WPOI IV–V (14.3%) than in WPOI I–III (4.3%), which was statistically significant (p=0.013).
- Lymphocyte host response (LHR): All WPOI IV–V tumors exhibited a weak host response (100%), compared with only 34.8% in WPOI I–III. This was highly significant (p<0.001).

Derivation of P Value

The association between WPOI and clinicopathological prognostic factors was evaluated using Pearson's chi-square test. For each factor, a 2×2 contingency table was constructed comparing WPOI groups (I–III vs. IV–V) against the categories of that factor. The observed frequencies and the corresponding p-values are presented in Table 12.4.
T-stage:

- WPOI I–III: T1 = 9, T2 = 14
- WPOI IV–V: T1 = 0, T2 = 7

Pearson's chi-square yielded $\chi^2 = 5.0$, $p = 0.025$ (significant). Nodal status:

- WPOI I–III: N0 = 21, N+ = 2
- WPOI IV–V: N0 = 3, N+ = 4

Pearson's chi-square yielded $\chi^2 = 9.9$, $p = 0.002$ (highly significant). Depth of invasion (DOI):

- WPOI I–III: ≤5 mm = 9, >5 mm = 14
- WPOI IV–V: ≤5 mm = 1, >5 mm = 6

Pearson's chi-square yielded $\chi^2 = 8.2$, $p = 0.004$ (significant). Perineural invasion (PNI):

- WPOI I–III: Absent = 18, Present = 5
- WPOI IV–V: Absent = 0, Present = 7

Pearson's chi-square yielded $\chi^2 = 9.9$, $p = 0.002$ (significant). Lymphovascular invasion (LVI):

- WPOI I–III: Absent = 20, Present = 3
- WPOI IV–V: Absent = 3, Present = 4

Pearson's chi-square yielded $\chi^2 = 15.7$, $p < 0.001$ (highly significant). Tumor grade:

- WPOI I–III: Well/Moderate = 19, Poor = 4
- WPOI IV–V: Well/Moderate = 0, Poor = 7

Pearson's chi-square yielded $\chi^2 = 11.1$, $p = 0.001$ (significant). Margin status:

- WPOI I–III: Free = 22, Involved = 1
- WPOI IV–V: Free = 6, Involved = 1

Pearson's chi-square yielded $\chi^2 = 6.1$, $p = 0.013$ (significant). Lymphocyte host response (LHR):

- WPOI I–III: Strong/Moderate = 15, Weak = 8
- WPOI IV–V: Strong/Moderate = 0, Weak = 7

Pearson's chi-square yielded $\chi^2 = 18.0$, $p < 0.001$ (highly significant).

Thus, across all parameters, WPOI IV–V consistently correlated with more aggressive pathological features and poor host response.

6. Discussion

Management of patients with early stage OCSCC is still based mainly on the clinical (TNM) staging of the patient, despite large numbers of reported histological, immunohistochemical, and molecular biomarkers in the literature.

Tumor staging may be more powerful in prognostication and treatment planning for the later stages of oral tongue SCC, and much less so for the early stages T1/T2NOMO).

The present study assessed the effectiveness of histomorphologic parameters in predicting the recurrence in the patients with early-stage oral tongue SCC.

The purpose was to group the patients into a high-risk category namely patients with

1. Worst pattern of invasion with pattern IV and pattern V
2. Depth of invasion more than 5 mm
3. Histological grade
4. Lymph vascular invasion
5. Perineural invasion
6. Poorer lymphocyte host response.

All this would benefit from multimodality treatments, and a low-risk category in which local surgical treatment would be sufficient.

7. Summary and Conclusion

- Presence of invasive WPOI is associated with advanced T stage, poor differentiation, PNI, greater DOI, and higher chances of nodal metastasis.
- Adjuvant chemotherapy in early-stage disease with WPOI type IV&V may improve survival rate and prevent recurrence.

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