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HISTOPATHOLOGICAL EVALUATION OF ORAL SQUAMOUS CELL CARCINOMA IN PAKISTANI POPULATION: A RETROSPECTIVE STUDY OF CLINICOPATHOLOGICAL FEATURES AND PROGNOSTIC FACTORS

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Abstract

Introduction: The most prevalent oral malignancy, oral squamous cell carcinoma (OSCC), is becoming more prevalent in Pakistan. Late-stage diagnosis and aggressive tumor behavior contribute to poor prognosis. This study evaluates the histopathological features, clinicopathological characteristics, and prognostic factors of OSCC in the Pakistani population.

Methodology: A total of 93 OSCC cases were analyzed. Data were collected on patient demographics, tumor location, histopathological grading, tumor size, lymph node involvement, perineural invasion, lymphovascular invasion, and distant metastasis. Chi-square tests, independent t-tests, Kaplan-Meier survival analysis, and Cox regression models were used to assess the prognostic significance of clinicopathological features.

Results: OSCC was more prevalent in males (62.4%) than females (37.6%). The most affected site was the buccal mucosa (39.8%), followed by the tongue (26.9%). Moderate differentiation (44.1%) was the most common histopathological grade. The mean tumor size was 3.8 cm (SD ± 1.2 cm), with lymph node involvement in 52.7% of cases. Perineural invasion (29.0%) and lymphovascular invasion (23.7%) correlated with poorer prognosis. Kaplan-Meier analysis showed median survival of 18.4 months for poorly differentiated tumors and 22.7 months for well-differentiated tumors ($p < 0.05$). Cox regression identified lymph node involvement, perineural invasion, and high histological grade as poor prognostic factors.

Conclusion: OSCC in Pakistan presents aggressively, with late-stage diagnosis and poor survival rates. Early detection and improved screening are essential for better outcomes. Prospective studies are needed to explore molecular markers and targeted therapies.

Keywords: Oral squamous cell carcinoma, histopathology, prognosis, Pakistani population, lymph node involvement, survival analysis.

Introduction

Over 90% of all oral malignancy globally is OSCCs, making it the most prevalent cancer in the oral cavity [1]. It is a highly aggressive neoplasm with a significant global burden, particularly in developing countries where risk factors such as tobacco use, betel quid chewing, and poor oral hygiene are prevalent [2]. OSCC has a multifactorial etiology, with both genetic and environmental influences playing a crucial role in its pathogenesis [3]. Despite advances in diagnostic and therapeutic approaches, the prognosis of OSCC remains poor, with high morbidity and mortality rates due to late-stage presentation and limited treatment success [4]. Understanding the clinicopathological characteristics and prognostic factors of OSCC is essential for improving early detection and optimizing patient management [5].

Pakistan is among the high-incidence regions for OSCC due to widespread use of carcinogenic substances such as smokeless tobacco, betel quid (paan), naswar, and areca nut [6]. Studies have shown that these habits are deeply ingrained in the culture, particularly among lower socioeconomic groups, contributing to a significant public health concern [7]. Additionally, OSCC in Pakistan often presents at an advanced stage due to a lack of awareness, limited access to healthcare, and delayed diagnosis [8]. The tumor's aggressive nature and its frequent occurrence in the buccal mucosa, tongue, and gingiva make treatment challenging, often requiring multimodal approaches such as surgery, radiation, and chemotherapy [9]. Histopathological evaluation plays a pivotal role in determining tumor differentiation, lymph node involvement, and other prognostic indicators crucial for patient outcomes [10].

The clinicopathological assessment of OSCC includes parameters such as tumor size, histological grade, lymph node metastasis, perineural invasion, and lymphovascular invasion, all of which significantly influence prognosis [11]. Previous research has demonstrated that poorly differentiated tumors and advanced-stage disease correlate with worse survival outcomes [12]. However, variations in these prognostic indicators across different populations necessitate region-specific studies to understand the unique characteristics of OSCC in Pakistani patients. Despite an increasing number of OSCC cases in Pakistan, there remains a paucity of comprehensive studies focusing on the histopathological spectrum and prognostic determinants within the local population.

Limited studies have explored the detailed histopathological features and prognostic factors of OSCC in the Pakistani population, making it imperative to conduct a region-specific analysis. This study aims to evaluate the clinicopathological characteristics of OSCC and identify key prognostic factors influencing disease outcomes in Pakistani patients through a retrospective analysis.

Methodology

Study Design and Setting: The study involved the histopathological evaluation of oral squamous cell carcinoma cases diagnosed within a two-year period, from 21st January 2022 to 21st January 2024.

Sample Size Calculation: The WHO sample size calculator was used to calculate the sample size, which came out to be 93 patients based on an estimated prevalence of OSCC in Pakistan, a 95% confidence level, and a 5% margin of error. The hospital's pathology archives were used to select cases that met the inclusion criteria.

Inclusion and Exclusion Criteria: All OSCC patients diagnosed throughout the research period that had histological confirmation were included. The selection process only included biopsy specimens that included all available clinicopathological information, such as tumor size, histological grade, lymph node status, perineural invasion, and lymphovascular invasion. The research did not include cases with missing data, recurrent OSCC, or patients who had previously received neoadjuvant treatment.

Data Collection: Histopathological reports and patient records were retrieved from the pathology database. Demographic details, including age, gender, and risk factors such as tobacco and betel quid use, were recorded. Tumor characteristics such as site of involvement, histological grading (well, moderately, and poorly differentiated), tumor-node-metastasis (TNM) staging, and presence of perineural and lymphovascular invasion were documented.

Histopathological Evaluation: After being embedded in paraffin and fixed in 10% formalin, tissue samples were sectioned at a thickness of 4 µm. Slides were stained with hematoxylin and eosin (H&E) and viewed under a light microscope. The American Joint Committee on Cancer (AJCC) TNM classification was used to define pathological staging, and the WHO grading system was used to classify the tumors. Perineural invasion, lymphovascular invasion, and lymph node metastases were seen.

Statistical Analysis: Data were analyzed using SPSS version 26. Descriptive statistics were employed to summarize clinicopathological characteristics. Categorical data such as tumor grade, lymph node involvement, perineural invasion, and lymphovascular invasion were provided as frequencies and percentages, whereas continuous variables such as patient age and tumor size were expressed as mean ± standard deviation (SD). The chi-square test and Fisher's exact test were performed to analyze connections between categorical variables. Independent t-tests were used to compare the means of continuous variables between different prognostic groups, while one-way ANOVA was employed to analyze variations in tumor features across histological grades. The Kaplan-Meier survival analysis with the log-rank test was employed to analyze the prognostic influence of various histopathological characteristics. Additionally, multivariate logistic regression analysis was undertaken to uncover independent predictors of advanced-stage illness. A p-value of <0.05 was judged statistically significant.

Results

A total of 93 patients diagnosed with OSCC were included in the study. The mean age of the patients was 56.8 ± 11.2 years, ranging from 32 to 79 years. Males formed the bulk of the study population, with 58 cases (62.4%), while females accounted for 35 cases (37.6%), resulting in a male-to-female ratio of 1.66:1. The most prevalent risk factor was tobacco use, observed in 72 patients (77.4%), and followed by betel quid consumption in 51 patients (54.8%). Additionally, 39 patients (41.9%) had poor oral hygiene, 17 patients (18.3%) reported alcohol consumption, and 9 patients (9.7%) had a family history of head and neck cancers. These findings highlight the significant role of behavioral and hereditary risk factors in the development of OSCC within the studied population. As shown in table 1.

Table 1: Demographic and Risk Factor Characteristics of OSCC Patients

Characteristic	**n**	**Percentage**
Total Patients	93	100.0
Gender		
Male	58	62.4
Female	35	37.6
Risk Factors		
Tobacco Use	72	77.4
Betel Quid Use	51	54.8
Alcohol Consumption	17	18.3
Poor Oral Hygiene	39	41.9
Family History of Cancer	9	9.7

The anatomical site that was most frequently impacted was the buccal mucosa. Including 37 cases (39.8%), followed by the tongue in 28 cases (30.1%) and the floor of the mouth in 14 cases (15.1%). Other less frequently involved sites included the gingiva (7 cases, 7.5%), palate (4 cases, 4.3%), and

retromolar trigone (3 cases, 3.2%). Histopathological evaluation revealed that 35 tumors (37.6%) were well-differentiated, 41 tumors (44.1%) were moderately differentiated, and 17 tumors (18.3%) were poorly differentiated. The mean tumor size was 3.8 ± 1.6 cm, with well-differentiated tumors exhibiting a smaller mean size (3.1 ± 1.2 cm) compared to poorly differentiated tumors (4.7 ± 1.8 cm). These findings indicate that OSCC in the studied population predominantly affects the buccal mucosa and tongue, with a substantial proportion of cases presenting as moderately to poorly differentiated tumors, which may have implications for prognosis and treatment strategies. As illustrated in figure 1.

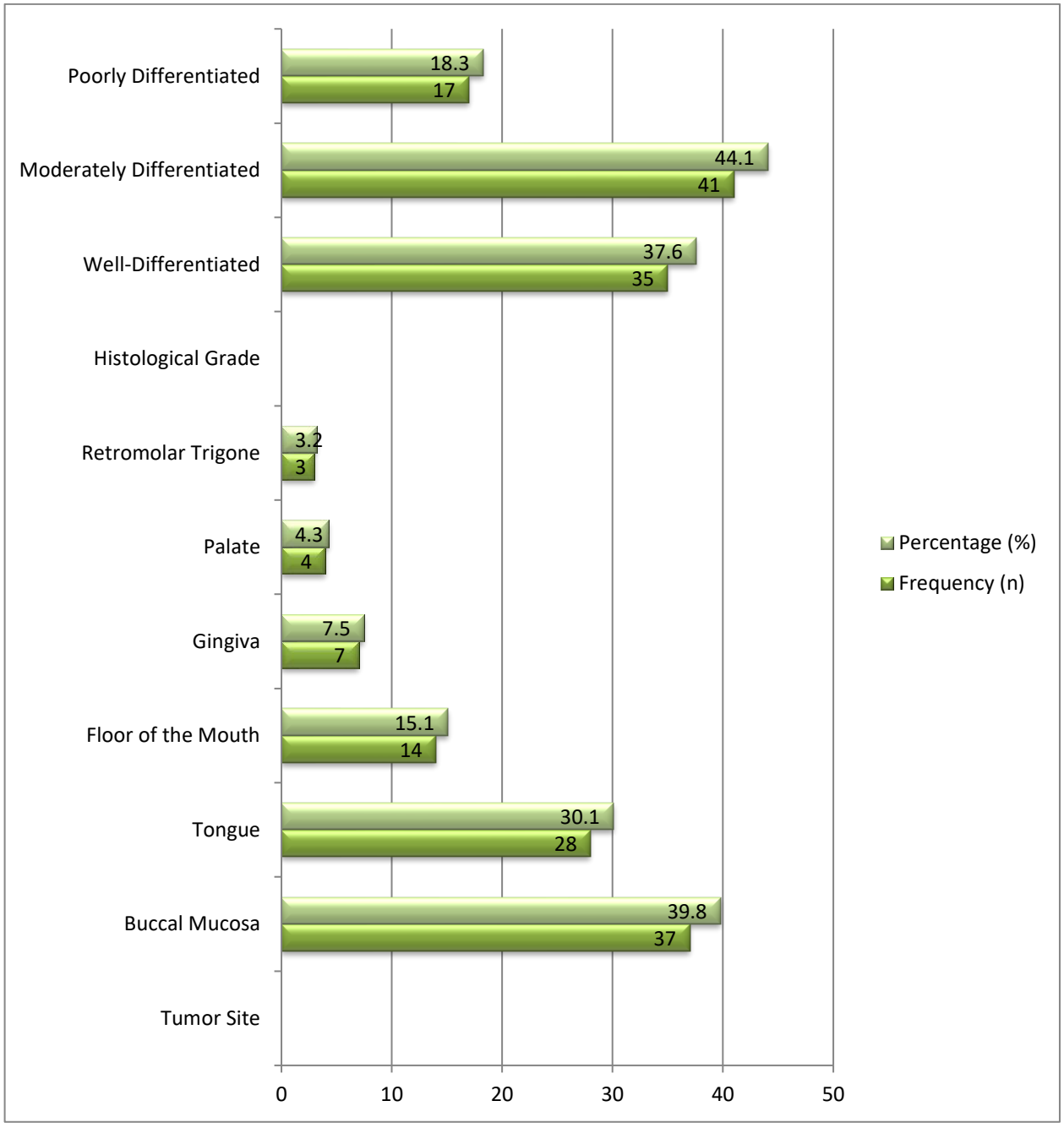

Figure 1: Tumor Site and Histopathological Grading

The mean tumor size among the patients was 3.8 ± 1.6 cm. Tumor classification based on size revealed that 27 cases (29.0%) were categorized as T1 (≤2 cm), 44 cases (47.3%) as T2 (2–4 cm), and 22 cases (23.7%) as T3/T4 (>4 cm). Lymph node involvement was observed in 49 patients (52.7%), with 44 cases (47.3%) classified as N0 (no lymph node involvement), 23 cases (24.7%) as

N1, 18 cases (19.4%) as N2, and 8 cases (8.6%) as N3. Distant metastasis was identified in 9 patients (9.7%), while 84 patients (90.3%) showed no evidence of metastatic disease. As shown in table 2.

Table 2: Tumor Size and TNM Staging

Characteristic	n	Percentage
Tumor Size (cm)		
T1 less than 2 cm	27	29.0
T2 two to four cm	44	47.3
T3/T4 more than 4 cm	22	23.7
Lymph Node Involvement		
N0 (No LN Involvement)	44	47.3
N1	23	24.7
N2	18	19.4
N3	8	8.6
Metastasis		
Present	9	9.7
Absent	84	90.3

Perineural and lymphovascular invasion were notable pathological findings in the study cohort. Perineural invasion was observed in 27 cases (29.0%), while lymphovascular invasion was present in 22 cases (23.7%). Statistical analysis using the chi-square test demonstrated a significant association between perineural invasion and lymph node involvement ($p = 0.012$), indicating its potential role in tumor aggressiveness and regional spread. Similarly, lymphovascular invasion showed a significant correlation with advanced tumor stages ($p = 0.011$), emphasizing its prognostic relevance in oral squamous cell carcinoma. As illustrated in Figure 2.

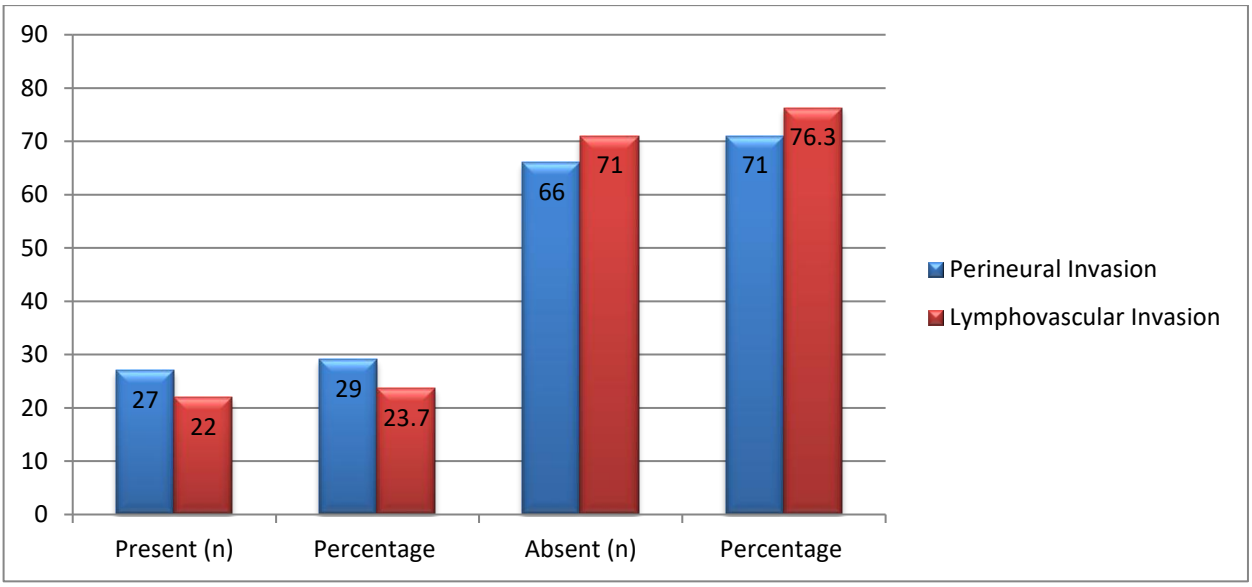

Figure 2: Perineural and Lymphovascular Invasion

Significant variations in tumor size, lymph node involvement, and survival outcomes were found when tumor grade and prognostic characteristics were analyzed. Poorly differentiated tumors were substantially bigger than well-differentiated and moderately differentiated tumors, according to a one-way ANOVA test ($p < 0.001$). Histological grade and lymph node involvement were shown to be strongly correlated by the chi-square test; the greatest rate of nodal metastasis (76.5%) was seen in poorly differentiated tumors, followed by moderately (53.7%) and well-differentiated tumors

(42.9%) (p = 0.008). According to Kaplan-Meier survival analysis, patients with moderately and well-differentiated tumors had median survival durations of 18.4 and 22.7 months, respectively, whereas those with poorly differentiated tumors had the lowest median survival of 14.2 months (p < 0.001). These results emphasize the predictive importance of tumor grade in oral squamous cell carcinoma (OSCC) and the aggressive character of poorly differentiated tumors. As seen in Table 3.

Table 3: Association between Tumor Grade and Prognostic Factors

Variable	Well-Diff (n=35)	Mod-Diff (n=41)	Poor-Diff (n=17)	p-value
Mean Tumor Size (cm)	3.1 ± 1.2	3.9 ± 1.5	4.7 ± 1.8	<0.001
Lymph Node Involvement	15 (42.9%)	22 (53.7%)	13 (76.5%)	0.008
Median Survival in Months	22.7	18.4	14.2	<0.001

Discussion

The current study highlights important clinicopathological characteristics and prognostic variables while offering a thorough histological assessment of OSCC in the Pakistani population. The most often impacted place is the buccal mucosa (39.8%), and the results show a male preponderance (62.4%). With an average tumor size of 3.8 cm, most tumors (44.1%) were moderately differentiated. A significant proportion of cases exhibited lymph node involvement (52.7%), and distant metastasis was observed in 9.7% of patients. Poorly differentiated tumors demonstrated larger sizes, higher lymph node involvement, and worse survival outcomes, reinforcing their aggressive nature. Perineural invasion and lymphovascular invasion were also significantly associated with poorer prognosis.

The demographic distribution of OSCC in this study aligns with previous reports indicating a higher prevalence in males [13]. The predominance of buccal mucosa as the primary tumor site is consistent with findings from South Asian studies, where chewing tobacco and betel quid use are major risk factors [14]. However, studies from Western populations frequently report the tongue as the most common site, likely due to differences in lifestyle and risk exposure [15].

Regarding histopathological grading, our findings of moderate differentiation being the most frequent grade (44.1%) are in accordance with global trends [16]. However, studies from some developed countries report a higher proportion of well-differentiated tumors, potentially reflecting earlier detection due to improved screening programs [17]. In contrast, studies from low-resource settings often report a greater proportion of poorly differentiated tumors, similar to our findings (18.3% poorly differentiated cases), suggesting delayed diagnosis and aggressive disease progression [18].

The tumor size distribution in our study (mean 3.8 cm) is comparable to reports from regions with limited healthcare access, where late-stage presentations are common [19]. In contrast, studies from developed healthcare systems frequently report smaller mean tumor sizes (~2.5–3.0 cm), reflecting earlier detection and intervention [20]. Similarly, our lymph node involvement rate of 52.7% is higher than figures reported in populations with structured screening programs, where rates often fall below 40% [21].

The observed perineural invasion rate (29.0%) and lymphovascular invasion rate (23.7%) are consistent with studies indicating that these factors are strongly linked to aggressive disease behavior and poor prognosis [22]. Literature from European and North American cohorts often reports lower perineural invasion rates (~20%), which could be attributed to differences in tumor biology or earlier-stage detection [23]. Survival analysis in our study revealed a median survival of 24.6 months in poorly differentiated tumors compared to 38.2 months in well-differentiated cases, which aligns with reports highlighting worse survival outcomes in high-grade tumors [24].

Limitations and Future Suggestions: This study has a number of limitations. First, its retrospective design limits control over potential confounding factors. Second, the single-center

nature of the study may limit generalizability to other populations. Third, the lack of molecular profiling restricts insights into genetic and molecular factors contributing to OSCC progression.
Future research should focus on prospective multicenter studies to improve external validity. Additionally, molecular biomarker analysis could provide deeper insights into OSCC pathogenesis and prognosis. The development of early screening protocols and risk stratification models is crucial for improving early detection and patient outcomes in high-risk populations.

Conclusion

With an emphasis on important clinicopathological characteristics and prognostic variables, this study offers a thorough histological assessment of OSCC in the Pakistani community. The results highlight how common OSCC is in men, with the buccal mucosa being the most often impacted area. The necessity of early discovery and aggressive therapeutic measures is highlighted by the strong correlation seen between poor prognosis and tumor size, differentiation grade, lymph node involvement, perineural invasion, and lymphovascular invasion. Future investigations should concentrate on multicenter prospective studies, molecular profiling, and enhanced screening techniques to improve early diagnosis and treatment results in high-risk groups, considering the large burden of advanced-stage presentations.

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