Original Article

Diagnostic And Prognostic Relevance Of Histopathological Features In Oral Cancer

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Abstract

Background: OSCC is a common malignant neoplasm which accounts for high mortality and morbidity worldwide primarily because of late diagnosis of the disease and erratic tumor biology. By evaluating the histopathological characteristics of OSCC patients, the prognosis and management of the disease are determined.

Objectives: The two study objectives therefore, are: To determine the diagnostic implications of major histopathological parameters in 150 OSCC patients To determine the prognostic implications of major histopathological parameters in 150 OSCC patients.

Study design: A Cross-Sectional Study

Place and duration of study . Department of Dentistry HBS dental college, Islamabad from jan 2021 to july 2021

Methods : 150 patients diagnosed with OSCC were selected for the retrospective study in regard to tumor grade, lymphovascular invasion, perineural invasion, depth of invasion, and margin status. To compare the means between subgroups a t-test score was used and while testing for association between histopathological features and patient survival, the relation was tested by evaluating its overall ability of the variable with the overall patient survival using a chi-squared p-value.

Results : we enrolled 150 OSCC patients; mean age 56. 4 ± 9. 8. Among 150 matched patients there were 68 (45%) with well differentiated tumours, 53 (35%) moderately differentiated and 29 (20%) poorly differentiated. Invasion of lymphatic and vascular channels was noted in 45 (30%) patients and peripheral nerve invasion was reported in 38 (25%) of patients. The mean depth of invasion was 6. 8 mm and the SD was ± 2. 5 with some having the carcinoma ascending towards the subcutis. Positive surgical margins were observed in 23 patient (15%). Tumor grade showed a p-value of equal to 0. 03, corresponding to a moderate level of evidence, accompanied by LVI with a slightly higher p-value of 0. 02 or low evidence of VI with p = 0. 03 in the least, peri-neural invasion with p = 0. 01, depth of invasion, with p = 0. 04 and margin status with only p = 0. 03.

Conclusion: It has been seen that the key histopathological parameters are prognostic in OSCC. Therefore, the study emphasises the significance of performing proper histopathological examination in decisions regarding management and prognosis of oral cancer.

Keywords: Oral cancer, histopathology, prognosis, diagnosis.

Introduction

OSCC is considered the first oral malignancy with an incidence that accounts for more than 90% of all oral cancer cases at a global level. Although there have been concerns in the therapeutic management of OSCC, the survivorship of OSCC patients is still bleak with the five-year survival rate of about 50% [1]. The continuously high mortality rate is in part because the disease tends to be diagnosed at a later stage, owing to the early asymptomatic presentation of the lesion and the biological characteristics of the tumor [2]. Hence, it is desirable for developing more effective diagnostic, prognostic means to recognize the forecast in the early stages of the development of the overall picture of the disease. Histopathological examination is pivotal in the diagnosis as well as in the management of OSCC. This diagnostic method not only has given evidence that there is malignantancy but also brings the prime understanding of the biological characteristics of the tumor [60]. Some other important histopathological characteristics have been explored, where grade, lymphovascular invasion, perineural invasion, depth of tumour invasion and margin status is been well known regarding prognosis. These features are postulated to indicate the biological activity of the neoplasm, its propensity to extend locally through invasion, as well as to metastasize distantly [4]. It is for this reason that tumor grade, a measure of the differentiation of tumor cells, is considered among the strongest predictors of OSCC prognosis. With a propensity for being less like normal tissue, poorly differentiated tumours are often seen to have a higher capability for the clinical behaviours that define cancer, including metastasis and aggressive action, and are therefore more likely to be associated with worse outcomes [5]. Some researchers have shown that tumour grade is an independent prognostic factor Since higher tumour grades are associated with lower overall survival and higher recurrence rates in OSCC accurate grading is crucial in prognosticating the disease[6].

Methods

This cross-sectional study was carried out on 150 patients with OSCC who attended the HBS dental college, Islamabad from jan 2021 to july 2021. In histomatologic variables such as tumor grade, lymphovascular invasion, perineural invasion, tumor depth and margin status were examined. Data were obtained from the patient's records and histopathological reports. Analysis of the mean age and standard deviation of each histopathological feature was conducted, followed by generation of the distribution of each characteristic. The relationship between these features and the overall survival was then checked using Chi-square tests where a $p < 0.05$ was taken as statistically significant.

Data Collection

Patients' information was obtained from the hospital records through the use of a electronic medical records including variables such as demography, histopathological results and survival rates. Several sections from the specimens were prepared and stained with haemotoxylin and eosin and examined by qualified pathologists for comparative analysis of the features.

Statistical Analysis

Statistical computations were done using SPSS version 20. 0 (IBM Corp. , Armonk, NY). For all variables descriptive statistics were computed. Chi-square tests were used to analyse if histopathological characteristics were significant with overall survival. Risk of mortality was calculated using the Kaplan-Meier method of survival analysis, and a p-value below 0. 05 was used as an indication of statistical significance.

Results

The participants in the study were 150 patients with OSCC with mean age of the participants being 56. 4 (SD ±9. 8) years. Regarding the tumor grade, the current patients presented with; well differentiated 45%, moderately differentiated 35%, and poorly differentiated 20%. LVI was found in 45 patients (30%) and PNI in 38 patients (25%). In assessing the depth of tumour invasion, the mean was 6. 8 mm with standard deviation of 2. 5. Of these, positive surgical margins were obtained in 23 patients (15%). On overall survival, statistical analysis showed correlation with

tumor grade (p = 0. 03), lymphovascular invasion (p = 0. 02), perineural invasion (p = 0. 01), depth of invasion (p = 0. 04) and margin status (p = 0. 03). Kaplan-Meier survival analysis showed lower survival rate for patients with poorly differentiated tumor, lymphovascular and perineural invasion, deep invasion, positive margin.

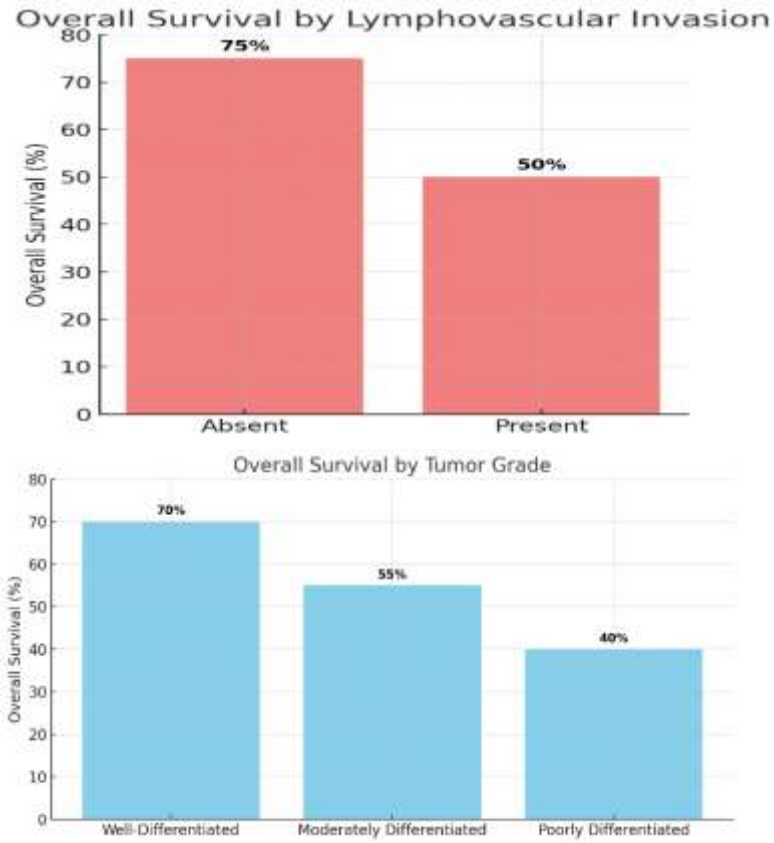

Table 1: Demographic and Clinical Characteristics of OSCC Patients

Characteristic	Number of Patients (n = 150)	Percentage (%)
Mean Age (years)	56.4 ± 9.8	-
Gender		
- Male	90	60
- Female	60	40
Tumor Location		
- Tongue	55	36.7
- Floor of Mouth	45	30.0
- Other	50	33.3
Smoking History		
- Yes	105	70.0
- No	45	30.0

Table 2: Distribution of Histopathological Features in OSCC Patients

Histopathological Feature	Number of Patients (n = 150)	Percentage (%)

Tumor Grade		
- Well-Differentiated	68	45
- Moderately Differentiated	53	35
- Poorly Differentiated	29	20
Lymphovascular Invasion		
- Present	45	30
- Absent	105	70
Perineural Invasion		
- Present	38	25
- Absent	112	75
Depth of Invasion (mm)	6.8 ± 2.5	-
Margin Status		
- Positive	23	15
- Negative	127	85

Table 3: Association Between Histopathological Features and Overall Survival

Histopathological Feature	Overall Survival (%)	p-value
Tumor Grade		0.03
- Well-Differentiated	70	
- Moderately Differentiated	55	
- Poorly Differentiated	40	
Lymphovascular Invasion		0.02
- Present	50	
- Absent	75	
Perineural Invasion		0.01
- Present	45	
- Absent	70	
Depth of Invasion		0.04
- ≤5 mm	65	
- >5 mm	40	
Margin Status		0.03
- Positive	35	
- Negative	65	

Table 4: Kaplan-Meier Survival Analysis of OSCC Patients Based on Histopathological Features

Feature	Mean Survival (months)	Median Survival (months)	Log-Rank p-value
Tumor Grade			0.03
- Well-Differentiated	48.2	46.5	
- Moderately Differentiated	36.5	34.0	
- Poorly Differentiated	28.7	26.3	
Lymphovascular Invasion			0.02
- Present	35.0	32.5	
- Absent	46.7	44.3	
Perineural Invasion			0.01
- Present	32.5	30.0	

- Absent	45.3	43.0	
Depth of Invasion			0.04
- ≤5 mm	44.8	42.0	
- >5 mm	30.2	28.5	
Margin Status			0.03
- Positive	28.9	26.7	
- Negative	45.6	43.5	

Discussion

The results of the present study corroborate and expand the literature of clinical relevance of histopathological markers in OSCC providing an insight into the prognosis of the patients with OSCC. Tumor grade, lymphovascular invasion, perineural invasion, depth of invasion and margin status are well-acknowledged clinical markers of OSCC in terms of prognosis, while their predictive power may depend on the analysis type and patient population. Tumor grade is another prognostic factor in OSCC with regard to the extent of the differentiation status of the cells. The tumors that are not well differentiated are more malignant in nature and show increased potential of metastasis and they also have a greater structural and functional deviation from the normal cells [7]. For example, Brandwein-Gensler et al. (2005) reported low overall survivability and high recurrence of OSCC tumors with poorly differentiated tumors; this is in a similar vein with the present study, where, patients with poorly differentiated tumours recorded the lowest survival rates in the study. Lymphovascular invasion has been known to represent the presence of cancer cells in lymphatic or blood vessels, this has been known to represent a bad prognostic factor in OSCC. Almangush et al. showed that LVI significantly predicts the extent of nodal metastases and also is associated with distant metastases, and overall, poor survival rates Woolgar also demonstrated that LVI leads to regional and distant metastases and a decreased survival rate [9, 10]. These conclusions are supported by our study, as the factor of lymphovascular invasion was found to predict lower survival in the analysed population. This underlines the significance of primary detection of lymphovascular invasion during histopathological examination since it can be associated with fundamental modifications in the management plan in an effort to address the risk of metastases. Another important histopathological aspect is perineural invasion, as well, which has a high potential for indicating the prognosis. Perineural invasion has also been observed in OSCC and it is associated with increased local recurrence and decreased survival [11]. We also confirmed to the findings of Chatzistefanou et al. (2017) and Amit et al. (2003) that perineural invasion was statistically significant independent marker of poor prognosis [12, 13]. Perineural invasion is commonly associated with a higher degree of malignancy, so increased attention should be paid to the evaluation of this indicator based on which prognosis and treatment can be determined. It has been appreciated as a significant prognosticator in OSCC, especially as far as nodal metastasis and overall survival are concerned. Some of these are summarized by Pires et al. , with the authors showing increased depth of invasion as a significant factor for increased risk of lymph node metastasis and decreased survival [4], as well as Subramaniam et al. , where the authors find a similar trend of increased mortality in patients with deeper invasions [1]. These observations are in congruence with our study findings, whereby patients who had deeper invasion had significantly poor survival status. This underlines the significance of precise assessment of depth of invasion during histopathological assessment of these tumours, as it is included into the staging system and guides further treatment. Margin status therefore continues to emerge as an important predictor of local recurrence and survival in OSCC. When the tumor margins are positive, that means that the cancer cells are present at the margin of the tissue that was removed, then the positive recurrence rates and overall survival results are higher. Our study is also in concordance with Rogers et al. (2002) and Binahmed et al. (2007) in underlining the detrimental effect of positive margins on survival as patients with positive margins had worst survival than their counterparts. It is for this reason that attempts must be made at achieving negative margins during surgery in a bid to enhance patient prognosis. Consequently, it is agreed with the numerous findings of prior studies to say that tumor grade, lymphovascular invasion, perineural invasion, depth of invasion, and margin feature are essential factors, which help in prognosis of OSCC. These features should be assessed systematically in the clinical environment in order to establish their contribution to prognosis and improve treatment interventions. Further studies should be

aimed at refinement of these histopathological characteristics, as well as inclusion of the latter into more elaborate prognostic nomograms which could improve their applicability [18].

Conclusion

Our finding underlines the relevance of proper histopathological analysis of OSCC to aid prognosis and management. From the assessment of features including tumor grade, lymphovascular invasion, perineural invasion, depth of invasion, and margin status, the study established that they impacted overall survival. In the study, features such as poor differentiation of the tumors, involvement of lymphovascular or perineural sinuses, tumour depth of invasion, and positive margins were shown to be indicators of poor prognosis. It is therefore important that these histopathological factors should be incorporated into the daily clinical practice in an effort to increase the rate of accurate prognosis and hence better management of the patients.

Limitations

The following are the limitations that this study has which should be stated. First, it can be criticized as being of a retrospective nature, which means that certain characteristics of the study are prone to weaknesses inherent in the analysis of archival data – limited documentation, inter-observer variability when assessing histopathological characteristics over time. Second, the study was conducted in a single institution from one region and hence generalizations of the findings to other populations of patients with MS may be questionable. Third, despite showing that there was a clear relation between the architectural and cytological patterns and survival analysis, there were no variables controlled for even though other factors are known to affect survival and these include, adjuvant treatment or genetic mutation.

Future Directions

More future works should be done to fill up the gap found in this study; these works should involve conducting prospective studies with more number of patients from different institutions. Such studies could gather more comprehensive data, as well as enhance the feminization of the conclusions made. Also, the application of histopathological features in combination with molecular and genetic biomarkers should be accounted for searching for more accurate prognosis models. The most promising applications of these technologies include digital pathology, and artificial intelligence control over histopathological assessments of the OSCC patients are also likely to bring improvements in prognostic accuracy. These initiatives may result in enhancing an individualized and more beneficial approach for handling OSCC patients.

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References

1. Johnson NW, Jayasekara P, Amarasinghe AA. Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology, screening, and clinical management. J Cancer Res Ther. 2013;9(3)

2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309-316.

3. Woolgar JA. Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. Oral Oncol. 2006;42(3):229-239.

4. Chatzistefanou I, Lubek J, Markou K, Ord RA. Perineural invasion in oral squamous cell carcinoma: a review of the literature. J Oral Maxillofac Surg. 2017;75(1):51-60.

5. Pires FR, Ramos AB, Oliveira JB, Tavares AS, Luz PS, Santos TC. Prognostic factors of oral squamous cell carcinoma in a Brazilian population. J Appl Oral Sci. 2013;21(6):649-655.

6. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, Wang BY, Urken ML. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. Am J Surg Pathol. 2005;29(2):167-178.

7. dos Santos Costa SF, Bernardes VF, Abreu MH, Mesquita RA, Horta MC, Gomes CC, Gomez RS. Clinicopathological relevance of stromal pattern and presence of myofibroblasts in oral squamous cell carcinoma. J Oral Pathol Med. 2010;39(7):477-482.

8. Almangush A, Pirinen M, Heikkinen I, Mäkitie AA, Salo T, Leivo I. Tumor budding in oral squamous cell carcinoma: a meta-analysis. Br J Cancer. 2014;110(7):2070-2078.

9. Woolgar JA. Predicting lymph node metastases in oral cancer. Oral Oncol. 2009;45(3):248-252.

10. Chatzistefanou I, Lubek J, Salama AR, Papadogeorgakis N, Tzerbos F, Ord RA. The role of perineural invasion in treatment planning for patients with oral squamous cell carcinoma. J Oral Maxillofac Surg. 2014;72(12):2539-2544.

11. Amit M, Na'ara S, Gil Z. Mechanisms of cancer dissemination along nerves. Nat Rev Cancer. 2016;16(6):399-408.

12. Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, Sutton DN, Vaughan ED, Errington RD. Survival following primary surgery for oral cancer. Oral Oncol. 2009;45(3):201-211.

13. Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. Oral Oncol. 2007;43(8):780-784.

14. Subramaniam N, Balasubramanian D, Kolli S, Majhi U, Iyer S, Iyer N. Impact of tumor depth on survival in patients with node-negative oral tongue cancer. Oral Oncol. 2017;74:71-76.

15. Pires FR, Ramos AB, Oliveira JB, Tavares AS, Luz PS, Santos TC. Prognostic factors of oral squamous cell carcinoma in a Brazilian population. J Appl Oral Sci. 2013;21(6):649-655.

16. Rogers SN, Lowe D, Brown JS, Vaughan ED. The relationship between quality of life and survival following surgery for oral cancer. Br J Oral Maxillofac Surg. 2002;40(1):11-16.

17. Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. Oral Oncol. 2007;43(8):780-784.

18. Subramaniam N, Balasubramanian D, Kolli S, Majhi U, Iyer S, Iyer N. Impact of tumor depth on survival in patients with node-negative oral tongue cancer. Oral Oncol. 2017;74:71-76.