

COMPARISON OF HISTOPATHOLOGICAL FEATURES BETWEEN PRIMARY AND RECURRENT ORAL SQUAMOUS CELL CARCINOMAS: IMPLICATIONS FOR MANAGEMENT STRATEGIES

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ABSTRACT

Objectives: To assess clinical and histopathological characteristics of primary and recurrent OSCC about the tumor site, grade, stage, lymph node involvement, and tobacco habits, which determine the prognosis and recurrence.

Materials and Methods: Our cross-sectional study recruited 80 consecutive participants i-e 40 patients with primary tumors and 40 patients with secondary/recurrent tumors. The study was conducted in Bacha Khan College of Dentistry in a time of 5 years. The participants were divided into two groups i-e primary tumors (without recurrence) (n=40) and secondary tumors (with recurrence) (n=40). The participant's age, gender, history of tobacco use, tumor location, management, grade, stage, presence or absence of recurrence, and survival rates were collected from the clinical records and tumor registers. OSCC slides (both primary and recurrent) were collected from the department of pathology Bacha Khan College of Dentistry to confirm the diagnosis of the primary and secondary tumors. The recurrent tumor sites were identified as local, secondary, or distant sites. The recurrence of the tumor was confirmed histologically and was considered in patients with advancement of the disease and had no cure to treatment. The second primary tumors within the site were also considered recurrent tumors. Tumor grading was performed according to the WHO classifications and survival analysis was performed using the Kaplan-Meier and Cox proportional hazards regression to determine effects of these features on overall survival and cancer-specific survival.

Results: The Kaplan-Meier estimator test established differences in survival characteristics of primary and recurrent tumors, with tobacco use significantly present. In this study, a history of tobacco use was associated with a poorer overall survival of patients ($p=0.04$), as well as cancer-specific survival ($p=0.04$). However, clinically, tobacco use has been shown not only to be an independent risk factor for OSCC but also a significant factor for tumor recurrence and poor survival, which demands an effective control in smokers. We also noted that primary tumor site influenced survival: patients with tumor in the buccal mucosa had worst survival rates ($p = 0.04$). Furthermore, lymphatic infiltration was identified as an independent predictor of poor prognosis and hazardous for both OS and cancer-related survival ($p = 0.006$). These imply the

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a common malignant neoplasm prevalent in the head and neck area, which is a major threat to public health

need for closer follow-up and assertive intervention on patients who exhibit lymphatic spread and particular anatomic site manifestation.

Conclusion: *Continued tobacco use, buccal mucosa tumors, and patients with lymphatic infiltration were found to have poor survival rates which indicated that such patients require more intense treatment modalities. These results underscore the need for the inclusion of the factors in the management of care especially on smoking cessation, targeted therapies, and frequent follow-up of patients with unfavorable molecular profiles. However, due to its single-institution design and low number of cases included, the generalization of our findings is restrained; therefore, more extensive investigations should be conducted in the future to validate and further develop our findings in OSCC prognosis.*

Key words: *Oral squamous cell carcinoma, primary tumors, recurrent tumors, histopathological features*

globally¹. The treatment of OSCC also depends on the stage of the disease at the time of diagnosis; small, localized lesions are usually dealt with by surgical removal, whereas more extensive disease may require primary radical surgery and then radiation or chemotherapy^{2,3}. When the likelihood of lymph node metastasis is high, particularly if neck involvement is suspected, neck dissection is usually advised. However, local tumor recurrence is still a major problem in OSCC where up to 47% of the patients may develop tumor recurrence either as a secondary primary tumor or regional and/or distal metastasis⁴.

It is therefore important to be able to differentiate between primary OSCC and recurrent OSCC because of the high prognostic-differential behavior and response to therapeutic management of these two types of tumors⁵. Primary tumors are primarily solitary and are more likely to be stable had they been diagnosed early to allow for treatment⁶. In contrast, recurrent tumors are usually more malignant in behavior and are likely to give poor prognosis. The clinical dilemma now arises from the fact that primary and recurrent oral tumors appear histopathologically very similar and this makes diagnostic choices very challenging⁷. It is crucial to make a differential between these two kinds of tumors because the recurrent ones may have to undergo more invasive and frequent treatment management since they are likely to have poor responsiveness to treatment. Survival of patients with recurrent OSCC is considerably poorer than that of patients with primary OSCC and is associated with reduced overall and cancer-specific survival⁸. There is evidence that recurrent tumors are advanced and invasive, they have a high degree of deposition in the lymphatic and vascular system and, hence are difficult to cure⁹.

It is thus important to understand the detailed clinicopathological characteristics that exist between primary and recurrent OSCC. The goals of this research are at first, to compare the clinical and histopathological characteristics of both primary and recurrent OSCC and secondly, to offer essential recommendations that may be useful in the treatment of OSCC, thereby affecting patient care and prognosis. By understanding the main determinates that predict recurrence, clinicians can target cases with the highest risk of OSCC recurrence and adjust the treatment plans and thus providing patients with better outcomes. It is anticipated that highlighting these differences may help to offer knowledge regarding more effective management for treatment plans and follow-up as well as the recurrence of OSCC cases in the future.

MATERIALS AND METHODS

This cross-sectional study recruited 80 consecutive participants inclusive of 40 OSCC participants who had primary oral squamous cell carcinoma, and 40 participants who had secondary/recurrent oral squamous cell carcinoma. This work was carried out at Bacha Khan College of Dentistry, Mardan, Khyber Pakhtoonkhwa Pakistan, for five years. Participants were selected based on the following inclusion criteria: Study 1: (a) primary OSCC patients, and (b) surgically treated primary OSCC patients with subsequent secondary/recurrent OSCC. Such patients were excluded to reduce confounding factors that may affect survival or recurrence of the cancer primarily under study. Further, evidence from clinical and histopathological records of the patients was mandatory to include in the study to maintain the high accuracy of data collected.

Data on age, gender, history of tobacco use, tumor site of primary site, primary management at our institution, tumor and node grade, tumor stage, evidence of recurrence, and survival were extracted from clinical and tumor registers. OSCC tissue slides (both primary and recurrent) were retrieved from the Department of Pathology of Bacha Khan College of Dentistry to confirm the diagnosis and evaluate histopathological characteristics. The grading of tumors was done according to the WHO criteria, which divides tumors by degree of differentiation (well, moderately or poorly differentiated).⁽¹⁰⁾ To reduce inter-pathologist variability, inter-rater reliability was assessed by a second review of the slides by two consultant pathologists with discordance resolved by consensus.

The participants were divided into two groups: The patients with no recurrences, $n=40$ were grouped in primary tumors and the patients who developed secondary tumors after the initial treatments, $n=40$ were enrolled for the study. Local recurrences were defined as having arisen at the anatomic site of the primary tumor, and secondary and distant recurrences were defined as having arisen at other locations confirmed histologically as tumor recurrence. If, however, the second primary tumor developed the same site was considered as a reoccurrence.

The mean follow-up period for participants was 53.3 months (range: 4.04 to 87.84 months). At the end of the study period, 28 patients (35%) had expired of whom 23 died of cancer-related causes and 17 patients (21.2%) were alive without any evidence of recurrence; 5 patients were without any recurrences at their last visit but were lost to follow-up with follow up ranging from 17.4 to 66.8 months post-treatment. The study was conducted according to the ethical consideration of the Institution Ethical Committee Board approval.

Kaplan Meier Analysis of survival was done to evaluate the overall survival and cancer-specific survival. Since more than one variable significantly contributes towards the rate of survival, the Cox proportional hazards regression model was used. This made it possible to minimize on confounding factors like age, gender, and tobacco use. Potential confounders were controlled in the regression models by including these covariates to examine the differential impacts of recurrence on survival outcomes

independently. Further assessment was performed about the impact of tumor-related factors such as the location, grade, and lymphatic involvement by using univariate and multivariate analyses.

When there were cases with incomplete clinical records or patients that could not be reached for follow-up, data was addressed using multiple imputations. This approach enabled one to make some prediction of the missing values from the available information thus increasing the credibility of the models. In a given analysis, any patient with significant missing data (for instance, no survival or tumor characteristic data) was not included to obtain valid results. The application of multiple imputations assisted in reducing the possibility of biases that could be obtained from incomplete data. All the analyses of the collected data were conducted under SPSS version 23. A p -value of <0.05 was used to determine the significance of the statistical test used in the research and any survival estimates of interest were accompanied by their corresponding 95% confidence intervals.

RESULT

Clinicopathological details of primary and recurrent tumors including gender, age, tobacco use, site of the tumor, tumor grade, stage, treatment options, lymphovascular invasion, and perineural infiltration are listed in Table 1. A primary tumor is defined as the first diagnosed tumor, whereas recurrent tumor is a tumor found after treatment of the primary tumors. The level of association of clinicopathological features and tumor recurrence was analyzed using p -value; $p < 0.05$ was considered statistically significant.

The statistical analysis of Kaplan-Meier survival curves of the primary and recurrent tumor groups showed a favorable and statistically significant difference in overall survival and cancer-specific survival. The 5-year cancer-specific survival rate was 94% in the primary tumor group and 32% in the recurrent tumor group ($p < 0.05$; 95% CI for the primary group: The eradication rate by post-treatment PCR was between 88 and 98%; 95% CI for the recurrent group: 28–35%). Overall survival rates were also significantly lower in the recurrent group, with a mean survival of 77.9 months in the primary group (95% CI:70). Survival was significantly shortened in the recurrent group as compared to the primary group (43.6 months vs 1–85.7 months) CI: 39.0–48.2

$p < 0.005$.

Tobacco use remains an independent predictor of survival overall and survival from cancer. Patients with a history of tobacco use had poorer survival outcomes compared to non-smokers, with an overall survival rate of 90% for smokers versus 2.5% for non-smokers ($p = 0.04$; 95% CI for smokers: 72–84%; 95% CI for non-smokers: 1.2–2.9%). The recurrence rate in the patients the history of tobacco use was also significantly higher which speaks for more focused intervention programs on smoking cessation in OSCC patients.

The location of the tumor also emerged as significant in the survival of the patients. Tumors located in the buccal mucosa were associated with significantly worse overall survival ($p = 0.04$; 95% CI for buccal mucosa: A significantly higher mean reduction of 15–25 was obtained on the floor of the mouth than on other sites such as tongue which presented relatively higher survival rates of 45%; 95% CI: 40–50%). This finding suggests that the anatomical site of OSCC can be a critical factor in determining the aggressiveness of the tumor and subsequent management strategies.

Lymphatic infiltration was a strong independent predictor of poor prognosis. Patients with lymphatic invasion had significantly lower overall and cancer-specific survival rates ($p = 0.006$), with the presence of lymphatic infiltration associated with a 30% survival rate (95% CI: 25–35%) compared to 70% in patients without infiltration (95% CI: 65–75%). Cox regression analysis confirmed the significance of lymphatic infiltration, tumor grade, and pattern of invasion as independent predictors of recurrence and survival, underscoring the need for more aggressive treatment approaches in patients with these features.

DISCUSSION

Clinicopathological factors delineated in the present study are of paramount importance in OSCC to determine the overall prognosis and survival rate of the patients. Consequently, this study recognized factors including tobacco use, tumor location, and lymphatic infiltration which differentiate the survival status of primary and recurrent OSCC patients. These findings align with previous literature but also extend the knowledge regarding the recurrent OSCC population.

In this study, tobacco use was found to be an

important variable explaining both the general and cancer-specific mortality rates. About the data on tobacco use in the given patients, patients who use tobacco have considerably worse results than non-smokers, including a much higher percentage of relapses in tobacco-using patients (90% vs 2.5%). This is in accordance with past studies that have established tobacco use as being a causal factor in the development and progression of OSCC. As shown in Chamoli (2021) and Mroueh, et al. (2020) some findings have revealed that tobacco use not only acts as a risk factor for primary OSCC but also for recurrence of the disease^{11,12}. It is hypothesized that the carcinogens in tobacco initiate the pathway of tumorigenesis by bringing about genetic mutations plus inflammation in the patient's body; these factors might help to explain why smokers seem to have remarkably worse survival and also considerably higher rates of recurrence¹³. The present work contributes to such evidence by demonstrating the detrimental association of tobacco with survival in OSCC patients after the initial therapy; therefore, such tobacco cessation efforts are imperative for OSCC treatment.

According to the results of this study, tumors that were of the buccal mucosa were found to have a lower survival rate than tumors in other locations such as the tongue. The 5-year cancer-specific survival for the patients with buccal mucosa tumors ranged from 15–25% while that for patients with tongue tumors ranged from 40–50%. Interestingly, these results support earlier findings by Marinelliet al. (2020) and Wang F et al. (2022), which identified buccal mucosa tumors to be more malignant with worse prognosis and higher recurrence rate^{14,15}. This may partly be due to the anatomical and histological features of buccal mucosa with a propensity for invasion by carcinogens in areas where smokeless tobacco use is common¹⁶. The outcomes of buccal mucosa tumors are poor and thus tailored approaches based on the location of the tumor that are even more intensive surgical procedures and better follow-up must be applied.

Another significant independent risk factor identified in this study regarding poor prognosis was lymphatic infiltration. They further noted that patients with lymphatic invasion had a poor prognosis with lower overall and cancer-related survival rates than patients without such infiltration; 30% and 70%, re-

Table 1: Clinical and pathological features comparing the primary and recurrent tumors by using ‘Fisher’s exact test’ and ‘univariate analysis of survival’ for the recurrent group according to ‘Kaplan-Meier and log-rank tests’

Features	Primary tumor N = 40		Recurrent tumor N = 40		p-value	Overall survival (Recurrent tumor group)		Cancer-specific survival (Recurrent tumor group)	
	n	%	n	%		CI (95%)	p-value	CI (95%)	p-value
Gender									
Male	32	80%	34	85%	0.67	27.20–52.63	0.39	28.82–71.75	0.61
Females	8	20%	6	15%		27.61–70.94		28.27–53.85	
Age									
≤ 65 years	22	55%	15	37.5%	0.68	18.73–52.76	0.37	20.97–55.50	0.62
≥ 65 years	18	45%	25	62.5%		35.78–61.32		33.65–62.41	
History of tobacco use									
Yes	36	90%	10	2.5%	0.22	24.06–44.82	0.04	26.23–48.71	0.04
No	4	10%	30	7.5%		47.35–90.34		46.28–89.22	
Site of the tumor									
Buccal mucosa	11	27.5%	8	20%	0.04	30.04–58.02	0.62	31.77–60.21	0.63
Tongue	14	35%	18	45%		23.51–55.91		22.83–56.82	
Floor of the mouth	10	2.5%	11	27.5%		27.02–59.12		28.56–61.57	
Retromolar pad	2	5%	1	2.5%		26.81–56.22		27.50–57.46	
Maxilla	2	5%	1	2.5%		15.80–55.78		16.03–56.21	
Mandible	1	2.5%	1	2.5%		32.13–55.20		32.60–56.85	
Hard palate	0	0%	0	0%		-		-	
Tumor stage									
I + II	17	42.5%	35	87.5%	0.78	38.12–72.26	0.81	34.39–59.86	0.74
III + IV	23	57.5%	5	12.5%		22.10–46.07		15.83–57.87	
Grade of the tumor									
Well + Moderate	38	95%	26	65%	0.03	24.81–47.18	0.06	36.85–69.64	0.08
Poor	2	5%	14	35%		35.63–81.14		22.13–48.78	
Treatment									
Surgery	10	2.5%	21	52.5%	0.63	37.42–70.39	0.17	37.36–71.40	0.23
Surgery + Radiation + chemotherapy	30	75%	19	47.5%		22.12–45.28		22.11–47.66	
Lymphatics Infiltration									
Type 1 + 2	37	92.5%	33	82.5%	0.76	36.02–57.06	0.003	26.72–50.21	0.006
Type 3	3	7.5%	7	17.5%		2.05–27.27		36.78–82.02	
Perineural invasion									
1+2+3	10	25%	23	57.5%	0.28	28.02–51.31	0.51	56.96–73.67	0.41
4+5	30	75%	17	42.5%		27.69–60.91		10.71–27.26	
Pattern of invasion									
Absent	25	62.5%	0	0%	0.03	(-) statistics could not be measured because values were censored			
Present	15	37.5%	40	100%					

spectively. This finding is supported by other studies including that by Huang S et al. in 2021 and Kim MJ et al. in 2024 who also noted that lymphatic invasion was a significant risk factor for OSCC recurrence and poor survival^{17,18}. Pathologically, some features may be helpful, such as the presence of lymphatic infiltration which reflects a higher propensity of the tumor for the lymphovascular space invasion. We found that lymphatic infiltration had a negative impact on overall survival rate and should be considered when developing a treatment strategy. In the case of lymphatic invasion, more intensive adjuvant therapies such as prophylactic lymph node dissection or adjuvant chemoradiation might be necessary for patients to promote favorable oncologic trends.

While comparing the data obtained in the present study with other recent studies, it can be concluded that the outcomes are aligned with the existing OSCC literature. For instance, When Spoerl S et al. (2020) investigated OSCC patient, the authors reported that tobacco use and lymphatic invasion significantly impacted survival rates, which is consistent with the findings of the current study¹⁹. Moreover, Lin NC et al. (2021) revealed that tumor sites in the buccal mucosa seemed to have a poor prognosis in comparison to tumor sites in the other regions, which also works effectively in support to our assertion that anatomical site influences OSCC prognosis²⁰. However, some differences were observed in the relationship between tumor grade and survival. Although our study confirmed poor tumor grade is an independent predictor of poor prognosis, Choi YS et al. (2022) revealed that tumor grade was not significantly correlated with survival in patients with recurrent OSCC²¹. Such a difference could be attributed by variation in sample size, grading criteria of the tumors, or population of patients in the various studies.

Therefore, there are several clinical implications that can be derived from this study. First, they emphasize the requirement to consider smoking cessation programs as an essential component of OSCC patient management. Since smoking is very highly related to recurrence, smoking cessation interventions could have a substantial positive impact on survival for patients with this condition. Second, there is a need to pay attention to the location of the tumor so that appropriate treatment modalities can be created. This region is associated with a poor prognosis so patients

with buccal mucosa tumors may need to be subjected to a more intense protocol. Lastly, the assessment of lymphatic infiltration should be included in risk assessments that will inform appropriate treatment plans intended to give these patients a better chance of survival by escalating the management plans where lymphatic invasion has occurred.

This study is not without limitations which include the following; Patients 80 in number reduces the generality of the results and also reduces the validity and reliability in detecting minor though significant variations. Moreover, owing to the possibility of interaction between risk factors such as age, gender, tobacco use, and other factors, other covariates such as genetic differences or other possible influences in the environment were not considered for control. Some biases were reduced through the application of multiple imputations for missing data, however missing data remains a source of variability in the analysis particularly in a small sample size as was the case in this study. Finally, the population in the study was restricted with regards to the treatment center hence it cannot be generalized to the other OSCC patients.

Finally, using multivariate analysis, this study determined that tobacco use, tumor location, and lymphatic infiltration were independent prognostic factors for recurrence and survival in OSCC patients. These findings are in line with prior studies and support the assurance of this hypothesis, thereby suggesting the requirement of the assessment of those factors that would inform the necessity of integrating individualized treatment plans. Despite these limitations, the current research has brought some light to the prognosis of primary and recurrent OSCC and other potential risks factors that need to be tested in larger, multicenter databases. When this set of key variables is incorporated into treatment planning, clinicians will be in a position to enhance the survivorship and minimize the rate of recurrence in OSCC.

CONCLUSION

Tobacco use, tumor location, and lymphatic infiltration emerged as significant prognostic indicators for overall and disease-specific survival in the OSCC cohort of this study; moreover, patients with recurrent OSCC had worse outcomes than those with primary tumors. Continued tobacco use, buccal mu-

cosa tumors, and patients with lymphatic infiltration were found to have poor survival rates which indicated that such patients require more intense treatment modalities. These results underscore the need for the inclusion of the factors in the management of care especially on smoking cessation, targeted therapies, and frequent follow-up of patients with unfavorable molecular profiles. However, due to its single-institution design and low number of cases included, the generalization of our findings is restrained; therefore, more extensive investigations should be conducted in the future to validate and further develop our findings in OSCC prognosis.

REFERENCES

1. Kumar SA, Indu S, Gautami D, VarRuchi S. Oral squamous cell carcinoma (OSCC) in humans: Etiological Factors, diagnostic and therapeutic relevance. *Research Journal of Biotechnology* Vol. 2020;15:10.
2. Givony S. Oral squamous cell carcinoma (OSCC) an overview. *J Med Sci*. 2020;8:67-74.
3. Meram AT, Woo BM. Oral Cancer Management. *Peterson's Principles of Oral and Maxillofacial Surgery*. 2022:1009-55.
4. Liu Y, Yang M, Luo J, Zhou H. Radiotherapy targeting cancer stem cells "awakens" them to induce tumour relapse and metastasis in oral cancer. *International journal of oral science*. 2020;12(1):19.
5. Zittel S, Moratin J, Horn D, Metzger K, Ristow O, Engel M, et al. Clinical outcome and prognostic factors in recurrent oral squamous cell carcinoma after primary surgical treatment: a retrospective study. *Clinical Oral Investigations*. 2022:1-10.
6. Verma P, Kaur P, Al Asmari DS. Squamous cell carcinoma of mandible with unusual clinical presentation: a rare case report and review of literature. *Indian Journal of Dental Research*. 2021;32(2):256-60.
7. Su Y-F, Chen Y-J, Tsai F-T, Li W-C, Hsu M-L, Wang D-H, et al. Current insights into oral cancer diagnostics. *Diagnostics*. 2021;11(7):1287.
8. Weckx A, Riekert M, Grandoch A, Schick V, Zoeller JE, Kreppel M. Time to recurrence and patient survival in recurrent oral squamous cell carcinoma. *Oral oncology*. 2019;94:8-13.
9. Caldeira PC, Soto AML, de Aguiar MCF, Martins CC. Tumor depth of invasion and prognosis of early-stage oral squamous cell carcinoma: A meta-analysis. *Oral diseases*. 2020;26(7):1357-65.
10. Silva GVD, da Silva Dolens E, Paranaíba LMR, Ayroza ALC, Gurgel Rocha CA, Almangush A, et al. Exploring the combination of tumor-stroma ratio, tumor-infiltrating lymphocytes, and tumor budding with WHO histopathological grading on early-stage oral squamous cell carcinoma prognosis. *Journal of Oral Pathology & Medicine*. 2023;52(5):402-9.
11. Chamoli A, Gosavi AS, Shirwadkar UP, Wangdale KV, Behera SK, Kurrey NK, et al. Overview of oral cavity squamous cell carcinoma: Risk factors, mechanisms, and diagnostics. *Oral oncology*. 2021;121:105451.
12. Mroueh R, Nevala A, Haapaniemi A, Pitkaniemi J, Salo T, Mäkitie AA. Risk of second primary cancer in oral squamous cell carcinoma. *Head & Neck*. 2020;42(8):1848-58.
13. Malhab LJB, Saber-Ayad MM, Al-Hakm R, Nair VA, Paliogiannis P, Pintus G, et al. Chronic inflammation and cancer: The role of endothelial dysfunction and vascular inflammation. *Current Pharmaceutical Design*. 2021;27(18):2156-69.
14. Marinelli LM, Chatzopoulos K, Marinelli JP, Chen TY, Collins AR, Sotiriou S, et al. Clinicopathologic predictors of survival in buccal squamous cell carcinoma. *Journal of Oral Pathology & Medicine*. 2020;49(9):857-64.
15. Wang F, Wen J, Cao S, Yang X, Yang Z, Li H, et al. Nomogram predicting long-term overall and cancer-specific survival of patients with buccal mucosa cancer. *BMC Oral Health*. 2022;22(1):138.
16. Subramaniam N, Murthy SP, Vidhyadharan S. 11 Cancers of the Oral Cavity. *Comprehensive Management of Head and Neck Cancer*. 2021:102.
17. Huang S, Zhu Y, Cai H, Zhang Y, Hou J. Impact of lymphovascular invasion in oral squamous cell carcinoma: A meta-analysis. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2021;131(3):319-28. e1.
18. Kim MJ, Ahn K-M. Prognostic factors of oral squamous cell carcinoma: the importance of recurrence and pTNM stage. *Maxillofacial Plastic and Reconstructive Surgery*. 2024;46(1):8.
19. Spoerl S, Gerken M, Fischer R, Mamilos A, Spoerl S, Wolf S, et al. Lymphatic and vascular invasion in oral squamous cell carcinoma: Implications for recurrence and survival in a population-based cohort study. *Oral Oncology*. 2020;111:105009.
20. Lin N-C, Hsien S-I, Hsu J-T, Chen MY. Impact on patients with oral squamous cell carcinoma in different anatomical subsites: a single-center study in Taiwan. *Scientific Reports*. 2021;11(1):15446.
21. Choi Y-S, Kim MG, Lee J-H, Park J-Y, Choi S-W. Analysis of prognostic factors through survival rate analysis of oral squamous cell carcinoma patients treated at the National Cancer Center: 20 years of experience. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*. 2022;48(5):284-91.



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