Original Article

Comparative Evaluation of Some Histopathological Parameters of Oral Squamous Cell Carcinoma With and Without Lymph Nodes Metastasis

Saeedeh Khalesi[1], Neda Karghahi[2], Negin Taqizadehvidjaee[3]

[1] Assistant Professor of Oral and Maxillofacial Pathology Department, Dental Material Research Center, Dental School, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Associate Professor of Oral and Maxillofacial Pathology Department, Dental Research Center, Dental School, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Graduate Student, Dental Student's Research Committee, Dental School, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background and Aim: Oral squamous cell carcinoma (OSCC) is the most common oral malignant tumor. Identification of histopathological parameters leads to accurate prognosis and appropriate treatment plans. Comparative evaluation of some histopathological parameters of OSCC with and without cervical lymph nodes (CLNs) metastasis is the aim of this study.

Materials and Methods: In this cross-sectional study, 20 OSCCs with CLNs metastasis (group1) and 20 samples without CLNs metastasis (group 2) who underwent excisional biopsy with neck dissection from the archives of Pathology Department of Kashani Hospital, Isfahan were included. Clinical information such as age, gender and site of tumor were extracted. Hematoxylin and eosin–stained sections were reviewed with light microscope by two blinded oral pathologists and some histopathological parameters such as pattern of invasion, histopathologic grade, CLNs metastasis, tumor budding and host lymphocytic response were determined. All data was entered into SPSS24 software and was analyzed by Mann-Whitney, Chi-Square, T and the Fisher exact tests. P value <0/05 was considered as a significant difference.

Results: Significant difference was found between two groups based on the tumor stage, tumor budding ($p<0.001$) and pattern of invasion ($p=0.025$). But no significant difference was found based on the tumor dimensions ($p=0.086$), age ($p=0.59$), gender ($p=0.206$), location ($p=0.407$), infiltration of inflammatory cells ($p=0.8$) and histopathologic grade ($p=0.98$) between two groups.

Conclusion: Histopathological parameters can be used as prognostic indicators and effective factors in determining the treatment plan of patients.

Key Words: Oral, Squamous cell carcinoma, Pathology

Corresponding author: Negin Taqizadehvidjaee, Graduate Student, Dental Student's Research Committee, Dental School, Isfahan University of Medical Sciences, Isfahan, Iran

ndiamond444@gmail.com

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Introduction

The most common cancer of the oral cavity is squamous cell carcinoma (SCC). This lesion accounts for about 94% of oral cancers. In the last two decades, the prevalence of head and neck cancer, including oral and pharyngeal SCC has increased. In the world, out of more than 500,000 people with oral SCC (OSCC are finally

sentenced to death (1). Smoking, tobacco and alcohol consumption are risk factors related to the development of this type of malignancy (2). Despite the progress in the treatment of this lesion, the mortality rate of patients is still reported to be high (3). Although, the oral cavity is easily accessible in terms of clinical and visual examinations, about 60% of patients come in advanced stages of the disease and the most of the patients present with CLNs metastasis (4). The tumor stage and the condition of the CLNS are two important factors in determining the treatment methods and prognosis of tumor. The treatment of this lesion also depends on two factors, the degree of malignancy of the tumor and the clinical stage of the tumor. Recent research has highlighted the limitations of traditional grading criteria based on World Health Organization standards, pointing to the necessity for more robust prognostic markers. The TNM classification remains a significant prognostic tool (1,5,6). The condition of CLNs is the most important factor determining the prognosis and survival rate of patients with SCC (4).

While various markers are employed in tumor diagnosis, histopathology remains the gold standard for making definitive diagnostic and therapeutic decisions. Considerable effort is being devoted to identifying histological parameters that can predict prognosis, including invasion patterns, tumor budding, and lymphocytic infiltration (2,7). Tumor budding is known with high severity as an unfavorable prognostic factor in several cancers such as colon, esophagus and larynx cancer and recently tongue cancer (8,9). The presence of single cells or clusters of small diffused cells in the connective tissue stroma is called tumor budding (10,11). Despite numerous studies on OSCC, there has been a lack of focused research comparing histopathological parameters between OSCC cases with and without CLNs metastasis. This study aims to fill that gap by investigating the frequency and significance of various histopathological parameters in these two groups.

Materials and Methods

In this cross-sectional study, 40 samples were selected from the archives of the Pathology Department of Kashani Hospital with a definite diagnosis of OSCC that were treated for neck dissection. All demographic information including age, gender, location and size of the lesion were extracted from the files. 20 samples of OSCCs with CLNS involvement (N1) (group 1) and 20 samples without CLNS involvement (N0) (group 2) were selected. Samples prepared by excisional biopsy and neck dissection surgery were included in the study. Then, three sections from the OSCC tissue blocks stained with hematoxylin-eosin staining (H & E) and examined by two oral pathologists blindly and at the same time with an optical microscope (Olympus BX41TF, Tokyo, Japan). Some histological parameters including invasion pattern (IP), degree of malignancy (grade), tumor budding (TB) and inflammatory response (IR) were determined and recorded in the relevant checklist. Histopathological grade was determined based on the Bryne classification (12). Tumor budding is the presence of single cells or cell cords of less than 5 cells in the front of tumor invasion. Initially, the specimens were assessed using a × 40 objective lens to choose areas with the highest tumor budding intensity and the number of tumor buddings was counted using a × 400 lens in the area.

Also, the pattern of tumor invasion into five categories, 1: pushing margin of tumor with a smooth outline, 2: tumor with broad and pushing finger-like projection, 3: presence of invasive tumor islands with more than 15 cells in each island, 4: presence of invasive tumor islands with less than 15 cells in each island, 5: the presence of tumor islands that are more than 1 mm away from the main tumor was divided and then categories 1-3 non-infiltrative and categories 4-5 were considered infiltrative. Host immune response was classified into mild, moderate, and severe categories such that a diffuse band-like lymphoid infiltrate with or without lymphoid accumulation was classified as severe, and the presence of only a few lymphocytes on the tumor surface was classified as mild, and lymphoid between these two groups was classified as moderate (13).

All the obtained data were entered into SPSS24 software and were statistically analyzed by Chi-square, Mann-Whitney, T and the Fisher tests. P<0.05 was considered as a significant difference.

Results

According to the results of the present study (Table 1), the mean age (mean±SD) of patients in group 1 was 58.05 ± 17.37 and in group 2 was 61.9 ± 15.46 years. The mean age of all patients was 59.97±16.35 years. According to the t-test, the mean age of patients between the two groups was not significantly different (P=0.59). Also, the number of men in group 1 (60%) was more than females, but in group 2, the number of females (60%) was more than men. According to Chi-square test, no significant difference was observed between two groups based on gender (P=0.206). According to Fisher's exact test, no significant difference was found between the study groups based on tumor location (P=0.407). Most of the lesions in the two groups were found in the tongue (82%) and 15% of OSCCs found in the alveolar mucosa. The mean size of the greatest dimension of the tumor in group 1 was 4.45±1.05 cm and its size in group 2 was 3.58±1.49 cm. Based on the t-test, no significant difference was observed in terms of tumor size between the two groups (P=0.086). Furthermore, according to the Mann-Whitney test, there was a significant difference between the studied groups based on tumor stage (p<0.001). But, there was no significant difference between the studied groups based on tumor grade (P=0.98). According to the chi-square test, there was a statistically significant difference between the study groups based on the invasion pattern (P=0.025). In group 1, 8 samples with IP 3, 11 samples with IP 4 and 1 sample with IP 5 were seen, and in group 2, 15 samples with IP 3 and 5 samples with IP 4 were seen. According to the Mann-Whitney test, there was no significant difference between the studied groups based on lymphocytic infiltration (P=0.8).

Most of the lesions (21, 52%) did not indicate tumor budding. According to the Chi-square test, there was a statistically significant difference between the studied groups based on the presence or absence of TB (P=0.027). Also, the mean (mean ± SD) of the number of TB in group 1 was 9±4, while in group 2 was 8±2, which was significant according to the Mann-Whitney test (P<0.001) (Table 1). Furthermore, tumor budding (TB) showed a significant difference with tumor location (P=0.013) and PI (P<0.001). Also, based on Spearman's correlation, a significant and inverse relationship was found between mean age of patient and TB (P=0.048, r= - 1.98) (Table 2) (Fig 1).

Discussion

In this study tumor stage, tumor budding and pattern of invasion showed a significant difference between the oral SCC with and without lymph node involvement. Considering that the rate of oral and maxillofacial cancer continues to increase, the role of dentists in early diagnosis and prevention has become increasingly important (14). Involvement of cervical lymph nodes is one of the influential factors in the outcome of oral cancer treatment and prognosis (15-17). In the present study, CLNs involvement in patients with OSCC did not show a significant relationship with the mean age (P=0.59). In Chatterjee's study, the mean age of patients without CLNs involvement was 48 years and patients with CLNs was 46 years, which did not show a statistically significant difference (p=0.31) (13). In the study of Wunschel (1), Nayanar (16), De Silva (18), Chakravarthy (19) and Yamada (20), no statistically significant difference was seen. All the results of other studies are in line with the results of our study. In the most studies, the risk of involvement of CLNs was higher in young patients than in elderly patients.

According to the present study, 60% of the lesions without CLNs involvement were female and 60% of the lesions with CLNs involvement were men, and there was also no statistically significant difference between two groups based on the gender (P=0.206). In Chatterjee's study (13), men were more involved than females in both study groups. In Nayanar's study (16), men accounted for 66% of the

Table 1. Clinicopathological parameters in studied groups

Parameters / Groups			Group 1 N (%)	Group 2 N (%)	P value (test)
Clinical parameters		Age (Mean±SD)	58.05±17.37	61/9±15.46	0.59 [1]
	Gender	Male	12 (60)	8 (40)	0.206 [2]
		Female	8 (40)	12 (60)	
	Site	Tongue	18 (90)	15 (75)	0.407 [3]
		Alveolar mucosa	2 (10)	4 (20)	
		Buccal mucosa	0 (0)	1 (5)	
		Size (Mean±SD)	4.45±1.05	3.58±1.49	0.086 [1]
Histopathological parameters	PI	Non-Infiltrative	8 (40)	15 (75)	0.025 [2]
		infiltrative	12 (60)	5 (25)	
	IR	Mild	1 (5)	3 (15)	0.8 [4]
		Moderate	7 (35)	5 (25)	
		Severe	12 (60)	12 (60)	
	TB	No	7 (35)	14(70)	< 0.001 [4]
		Yes	13 (65)	6 (30)	
	Grade	WDSCC	11 (55)	12 (60)	0.98 [4]
		MDSCC	8 (40)	5 (25)	
		PDSCC	1 (5)	3 (15)	
	Stage	Stage I	0 (0)	10 (50)	< 0.001 [4]
		Stage II	0 (0)	9 (45)	
		Stage III	14 (70)	1 (5)	
		Stage IVA	6(30)	0(0)	

1.t-test, 2. Chi-square test, 3. Fisher's exact test, 4. Mann-Whitney test

Table2. Tumor budding frequency in studied groups

TB / Parameters			Present N (%)	Absent N (%)	P value (test)
Clinical parameters	Gender	Male	11 (55)	9 (45)	0.342 [1]
		Female	8 (40)	12 (60)	
	Site	Tongue	19 (57.6)	14 (42.4)	0.013 [2]
		Alveolar mucosa	0 (0)	6 (100)	
		Buccal mucosa	0 (0)	1 (100)	
Histopathological parameters	PI	Infiltrative	17 (100)	0 (0)	< 0.001 [1]
		Non-infiltrative	2 (8.7)	21 (91.3)	
	IR	Mild	1 (25)	3 (75)	0.6 [2]
		Moderate	5 (41.7)	7 (58.3)	
		Severe	13 (54.2)	11 (45.8)	
	Grade	WDSCC	9 (39.1)	14 (60.9)	0.333 [2]
		MDSCC	7 (53.8)	6 (46.2)	
		PDSCC	3 (75)	1 (25)	
	Stage	Stage I	3 (30)	7 (70)	0.722 [2]
		Stage II	2 (22.2)	7 (77.8)	
		Stage III	7 (46.7)	8 (53.3)	
		Stage IVA	4(66.6)	0 (33.3)	

1.Chi-square test, 2. Fisher's exact test

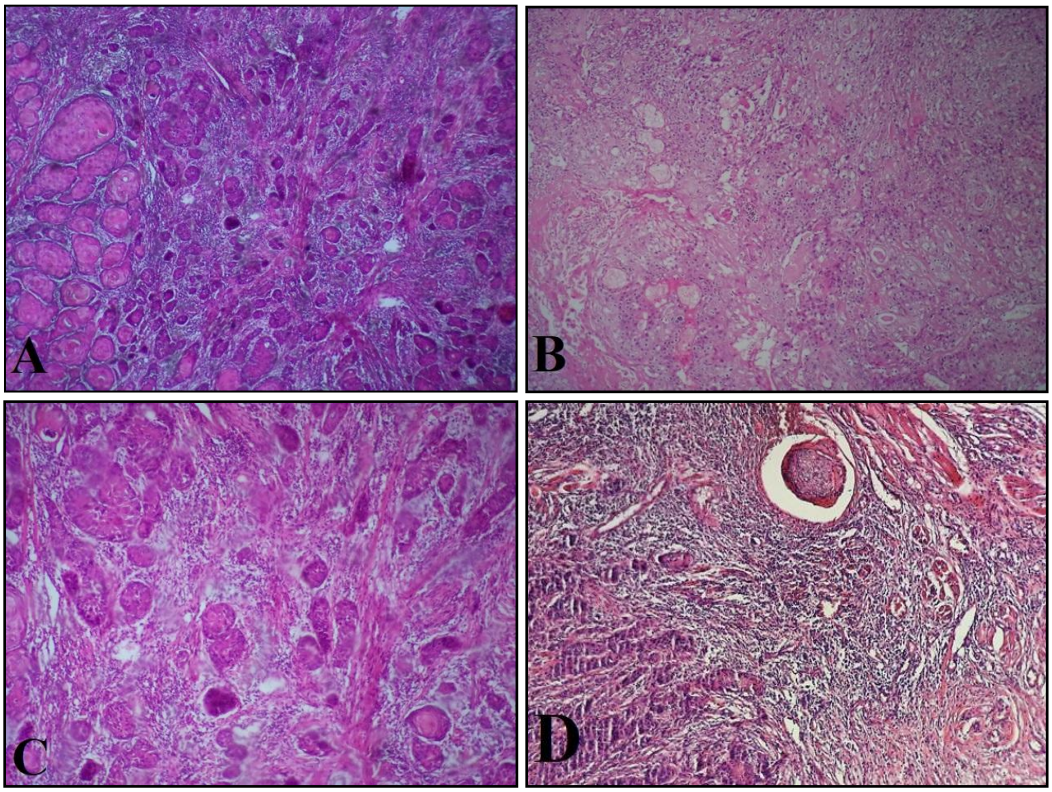

Figure1. (A)Tumor budding in OSCC, (B) Tumor with invasion pattern 3, (C) invasion pattern 4, (D) Invasion pattern 5 4 (H & E, ×400)

studied population. In the studies of De Silva and Yamada no correlation between gender and CLNs involvement has been reported (18,20). According to the results of these studies and our study, cervical lymph node involvement is generally reported more in men than in female. In the present study, the tongue (82%) was the most common site of OSCC in both groups, followed by the alveolar mucosa (15%). There was no significant relationship based on the location of the lesions between the studied groups (P=0.407). In Chatterjee's study (13) 52.2% and in Yamada's study (20) 51.4% of lesions were reported in the tongue. In meta-analysis study of Wahab (21), tongue was the most common site of lesions. In De Silva's study (P<0.01), the tongue significantly was the most common site of involvement in samples with CLNs involvement (18). But in Nayanar's study (16), the buccal mucosa was the most common site of involvement. In Chakravarthy's study, tumor location has a significant r elationship with lymph node involvement (19). Therefore, SCC of tongue is the most dangerous area for CLNs involvement, which further reveals the need for preventive methods and appropriate treatment.

In the present study, no significant difference was observed in tumor size based on the biggest dimension between the two groups (P=0.086). This result was the same with Chatterjee's study (13), but it was in conflict with De Silva's study (18). The difference in the number of examined samples and the location of tumor can be the reason for the difference in the results.

In this study, a significant relationship was found between tumor stage and CLNs involvement in patients with OSCC (p<0.001), which is in line with the results of Yamada's study (20), but with the results of the study Chatterjee (13) and Nayanar (16) were in conflict. In the present study, 70% of patients with CLNs involvement were in stage III and 30% of them were in stage IVa. Also, 50% of patients without involvement of CLNs were detected in stage I, 45% in stage II and only 5%

in stage III, which, as it is known, increases the risk of regional and distant metastasis with the increase of the stage of the disease (22,23).

In this study, it was found that there is no significant relationship between tumor grade and CLNs involvement (P=0.98), which is in line with Yadama's study (20). In the present study, most lesions with CLNS involvement (55%) were well differentiated and 40% of them were moderately differentiated. While lesions without involvement of CLNs, most of them (60%) were well differentiated, 25% of them were moderately differentiated, and 15% were poorly differentiated. However, in the study of Chatterjee (13) and Nayanar (16) a statistically significant relationship was found. In Alqutub's study, the poorly differentiated SCC had a higher risk of lymph node metastasis (17). The difference in the sample size, including the small number of samples with poorly differentiated OSCC in the present study can cause differences in the results of our study with other studies.

Based on the results of the present study, there was a significant relationship between the involvement of CLNS and the pattern of invasion, which is similar to the results of the studies of Chatterjee (13) and Chaitra (24), Nayanar (16) and De Silva (18) and Shimizu (25). In this study, the most of lesions in group 2 were non-infiltrative (75%), while most of the lesions in group 1 were infiltrative (60%), so it can be said that the pattern of invasion is the important parameter to predict the risk of lymph node involvement (13). Furthermore, Alqutub in a systematic review study showed the groups and single invasion patterns had a significantly higher risk for CLNs involvement than tumors with pushing borders and tumors advancing in cord, band, or strand patterns of invasion (17).

In our study, there was no significant relationship between CLNs involvement and the inflammatory response (p=0.08), which was consistent with the study of Chatterjee (13), Alqutub (17), Chaitra (24) and Mohtasham (26).

In this study, there was a significant relationship between CLNs involvement and tumor budding (P<0.001), which is in line with the results of studies by Mohtasham (26), Kale (27), Chatterjee (13), Noda (28), Chaitra (24), Yamada (20), Shimizu (25), Angadi (29) and Hong (30). It is clear that tumor budding (TB) is a powerful predictive histopathological parameter for cervical lymph node involvement in OSCC (25, 13). In study of Panchannavar, tumor budding though is strongly associated with CLNs involvement did not show significant relationship which contradicts the results of our study (31). As a result, we believe that tumor budding is an important factor in determining tumor behavior. Clinical importance and special attention to tumor budding in OSCC is a relatively simple and cost-effective method that can be detected using routine H&E sections, which makes it cost-effective and does not require the use of molecular methods. However, the use of pancytokeratin immunohistochemistry is a more specific and reliable method that helps to identify it.

The limitations of this study include the small sample size, the lack of access to more information on the patients including the level of involvement of the CLNs and the follow-up of the patients in terms of the mortality rate.

Conclusion

Tumor budding and pattern of tumor invasion is an essential factor for determining the behavior of oral SCC .These histopathological indicators are reproducible, easy and Affordable to identify which highlights their evaluation in the routine management of OSCC.

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