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Comparison of Immunohistochemical Expression of Oct4 in Oral and Cutaneous Squamous Cell Carcinoma

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ABSTRACT

Background and Objective: Oral squamous cell carcinoma (OSCC) is the most common oral cancer in the world, and cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer. Oct4 acts as a master regulator for self-renewal ability and in cancer stem cells and regulates tumor proliferation. The present study was conducted to compare the immunohistochemical expression of Oct4 in OSCC and CSCC, considering the different biological behavior of these two lesions.

Methods: In this cross-sectional study, immunohistochemical staining for Oct4 was performed on 60 paraffin-embedded blocks (30 OSCC and 30 CSCC). Clinical information was extracted from the patients' medical records. Oct4 expression was graded and compared according to the percentage of stained cells and the staining intensity of cells and their sum.

Findings: In this study, 63.3% of OSCC lesions and 56.7% of CSCC lesions had staining above 50%, and the difference between them was not significant. The two types of lesions did not differ in terms of staining intensity, percentage of tumoral cells staining, and final score. There was no association between Oct4 expression and lesion differentiation, clinical stage, lymph node involvement, and lesion location in OSCC patients. In CSCC patients, tumor differentiation and lesion location were also not associated with Oct4 expression.

Conclusion: The results of the present study showed that Oct4 may not be a suitable marker to explain the different clinical behavior of OSCC and CSCC, but the high expression of Oct4 in a high percentage of OSCC and CSCC samples supports the oncofetal role of this marker in these lesions.

Keywords: *Squamous Cell Carcinoma, Metastasis, Prognosis, Transcription Factor Oct4*.

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Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common cancer in the world. More than 300,000 cases of oral squamous cell carcinoma are reported annually worldwide (1) and the risk of metastasis is approximately 6.2% to 9.1% (2). Despite advances in diagnostic techniques and the use of current treatments (including surgery combined with radiotherapy as adjuvant therapy), survival rates are still low, with a 5-year survival rate of approximately 50% from the time of diagnosis (1, 3). As a result, there is a need for further investigation regarding the proliferative activity, degree of differentiation, and tumor invasion and metastasis capacity (4). Therefore, the investigation of target molecules that are related to the clinical behavior and prognosis of the tumor seems essential for molecularly targeted therapy (5, 6). Most oral and oropharyngeal tumors are squamous cell carcinomas, some of which originate from pre-existing premalignant oral lesions. It seems that the patient's prognosis and overall survival are highly dependent on the clinical stage of the tumor at the time of diagnosis (7).

The incidence of non-melanoma skin cancer is increasing worldwide, with cutaneous squamous cell carcinoma (CSCC) being the second most common type. 60% of cutaneous squamous cell carcinomas occur in the head and neck area, and there is a possibility of metastasis to the parotid gland or cervical lymph nodes in 2% of cases. The overall 5-year survival rate for metastatic cases in the head and neck is 48%. This poor prognosis has been attributed to the presence of cancer stem cells (3).

Cancer stem cells are a special population of cells in cancer tissue that have the ability to initiate tumorigenesis and are responsible for tumor self-renewal. Self-renewal is typically controlled by cells of the embryonic lineage, known as embryonic stem cells. This population of cells has a high tumorigenic potential and is believed to contribute to the biological characteristics of cancer, such as rapid growth, invasion, and metastasis (8).

One of the few plausible theories suggests that cancer stem cells (CSCs) arise as a result of genetic or epigenetic changes in stem cells. The discovery of cancer stem cells in cancer tissue is a new field of research that is being pursued by finding molecules shared between cancer stem cells and embryonic stem cells (8). Therefore, the expression of a large number of protein markers as active markers of cancer stem cells in oral squamous cell carcinoma samples has been noticed (8). In this regard, some studies have shown that Oct4 can be considered as a prognostic marker in cancers. A study by Hatefi et al. on bladder cancer showed that the level of Oct4 gene expression correlates with clinical and histopathological prognostic indicators of tumors and therefore can be considered as a potential prognostic tumor marker (9). Lambis-Anaya et al. showed that high expression of OCT4 is associated with a more aggressive phenotype of rectal cancer and with a higher probability of progression and metastasis (10).

According to the research, Oct4 can be considered as a prognostic marker for oral squamous cell carcinoma. This marker also plays a key role in the proliferation of embryonic stem cells that regulate CSC (7). In addition, OCT4 reactivation has been reported in many cancers, such as lung cancer (11, 12), esophageal cancer (8), gastric cancer (13, 14), breast cancer (15), and bladder cancer (16), suggesting its role as a biomarker and tumor promoter in multiple malignancies. Chiou et al. observed increased Oct4 expression in oral SCC (17). Vijayakumar et al. also found that Oct4 is increased in patients with OSCC and oral dysplasia but its expression is higher in SCC (8). Tsai et al. also introduced Oct4 as a target molecule for the treatment of OSCC (18).

Oct4 is an octamer-binding protein 4 (OC4), a member of the POU domain transcription factor family, and is a master regulator of self-renewal in cancer stem cells (8) and plays an important role in regulating proliferation. A direct relationship between Oct4 expression and prognosis of some malignancies has also been observed. With increased expression of Oct4 in stem cells, self-renewal, invasion, and migration

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potential are also increased in stem cells, and blocking the Oct4 gene in combination with radiotherapy significantly reduces these properties (19). The present study was conducted to investigate the immunohistochemical expression of Oct4 and determine the possible role of this biomarker in the development of OSCC and CSCC, considering the different biological behavior of these two lesions.

Methods

This cross-sectional study was conducted after approval by the Ethics Committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRI.REC.1401.098, according to previous studies (7) and available facilities. 30 paraffin blocks of primary OSCC and 30 paraffin blocks of primary CSCC from patients who had not previously received treatment for their tumor were selected from the archives of the pathology department of Shahid Beheshti Hospital in Babol. Cases of recurrent tumors were not included in the study. Clinical information included the patient's age and sex, as well as the location and histopathological grade of the lesion. In the case of OSCC, in addition to the aforementioned cases, metastasis to lymph nodes, clinical stage, and tumor size were extracted from the patient's file and recorded.

First, 4-micron-thick sections were prepared from paraffin blocks of lesions and stained with hematoxylin-eosin to confirm the diagnosis. For immunohistochemical staining, additional 4-micron sections were prepared from paraffin blocks. These sections were first placed in xylene for deparaffinization and then in alcohol of different degrees (75, 85, 95, and 100%) for dehydration. The sections were then incubated for five minutes in phosphate-buffered saline (Tris-Buffer Saline=TBS).

Antigen retrieval was performed in a microwave oven at 120°C for 10 minutes at 12 atm pressure and the internal peroxidase activity was inhibited by 3% hydrogen peroxide. Then, the tissue sections were incubated for 40 minutes with a 1/50 dilution of anti-Oct4 antibody (mouse monoclonal antibody, IgG2b/κ, Zeta Corporation, USA) and then incubated with a 30-minute secondary antibody HRP (Horseradish Peroxidase) (Cell Marque, Sigma-Aldrich California, USA). Then, they were counterstained with 3,3-Diaminobenzidine (DAB) and then with Mayers hematoxylin for background staining.

Nuclear staining for Oct4 was considered positive. Slides were evaluated by a pathologist using a Labomed light microscope (Labo America, Inc, USA) at 400x magnification. Oct4 grading was performed based on the percentage of tumor epithelial cells positive (ratio of the number of stained tumor epithelial cells to the total tumor epithelial cells in the tissue section) and the intensity of their staining. The percentage of positive cells (P) (less than 5%= 0, 5 to 24%= 1, 25 to 49%= 2, 50 to 74%= 3, greater than 75%= 4) and the intensity of staining (I) (no staining= 0, weak staining= 1, moderate staining= 2, strong staining= 3) were scored, and ultimately the final score or total immunoreactivity was determined by summing the percentage of positive cells and their intensity of staining (such that if P + I was equal to 0-3, it indicated low expression and if it was equal to 4-7, it indicated high expression) (8).

On the other hand, when more than 50% of the epithelial cells showed staining, the tumor was considered positive for Oct4 (8). The positive control consisted of sections from seminoma and the negative control was obtained by omitting the primary antibody.

Data were statistically analyzed using SPSS 22. While reporting the expression level of Oct4 in oral squamous cell carcinoma and cutaneous squamous cell carcinoma by descriptive statistical indices, chi-square, Fisher's exact and t-test tests were used to compare their means between the study groups, and $p<0.05$ was considered significant.

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Results

30 cases of oral squamous cell carcinoma and 30 cases of head and neck squamous cell carcinoma were included in the study from the paraffin blocks available in the archive of the pathology department of Shahid Beheshti Hospital, Babol (from 2014 to 2022). The mean age of the patients was 70.45±15.62 years, the lowest age was 23 and the highest was 96 years (Table 1).

Table 1. Demographic characteristics of the study subjects

Group Variable	OSCC Number(%)	CSCC Number(%)	p-value
Gender			
Male	14(46.7)	27(90)	0.001*
Female	16(53.3)	3(10)	
Age (Mean±SD)	68.43±15.33	72.47±16	0.321**

*Chi-square test, **Independent samples t-test

The most common OSCC lesions were in the buccal mucosa with a frequency of 33.3% and the least common were in the submandibular region with 10%. Regarding CSCC lesions, the most common lesions were in the scalp with a frequency of 46.7% and the least common lesions were in the lip, ear and eyelid with 3.3% each (Table 2). 11 (36.7%) of OSCC cases were well differentiated, 15 (50%) were moderately differentiated and 4 (13.3%) were poorly differentiated. 20 (66.7%) of CSCC cases were well differentiated, 8 (26.7%) were moderately differentiated and 2 (6.6%) were poorly differentiated. There was no significant statistical relationship between the degree of tumor differentiation and the type of lesion based on the chi-square test.

Table 2. Frequency of lesions by location of involvement

Location of lesion	Number(%)
OSCC	
Submandibular region	3(10)
Hard palate	4(3.13)
Buccal mucosa	10(3.33)
Floor of mouth	6(20)
Tongue	7(3.23)
Total	30(100)
CSCC	
Scalp	14(7.46)
Face	4(3.13)
Cheek	3(10)
Lip	4(3.13)
Ear	1(3.3)
Submentum	1(3.3)
Nose	2(7.6)
Eyelid	1(3.3)
Total	30(100)

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63.3% of OSCC lesions and 56.7% of CSCC lesions had staining intensity above 50%, which was not significantly different. There was also no statistically significant relationship between the intensity of tumor cell staining and lesion type (Table 3).

Table 3. Frequency of lesions by percentage and intensity of tumor cell staining with Oct4

	Percentage of tumor cell staining					
Lesion type	**Less than 5% Number(%)**	**5-24% Number(%)**	**25-49% Number(%)**	**50-74% Number(%)**	**More than 75% Number(%)**	**p-value**
OSCC	0(0)	5(16.7)	6(20)	6(20)	13(43.3)	0.718*
CSCC	0(0)	7(23.3)	6(20)	8(26.7)	9(30)	0.718*

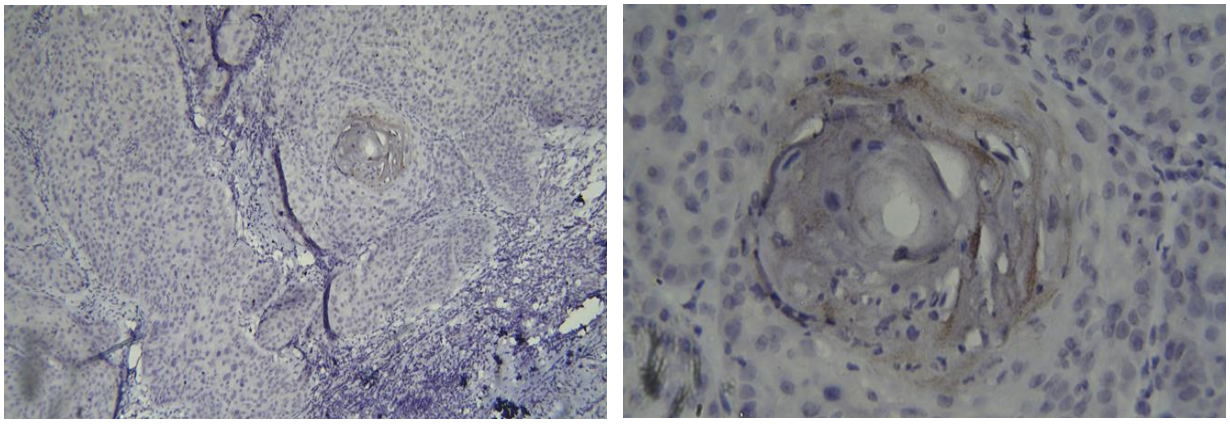
	Intensity of staining of tumor cells			
Lesion type	**Poor Number(%)**	**Moderate Number(%)**	**Strong Number(%)**	**p-value**
OSCC	22(73.3)	7(23.3)	1(3.4)	0.578*
CSCC	22(73.3)	8(26.7)	0(0)	0.578*

Total immunoreactivity was obtained from the sum of the scores for the percentage of stained tumor cells and the intensity of tumor cell staining, which had a mean of 4.2±1.13 for OCSS and 3.9±1.32 for CSCC. According to the independent samples T-test, there was no significant difference in the mean total immunoreactivity between the OCSS and CSCC groups. There was also no significant statistical relationship between the level of Oct4 marker expression (low and high expression) and the type of lesion (Table 4) (Figures 1 and 2).

Table 4. Frequency of lesions by Oct4 marker expression level

Type of lesion	Expression level	Number(%)	p-value
OSCC	Low	9(30)	0.417*
	High	21(70)	
CSCC	Low	12(40)	0.417*
	High	18(60)	

*Chi-square test



A B

Figure 1. Immunohistochemical expression of Oct4 in OSCC lesions (A: 100x and B: 400x)

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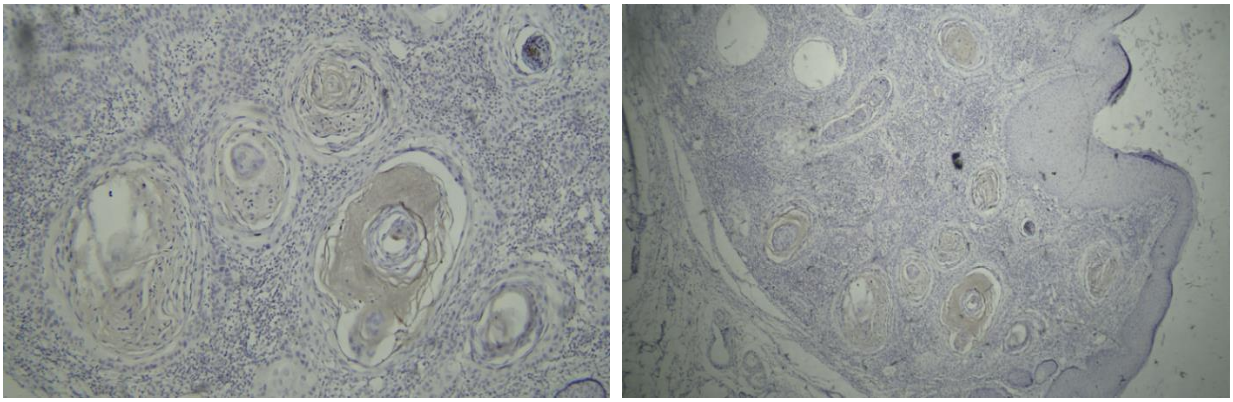

A B

Figure 2. Immunohistochemical expression of Oct4 in CSCC (A: 100x and B: 400x)

In well-differentiated OSCC, Oct4 expression was high in most cases (72.7%), and in poorly differentiated OSCC, Oct4 expression was low in most cases (75%) (Table 5). No association was seen between Oct4 marker expression and differentiation in OSCC patients. Most patients were in clinical stage II, with a frequency of 14 patients (46.7%) and had high Oct4 expression with a frequency of 78.6% of all cases. No association was seen between clinical stage and Oct4 expression. Most patients (76.7%) were without lymph node involvement, and 65.2% of them had high Oct4 expression. However, no significant association was seen between Oct4 expression and lymph node involvement. Oct4 expression was seen in most lesions in the tongue (85.7%) and buccal mucosa (80%). However, the results of the study did not show a significant association between lesion location and Oct4 expression.

Table 5. The relationship between Oct4 expression level with differentiation grade, clinical stage, lymph node involvement, and lesion location in OSCC patients

Variable	Expression level		p-value
	Low Number(%)	High Number(%)	
Differentiation			
Strong	3(27.3)	8(72.7)	
Moderate	3(20)	12(80)	0.100*
Poor	3(75)	1(25)	
Clinical stage			
I	3(75)	1(25)	
II	3(21.4)	11(78.6)	0.144*
III	2(40)	3(60)	
IV	1(14.3)	6(85.7)	
Lymph node involvement			
No	8(34.8)	15(65.2)	0.300*
Yes	1(14.3)	6(85.7)	
Location of lesion			
Submandibular area	1(33.3)	2(66.7)	
Hard palate	2(50)	2(50)	
Buccal mucosa	2 (20)	8 (80)	0.522*
Floor of the mouth	3(50)	3(50)	
Tongue	1(14.3)	6(85.7)	

*Chi-square test

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In the case of OSCC, the mean size of lesions with low Oct4 expression was 2.97±1.71 cm and for lesions with high Oct4 expression was 3.50±1.33 cm, with no significant difference between these two groups based on the independent samples T-test. High expression (at 65%) was most frequent in well-differentiated lesions. However, no relationship was observed between lesion differentiation and Oct4 expression in CSCC. The highest level of high Oct4 expression among CSCC lesions in different areas belonged to the scalp with 50% of all lesions with high expression. However, no significant relationship was observed between lesion location and Oct4 expression (Table 6).

Table 6. Relationship between Oct4 expression level and differentiation grade and lesion location in CSCC patients

Variable	Expression level		p-value
	Low Number(%)	High Number(%)	
Differentiation			
Strong	7(35)	13(65)	
Moderate	4(50)	4(50)	0.732*
Poor	1(50)	1(50)	
Lesion location			
Scalp	5(35.7)	9(64.3)	
Face	3(75)	1(25)	
Cheek	2(66.7)	1(33.3)	
Lip	1(25)	3(75)	0.371*
Ear	0(0)	1(100)	
Submentum	0(0)	1(100)	
Nose	0(0)	2(100)	
Eyelid	1(100)	0(0)	

*Chi-square test

Discussion

The results of the present study showed that high expression of Oct4 was higher in OSCC compared to in CSCC, but there was no difference between the two lesions. The percentage and intensity of tumoral cell staining and total immunoreactivity also did not differ between the two lesions. In OSCC, Oct4 expression did not have a significant relationship with lesion differentiation, clinical stage, lymph node involvement, and lesion location. In CSCC, there was no relationship between Oct4 expression and lesion differentiation and lesion location. On the other hand, it can be seen that considering the high expression of Oct4 in both lesions, it seems that Oct4 plays a role in the pathogenesis and progression of these tumors.

Several histopathological and clinical criteria have been proposed to assess the prognosis of cancer; however, the most important prognostic factor is the TNM staging system. On the other hand, there is currently great interest in investigating new molecular markers in various cancers to predict prognosis and estimate overall survival rate (20-22), and it seems that molecular markers can be effective in improving the ability of the staging system (23). Despite extensive knowledge about the pathogenesis and diagnosis and new therapeutic approaches for cancer, most patients are still dissatisfied with the current situation. Lymph node metastasis, tumor staging, tumor grade, and their combination with the patient's health status are important factors in determining the treatment strategy (24). Researchers are trying to identify markers that

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can be used for the diagnosis and treatment of cancers. A suitable diagnostic marker should have disease-specific properties and be able to indicate the course of the disease, differentiate between healthy and tumoral tissue, and assess response to treatment (18).

The transformation of precancerous lesions into oral cancer is caused by genomic changes. Apart from the somatic mutation theory of carcinogenesis (24), the cancer stem cell hypothesis is an important principle for new therapeutic strategies for cancer. According to this hypothesis, a small population of cells in cancerous tissues have tumor-inducing and oncogenic properties and are responsible for the carcinogenesis process (24).

Cancer stem cells are tumor-initiating cells. These cells may form tumors when they self-renew or differentiate into other cells. Such cells appear to be maintained as a distinct population within the tumor and, as they grow, cause tumor recurrence and metastasis. Therefore, molecular therapies targeting cancer stem cells may be promising for these patients. Recently, Oct4 expression has been proposed as a stem cell marker, which is naturally expressed in the developing embryo and its expression indicates pluripotent properties in embryonic stem cells (25). Oct4 has been shown to be a master transcription factor that can enable an adult cell to reprogram itself to become a pluripotent stem cell. Furthermore, Oct4 expression has been reported in cancer stem cells. Oct4 may play an important role in carcinogenesis and tumor progression and may be used as an indicator for patient prognosis (26).

Several studies have highlighted the important role of pluripotent markers and stem cell pathways in carcinogenesis. However, the molecular basis for the maintenance of cancer stem cell properties in oral squamous cell carcinoma has not been extensively studied (24). Studies have shown that Oct4 is upregulated in OSCC (18, 27). Hochedlinger et al. also investigated the effect of deficient expression of the Oct4 gene in somatic tissue of adult mice. They found that overexpression of this gene resulted in tissue dysplasia in the epithelium (24).

According to the results of the present study, high expression of Oct4 was observed in 70% of OSCC cases and 60% of CSCC cases, indicating the role of this marker in the carcinogenesis process in both lesions. Chiou et al. also reported increased Oct4 expression in oral SCC by both PCR and immunohistochemistry methods (25). Vijayakumar et al. also reported that Oct4 is increased in patients with OSCC and oral dysplasia, but its expression is higher in SCC (8). Tsai et al. also introduced Oct4 as a target molecule for the treatment of OSCC (18). In contrast to the present study, in the study of Baghai Naini et al., Oct4 gene expression by qRT-PCR did not differ between the two control and cancer groups (28). Although there was no control group in the present study, the expression of this gene was still expressed in 63.3% of cases and in more than 50% of the tumor cell population.

In the present study, there was no association between lesion differentiation, clinical stage, lesion location, and lymph node involvement with Oct4 expression in OSCC and CSCC lesions, which is consistent with the results obtained. Baghai Naini et al. also observed that there was no association between lesion grade, clinical stage, and lymph node metastasis with Oct4 expression in OSCC (28). On the other hand, Ravindran et al. showed that Oct4 expression is directly and significantly associated with lower differentiation, higher stage, larger tumor size, and worse prognosis. Moreover, Oct4 was introduced as a prognostic marker in their study (27). In the study of Ghazi et al., an increase in Oct4 expression was observed with the progression of tumor malignancy, such that in malignancy grades I & II, Oct4 expression was less than or equal to grade III (7). Ravindran et al. also showed the association between Oct4 gene expression and regional lymph node metastasis, clinical stage, grade of malignancy, and prognosis in OSCC (27).

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The results of the present study showed no significant difference in Oct4 expression in OSCC tumor tissue compared to CSCC samples, indicating lack of a possible role of this marker in the difference in the biological behavior of the two lesions. It also seems that high Oct4 expression cannot be considered as a prognostic factor in OSCC and CSCC and is not associated with clinical and pathological factors in the patient. On the other hand, it can be said that high Oct4 expression in a high percentage of OSCC and CSCC samples supports the oncofetal role of this marker in the aforementioned lesions, but it plays an equal role in determining the biological behavior of the studied lesions and does not cause any difference from this perspective.

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