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SIGNIFICANCE OF OCTAMER-BINDING TRANSCRIPTION FACTOR 4 (OCT4) EXPRESSION IN ORAL EPITHELIAL DYSPLASIA AND ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

BACKGROUND: Cancer stem cells (CSCs) play a role in both oral epithelial dysplasia (OED) and oral squamous cell carcinoma (OSCC). Octamer-binding protein 4 (OCT4) is one of the CSC indicators that shows an increase in OSCC. OCT4 has been recognized as a potential CSC marker in OSCC samples and cell lines. This protein is fundamental for self-renewal of immature embryonic stem cells and pluripotency. Premalignant lesions commonly precede OSCC, and signaling proteins play a significant role in transformation.
AIM OF THE STUDY: To Assess the expression of OCT4 in oral epithelial dysplasia and different grades of squamous cell carcinoma affecting the oral cavity.
MATERIAL AND METHODS: Eighty cases of OED and OSCC, noticed in the oral pathology department, Faculty of Dentistry, Alexandria University were included. Tissue sections were stained with hematoxylin and eosin for histological differentiation. Immunohistochemistry was carried out using the antibody against OCT4.
RESULTS: Almost all of the epithelial dysplasia cases examined in the study had a negative immunoreaction to OCT4 However, OCT4 exhibited a considerable immunopositivity in different phases of squamous cell carcinoma, with increased OCT4 immunopositivity in moderately to poorly differentiated OSCC.
CONCLUSION: The elevated expression of OCT4 from dysplastic mucosa to squamous cell carcinoma could indicate that this gene assumes a part in oral mucosal carcinogenesis. Overall, increasing the grade of squamous cell carcinoma and diminishing cellular differentiation resulted in a greater expression of this gene.
KEYWORDS: Oral squamous cell carcinoma, Oral epithelial dysplasia, OCT4.
RUNNING TITLE: Expression of OCT-4 in premalignant and oral cancer.

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INTRODUCTION

Oral squamous cell carcinoma is a particularly prevalent type of oral and maxillofacial cancer, accounting for around 3% of all malignant tumours (1). The overall survival rate after five years is between 50 and 55 % due to the frequent development of localized invasion and distant metastases following detection and therapy (2). Patients with restricted or localized invasion have only a 30% cure rate. It is particularly difficult to enhance the survival rate, because oral cancer is rarely identified in its early stages (2-4).
Cancer stem cell (CSC) theory has received much of attention (5-8). CSCs are a type of cell found in malignant tissue that may both grow tumors and maintain self-renewal potential this characteristic is frequently exhibited by embryonic stem cells (ESCs) (9-11). These cell populations have a high tumorigenic capacity and are expected to contribute significantly to cancer's biological features, such as rapid growth, invasion, and metastasis (9).
Several cancers have an extended pre-cancerous stage, which is histological distinct from the cancerous stage (12,13). The precancerous stage is critical in cancer formation because massive heterogeneous alterations can still be reversed (12-15). This status must be defined as precancerous stem cells (pCSCs), not cancer stem cells (CSCs), because pCSCs have the ability to promote (malignant transformation) or regress (benign differentiation) (16). The study of pCSCs in precancerous lesions has implications for malignant growth avoidance and early recognition.
One of the few recognised theories argues that

CSCs form due to epigenetic or genetic changes in resident tissue stem cells (17). The discovery of these CSCs in tumor tissue is another area of study.
Several protein markers, including ALDH1, OCT4, CD44, CD133 and SOX2, have been studied as possible cancer stem cell indicators in OSCC samples and cell lines (17-22).
The POU5F1 gene encodes a human protein known as OCT4 or POU domain, class 5, transcription factor 1 (POU5F1). It was first identified as a DNA-binding protein and can be encountered in totipotent embryonic stem cells, germ cells (23), and pluripotency.
OCT4 isn't just an expert controller of pluripotency that controls lineage commitment, yet it is likewise the first and most perceived marker utilized for the distinguishing proof of totipotent embryonic stem cells. It has been associated in tumourigenesis of adult germ cells (23).
This research was intended to investigate the immunohistochemical expression of OCT4 in formalin fixed paraffin embedded tissues of oral epithelial dysplasia and OSCC and compare it to normal oral mucosa.

MATERIAL AND METHODS

Material

The study included 80 cases clinically classified as normal oral mucosa (16 cases), OED (16 cases), and oral squamous cell carcinoma (48 cases) from the Cranio-Maxillofacial and Plastic Surgery Department at the Faculty of Dentistry, Alexandria University. The Oral Pathology Department at Alexandria University's Faculty of Dentistry confirmed the cases histopathologically.

Inclusion criteria

All patients of both sexes have been histologically proven epithelial dysplasia or squamous cell carcinoma of the oral mucosa. Some specimens were recent, and others were archival.

Exclusion criteria

Patients suffering from active infection, autoimmune diseases and inflammatory diseases were excluded from the study as well as patients who previously received any cancer therapy.
Patients were given both oral and written information about the study protocol and were required to sign informed consent forms to participate in the study. Biopsies were obtained from the oral lesions.
Streptavidin immunohistochemical universal kit and a monoclonal antibody for OCT4 were used.
Sixteen normal oral mucosa biopsies which were be excised in alveloplasty and alveolectomy were served as negative control.

Methods

1) Sample size calculations

Sample size was calculated expecting 5% alpha error and 80% study power. The mean OCT4 gene expression in OSCC patients was 3.46 ± 0.94 in grade I, 4.47 ± 1.76 in grade II, and 8.90 ± 4.61 in grade III (1). Based on the difference between independent means using F test and the highest SD = 4.61 to ensure power, a sample of 14 patients per group was required, yielding an effect size of 0.512. This has been enhanced to 16 to compensate for processing errors. Total sample = Number per group x Number of groups = 16 x 5 = 80 patient's samples.

2) Clinical evaluation

Patients' clinical data was collected including age, gender, location of lesions, medical and dental history. The included cases were those diagnosed as oral epithelial dysplasia or OSCC and who did not previously receive any cancer therapy.

3) Histopathological examination

Biopsies from tumour tissue and negative control samples were stored in 10% neutral buffered formalin, then handled and embedded in paraffin wax utilizing standard techniques and stained with hematoxylin and eosin for microscopic analysis

4) Immunohistochemical examination

The technique used in the labeled Strept-Avidin Biotin-peroxiadase complex method (LSAB).

a) Poly-L-lysine coated glass slides were used to mount 4-5 µm thick serial sections from the same tissue block. Two sections were gotten for positive test slides, and a third for negative control by deleting the primary antibody.

b) Tissue sections were deparaffinized in xylene, rehydrated in graded ethanol, and treated with 0.3% hydrogen peroxide to inhibit endogenous peroxidase.

c) Specimens were rinsed with diluted normal rabbit, mouse, or goat serum before incubating with the OCT4 primary antibody. (Primary antibody from Abnova, Gene ID: 5460|18999|294562, Code PAB12773, Rabbit anti-human polyclonal raised against synthetic peptide of POU5F1, no specific isoform). The secondary detection kit (Abcam) code ab64261 rabbit specific HRP/ DAB were used. Formalin fixed samples and paraffin embedded tissue sections were dewaxed using xylene, and progressively hydrated. Antigen retrieval was done by pressure cooking using citrate buffer for 20 minutes. The primary anti-OCT4 antibody was diluted as 1:200 using a reducing dilution buffer (Abcam code ab64211) and kept warm at room temperature for 30 minutes.

d) A biotinylated link antibody and labeled streptavidin-biotin-peroxidase complex were used to bind the primary antibody. Incubation in substrate-chromogen solution followed by Mayer's hematoxylin counter stain finished the staining process is nuclear .

e) OCT4 On an image analyzer computer system, immuno-expression was assessed utilizing this Leica Qwin 500 program. The apparatus comprises of a light microscope linked to a

microcomputer capable of processing the digital image with high speed.

Statistical analysis

The collected information was analysed using SPSS 17 (Statistical Package for Scientific Studies) on Windows.

The variations in the mean area percent and mean optical density of oct-4 immunoexpression between more than two groups, such as different grades of OSCC and OED, was calculated using the analysis of variance (ANOVA) test.

A P-value of less than 0.05 was regarded very significant. The values are expressed as a mean ± SD (standard deviation).

RESULTS

In the current research, 80 patients with epithelial dysplasia and oral squamous cell carcinoma were included. Sixteen cases are evenly divided across the research groups (16.6%).

The patients' ages ranged from 26 to 70, with a mean age of 40 years. Thirty cases (45%) were males, while fifty cases (54%) were females, for a ratio of 1:1.

I. Histopathological results

Sixteen cases of oral epithelial dysplasia (Seven mild, eight moderate and one severe) included in the current study. The mild cases showed alterations confined mainly to the basal and parabasal layers that showed hyperchromatic and slightly pleomorphic nuclei (Figure 1A).

The eight cases of moderate epithelial dysplasia demonstrated dysplastic changes involvement from the basal layer to the midportion of the spinous layer. Dysplastic changes were nuclear hyperchromatism, pleomorphism, and loss of polarity of the basal cells (Figure 1B).

The one case of severe dysplasia showed dysplastic changes from the basal layer to a level above the midpoint of the epithelium. This case revealed almost all criteria of dysplasia such as pleomorphic and hyperchromatic nuclei with prominent nucleoli and increase normal and abnormal mitotic figures.

Out of the 48 oral squamous cell carcinoma cases studied, 16 had well differentiated squamous cells clustered as islands of diverse shapes and sizes, with keratinous pearls inside. The nuclei of malignant epithelial cells varied in shape and size, and they were larger than those of normal epithelium. They also exhibited varied degrees of hyperchromatism, pleomorphism, increased nuclear cytoplasmic ratio, and normal mitosis (Figure 2A).

The 16 cases of moderate differentiated were included in this study, showed islands and cell nests of neoplastic atypical epithelial cells penetrated the tumoral stroma. Nuclei of neoplastic cells had various shapes and sizes, the vast majority of them hypochromic with enormous nucleoli. Tumor cells showed atypical mitotic figures (Figure 2 B).

The 16 cases of poorly differentiated included in this study, showed cords, islands of malignant epithelial cells of various shapes and sizes. These cells are large and bizarre showing extreme degrees of pleomorphism and nuclear hyperchromatism, increase nuclear cytoplasmic ratio, increase abnormal mitotic figures and loss of cellular adhesion (Figure 2 C).

II. Immunohistochemical results

OED and oral squamous cell carcinoma tissues were stained with OCT4 and examined under a microscope as part of the current immunohistochemistry investigation.

The intensity of OCT4 immunostaining was calculated in terms of mean area percentage and mean optical density using the Computer Image Analyzer System.

Pattern of OCT4 immunostaining in normal oral mucosa (control group)

The oral mucosa used in this research demonstrated negative immunoreactivity for OCT4 in the epithelial cells of various layer.

Pattern of OCT4 immunostaining in epithelial dysplasia

All the cases of epithelial dysplasia included in this study showed negative immunoreaction for oct-4 (Figure 3).

Pattern of OCT4 immunostaining in oral squamous cell carcinoma

Out of the 48 examined OSCC cases, 16 were of well differentiated type. All the 16 well differentiated cases showed immunonegativity for OCT4(Figure 4).

The 16 cases of moderate differentiated type which were included in the present study showed weak immunopositivity for OCT4 (Figure 5) while the 16 cases of poorly differentiated type showed strong immunopositivity for Oct-4 (Figure 6 A & B).

The image analyzer computer system was used to correlate the mean area percentage and mean optical density of OCT4 in all cases of OSCC and OED.

The F test (ANOVA) revealed a highly significant difference ($p<0.001$) in the mean OCT4 area percent between oral epithelial dysplasia and different grades of OSCC; however, there was no statistically significant difference in the mean optical density among the study groups (Table 1,2).

Table (1): Comparison between the different studied groups according to Optical

	Dysplasia (n = 16)	Well scc (n = 16)	Mod scc (n = 16)	Poorly scc (n = 16)	F	p
Optical						
Min. – Max.	65.41 – 71.76	63.79 – 71.76	60.85 – 70.58	71.85 – 80.59		
Mean ± SD.	67.97 ± 2.73	67.05 ± 3.41	65.07 ± 4.08	77.18 ± 3.82	36.834*	<0.001*
Median (IQR)	66.76 (65.4 – 71.7)	65.59 (63.8 – 71.8)	63.77 (60.9 – 70.6)	79.09 (71.9 – 80.6)		
p_1		0.880	0.105	<0.001*		
Sig. bet. grps.		p_2=0.399,p_3<0.001*,p_4<0.001*				

IQR: **Inter quartile range** SD: **Standard deviation**
F: **F for One way ANOVA test**, Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Tukey)**
p: p value for comparing between the studied groups
p_1: p value for comparing between **Dysplasia** and each other group
p_2: p value for comparing between **Well** and **Mod**
p_3: p value for comparing between **Well** and **Poorly**
p_4: p value for comparing between **Mod** and **Poorly**
*: Statistically significant at $p \leq 0.05$

Table (2): Comparison between the different studied groups according to Area %

	Dysplasia (n = 16)	Well scc (n = 16)	Mod scc (n = 16)	Poorly scc (n = 16)	F	p
Area %						
Min. – Max.	1.78 – 4.53	7.88 – 11.45	19.84 – 23.19	32.52 – 36.89		
Mean ± SD.	3.51 ± 1.23	9.69 ± 1.46	21.92 ± 1.49	34.65 ± 1.79	1344.45*	<0.001*
Median (IQR)	4.23 (1.8 – 4.5)	9.73 (7.9 – 11.5)	22.74 (19.8 – 23.2)	34.56 (32.5 – 36.9)		
p_1		<0.001*	<0.001*	<0.001*		
Sig. bet. grps.		p_2<0.001*,p_3<0.001*,p_4<0.001*				

IQR: **Inter quartile range** SD: **Standard deviation**
F: **F for One way ANOVA test**, Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Tukey)**
p: p value for comparing between the studied groups
p_1: p value for comparing between **Dysplasia** and each other group
p_2: p value for comparing between **Well** and **Mod**
p_3: p value for comparing between **Well** and **Poorly**
p_4: p value for comparing between **Mod** and **Poorly**
*: Statistically significant at $p \leq 0.05$

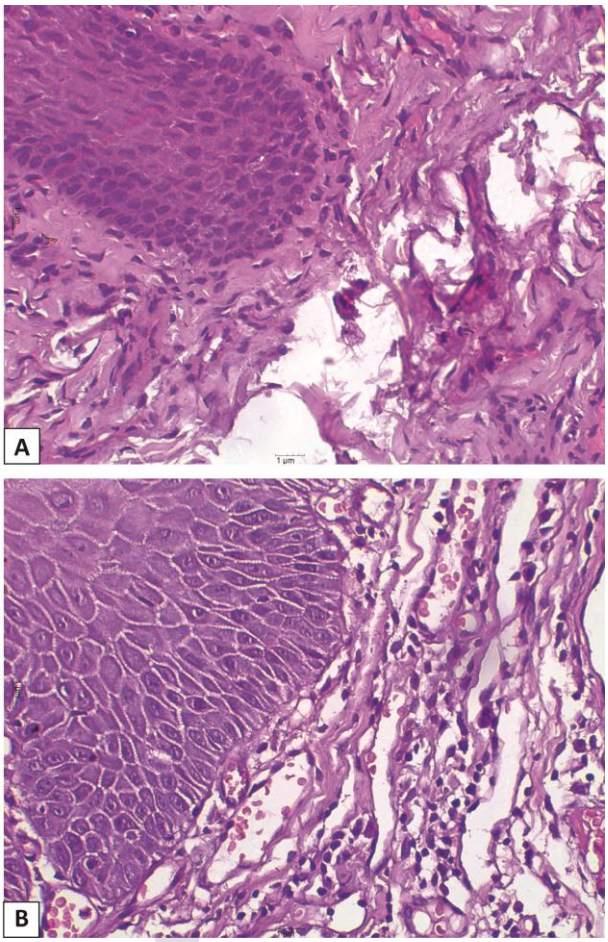

Figure 1: A- mild epithelial dysplasia revealed bulbous rete process with basilar hyperplasia (H&E x 400).
B- moderate epithelial dysplasia revealed nuclear hyperchromatism, pleomorphism, and loss of polarity of basal cells (H&E x 400).

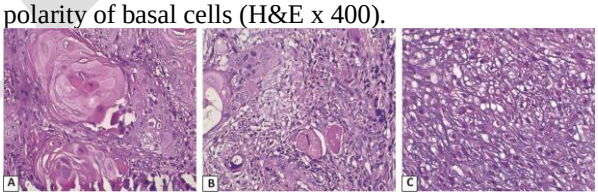

Figure 2: A- well differentiated SCC showed keratin pearls and epithelial pearls with varying degrees of hyperchromatism, pleomorphism and normal mitotic figures (H&E x 400).

B- moderate differentiated SCC showed islands and cell nests of neoplastic atypical epithelial cells with pleomorphic and hypochromic nuclei with large nucleoli and atypical mitotic figures (H&E x400).

C- poorly differentiated SCC showed cords, islands of malignant epithelial cells of various shapes and sizes. Large and bizarre cells with extreme degrees of pleomorphism and nuclear hyperchromatism, increase nuclear cytoplasmic ratio, increase abnormal mitotic figures and loss of cellular adhesion were detected (H&E x 400).

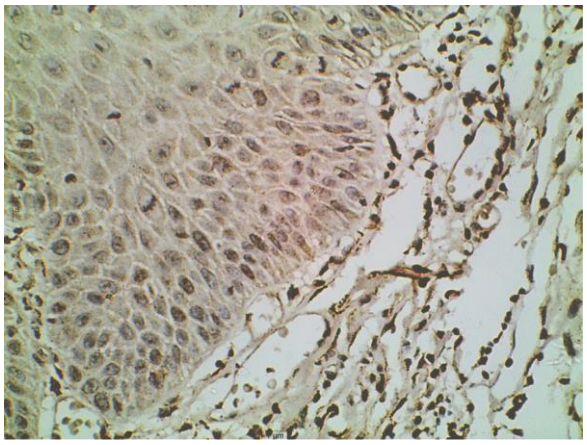

Figure 3: Immunohistochemical image demonstrated moderate epithelial dysplasia with negative immunoreaction to Oct-4 (x 400).

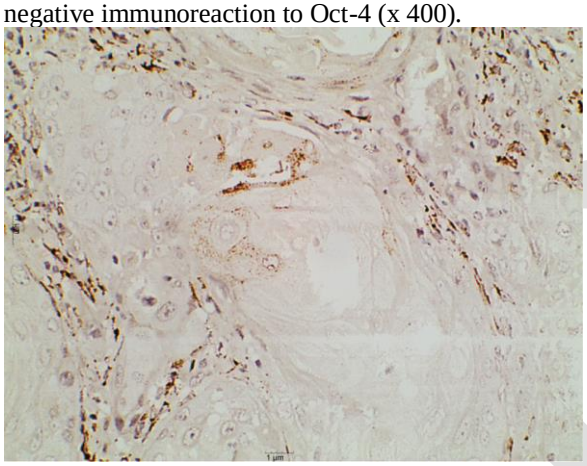

Figure 4: Immunohistochemical image revealed well differentiated SCC with immunonegativity for Oct-4 (x 400).

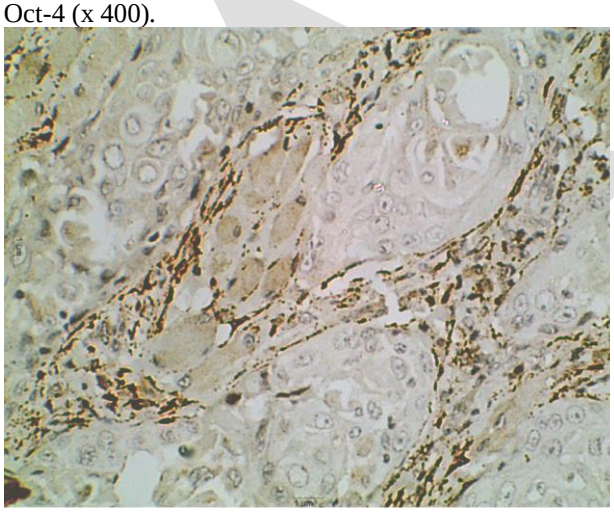

Figure 5: Immunohistochemical image revealed moderate differentiated SCC with weak immunopositivity for Oct-4 (x 400).

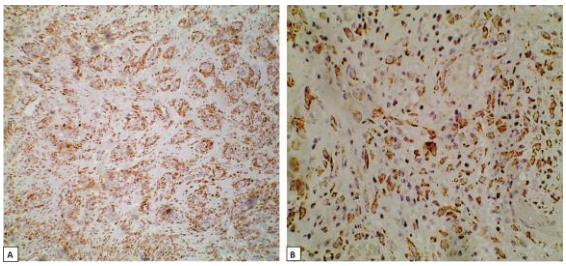

Figure 6: Both A& B are immunohistochemical image revealed poorly differentiated SCC with strong immunopositivity for Oct-4 (x 400).

DISCUSSION

It is widely accepted that the formation of cancer of the oral cavity is a multifaceted process involving numerous hereditary traits that impact oncogenes' and tumour suppressor genes' typical functions. Of all malignant tumours of the head and neck, oral cancer makes up 48%, of which 90% are squamous cell carcinomas.

The incidence of OSCC increase with age, with the majority of cases appearing over the age of 40 (24). Histopathological examination is required to confirm the diagnosis. Many inaccurate diagnoses of histological stages of SCC are caused by insufficient biopsy samples or the difficulty of establishing a diagnosis based on histopathological results using routine hematoxylin-eosin staining (24). Biopsy and histological analysis, along with additional research, are used in the ultimate diagnosis of oral carcinomas.

Although the cancer stem cell idea has been demonstrated to work for other cancers, additional investigation is needed to determine how CSCs contribute to the onset and progression of OSCC. Major CSC transcription factors, including as OCT4, were expressed in both oral squamous cell carcinoma and normal oral mucosa, according to research (25).

Octamer-binding protein 4, the key of cancer stem cell marker engaged with the maintenance of pluripotency and self-renewal in undifferentiated embryonic stem (ES) cells (26). This marker could reinvent human somatic fibroblasts into embryonic stem cell-like pluripotent cells (PSC) (27). The molecular processes underlying OCT4's upregulation in OSCC-CSCs remain unclear.

Since the present work aimed to evaluate the expression of OCT4 in OED and different grades of OSCC affecting the oral cavity, the current investigation concluded that OCT4 exhibited no significant influence on the identification of epithelial dysplasia, however OCT4 showed a significant effect on the identification of different stages of squamous cell carcinoma.

These observations can be credited to the presence of stem cell-like markers in poorly differentiated, more aggressive tumor morphologies. The association between stem cell marker expression and tumor differentiation status highlights the

concept that oral cancer stem like cells (OC-SLCs) may drive the growth and aggressiveness of OSCC, perhaps impacting treatment responses and outcomes.

The current investigation tracked down a definite connection between OCT4 expression and the differentiation status of OSCC. Specifically, we identified greater OCT4 immunopositivity in moderately to poorly differentiated OSCC patients, indicating that OCT4 expression correlates with poorly differentiation and, perhaps, combative form of the tumour.

This conclusion is consistent with the findings of Ghazi *et al.,*who demonstrated a substantial overexpression of OCT4 in OSCC compared to OED, with the upregulation considerably more prominent in higher grades of OSCC. This parallel highlight the potential of OCT4 as a marker for tumor growth and its relationship with histological features that indicate an unfavorable prognosis (25).

Also, Chiou *et al*. agreed with our results in which they enriched oral cancer stem like cells (OC-SLC) from OSCC, revealing that these cells exhibited high expression levels of stem cell markers, including OCT4 , which are associated with stemness and self-renewal capabilities. Our histopathological findngs, which indicated increased OCT4 immunopositivity in moderately to poorly differentiated OSCC cases, complement these observations by linking the presence of stem cell-like markers to less differentiated, more aggressive tumor phenotypes. The correlation between stem cell marker expression and tumor differentiation status underscores the hypothesis that OC-SLCs may drive the progression and aggressiveness of OSCC, potentially influencing treatment responses and outcomes (28).

Our findings showed that tumour tissue expresses the stem cell marker OCT4, but not adjacent non-tumor tissue. This is corresponds with earlier findings that the OCT4 protein is expressed in human cancer tissues, such as the stomach (29).

In contrast, BR *et al*. stated that OCT4 expression was detected in 80% of OED and 75% of OSCC samples in comparison to 40% positivity in normal oral mucosa, which conflicts the results of the current investigation in which the influence of oct-4 in OSCC was greater than in OED (30).

Furthermore, Qiao *et al*. isagreed with the results of the current study. They reported 70% positivity in patients with potentially malignant diseases (PMD) and 60% positivity in OSCC samples (31).

This conflicts with *et al.* who found no significant difference in OCT4 expression between tumor and tumor-adjacent normal tissue (32).

Fu *et al*. demonstrated the immunohistochemistry expression of OCT4 in OSCC samples, corresponding tumor adjacent normal tissue (CTAN), and regular uvula epithelial cells was much greater in normal and CTAN tissues compared to tumor tissue. Higher expression of OCT4 in tumor-near normal tissue could imply that the cells near to the tumor tissue are undergoing early molecular changes comparable to pre-invasive lesions (33).

Also, Tsai *et al*.discovered that OCT4 expression wasn't significant between different grades of OSCC (34).

CONCLUSION

OCT4 could be used as a marker to regulate tumour invasion potential, signalling the progression from dysplasia to malignancy.

It could be relied on as individual prognostic markers to determine prognosis. OCT4 is related with a poor prognosis, making it a viable individual prognostic biomarker.

By using this marker to identify the CSC population in OPMDs or OSCCs early on, it may be possible to differentiate between high-risk OPMD cases and future OSCC cases that require careful surveillance.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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