



## Original Research Article

## SOX2 expression inversely correlates with histological grading, nodal metastasis and clinical staging of Oral Squamous Cell Carcinoma

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## ABSTRACT

Oral squamous cell carcinoma (OSCC) accounts for 95% of entire oral malignant tumors. The development as well as the distribution of many tumors such as OSCC is driven by cancer stem cells (CSCs). Sex determining region Y-box 2 (SOX2) is a functional CSCs marker; it is a transcription factor coding gene, present at chromosomal 3q26.33 area. The current study was conducted to evaluate SOX2 immunohistochemical expression in OSCC in addition to correlation of its expression in various histologic grades and the existing clinical parameters. Paraffin blocks tumor tissues from forty patients of OSCC were utilized to assess SOX2 immunohistochemical expression. The present study demonstrated that SOX2 expression displayed highly significant inverse association with histologic differentiation of OSCC (P=0.001), clinical stages (P=0.007) and lymph node metastases (LNM) (P=0.035). The current study recommended that, SOX2 expression might be utilized as a prognostic predictor for OSCC, and might help in establishment of the diagnosis as well as proper selection of therapeutic modality of cancers.

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### 1. Introduction

OSCC is the commonest tumor in the oro-facial region accounts for 95% of overall oral malignant tumors, with increasing incidence in the recent years in developing countries.<sup>1</sup> The disease is challenging as it still represents a high morbidity and mortality rate with a recurrence rate of 32.7% and 40%-50% with disease advancement.<sup>2</sup> OSCC may be developed due to several causes, it is induced by association of genetic together with environmental factors. Major predisposing factors are tobacco smoking, consumption of alcohols and Human Papilloma Virus.<sup>3</sup> CSCs are origin of multiple types of tumors, such as OSCC, they have an important role in carcinogenesis owing to their capability for self-renewal as well as differentiation.<sup>4</sup> Sex determining region y-box 2 (SOX2) is a transcription factor coding gene, present at chromosomal 3q26.33; it regulates cell self-renewal as well as differentiation processes in

pluripotent stem cells.<sup>5</sup> SOX2 has a main role in multiple signal transduction pathways, normal development, and multiple pathologic processes such as cellular proliferation, differentiation, invasion, tumorigenesis, anti-apoptosis, and chemoresistance.<sup>6,7</sup> In addition, it is considered a functional marker of CSCs as it serves as a prognostic predictor in multiple tumors such as head and neck squamous cell carcinoma.<sup>8</sup> The present study was conducted to evaluate the SOX2 immunohistochemical expression in OSCC and its relation to clinicopathological variables.

### 2. Materials and Methods

#### 2.1. Patients

Forty paraffin embedded OSCC tissue blocks were gathered in the period from 2013 to 2017 from archives of Oral pathology Department, Faculty of Dentistry, Pathology Department, Faculty of Medicine and, Oncology Center (OCMU), after the approval by Ethical Committee. The

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accessible data were gathered in a retrospective manner by using software retrospective database from the tumor records as regards age, gender, tumor site, clinical manifestation, TNM staging system and tumor recurrence. Entire patients of oral SCC were assessed by histological evaluation and graded as regards world health organization (WHO) grading systems 4th edition.<sup>9</sup>

## 2.2. Immunohistochemistry

IHC in this study was conducted on forty paraffin embedded OSCC samples. It was conducted on about 4 $\mu$ m-thick paraffin sections on heat fixed positively charged slides. Deparaffinization, rehydration and epitope exposure were performed with use of 0.01 M citrate buffer (pH 6.0) for 10 minutes in microwave. Activity of endogenous peroxidase was blocked by 3% hydrogen peroxide incubation for 10 min. All sections were rinsed with phosphate buffer saline (PBS) and incubated for one hour at room temperature with the primary antibodies directed against: monoclonal mouse anti-human SOX2 antibody, dilution by 1:50 (required from Biocare Medical, USA code BC36). Standard avidin-biotin-peroxidase technique was applied using diaminobenzidine (DAB, 5 minutes incubation) for visualization and hematoxylin for counterstaining (30 seconds). Glioblastoma tissue sections were immunostained as positive controls. Appropriate negative controls, consisting of histologic sections processed without the addition of primary antibody, were prepared.

## 2.3. Assessment of SOX2 expression

The sections were examined under a light microscope (Olympus-BX21). A dark brown staining in the nucleus of epithelial cells was considered positive for the expression of SOX2. The expression of the biomarker was analyzed in a semi-quantitatively by two observers.

## 2.4. Scoring system for SOX2

The immunohistochemical expression pattern of SOX2 was evaluated according to the criteria given by Ge et al.<sup>10</sup> and Pradhan et al.<sup>11</sup> where the percentage of positive tumor cells was assessed. Five areas in the whole tumor sections were selected for all patients. The percentages of positive tumor cells in all five fields were summed up and the mean of the percentages was recorded. Score 0=Negative Expression, Score 1 (Weak expression)  $\leq 25\%$  cells were positive, Score 2 (Moderate Expression) = 26–50% cells were positive and Score 3 (Strong expression)  $> 50\%$  of cells were positive.

## 2.5. Statistical analysis

Computer-fed data were analyzed using IBM Corp. SPSS (International Business Machines Corporation Statistical Product and Service Solutions), released 2013 for Windows,

Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using numbers and percentages. Quantitative data were described using mean $\pm$ SD (standard deviation) after testing normality. Data was assessed by using the computer program SPSS version 19. Comparison and correlations between groups were performed by utilizing Chi-Square test and Pearson correlation in which p value less than 0.05 denotes significant changes.

## 3. Results

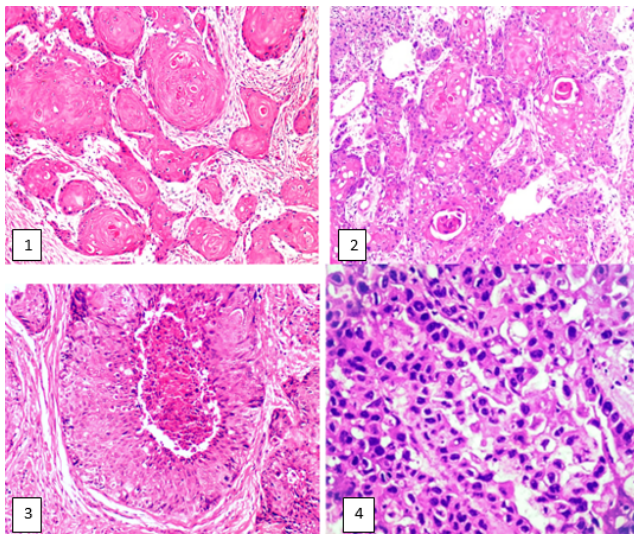
The present study was conducted on forty OSCC patients. The age of the patients ranged from 20-87 years with an average age of 58 $\pm$  15 and high tendency of occurrence among old age (75%) were above 50 years. The percentage of male to female (M/F) ratio was 1:1. The tongue was the commonest site (40%) then lips 8 (20%) patients, seven patients (17.5%) developed in the cheek mucosa, four patients (10%) in the mandible, the floor of the mouth two patients (5%) and the maxilla two patients (5%) were recorded and only one patient (2.5%) was detected in the hard palate. The clinical manifestation of OSCC was often non-healing ulcers (55%) whereas the remaining 18 patients (45%) were presented as masses (Table1). According to WHO classification system 4<sup>th</sup> edition (9), patients were classified as 20 patients (50%) well differentiated which represented most patients, whereas 14 patients (35%) had moderate differentiated SCC and six patients (15%) had poor differentiated SCC (Figure 1).

As regard TNM clinical staging, 12 patients were clinically categorized as stage I, Stage II presented in 8 patients, Stage III presented in 12 patients and lastly 8 patients presented clinically as stage IV.

The current study revealed that, 24 patients (60%) were free from LNM and 16 patients (40%) had LNM. Between OSCC patients of the current study only ten patients (25%) had tumor recurrence and the remaining 30 patients (75%) had complete cure with no tumor recurrence. As regard distant metastases, only three patients (7.5%) were recorded to have distant metastases and 37 patients (92.5%) were free.

Concerning SOX expression, Low SOX2 expression was recorded in the current study in 13 patients; moderate SOX2 expression was recorded in eight patients whereas high SOX2 expression was recorded in 19 patients (Figure 2 ). There was no statistically significant association between SOX2 expression and age, sex, clinical manifestations or tumor recurrence of the OSCC patients whereas there was significant difference among SOX2 expression and LNM (p=0.0001), high SOX2 expression was noticed in 79.1% of the patients with no LNM whereas low SOX2 expression was noticed in 68.7% in patients with LNM. In addition, there was significant strong inverse association among histologic differentiation of OSCC patients and SOX2 expression (p=0.001, r=-0.621) as high SOX2 expression

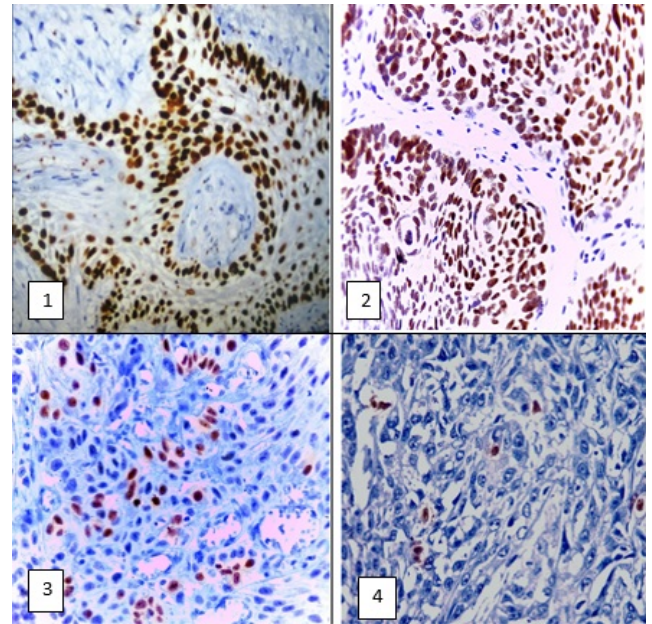
was noticed in 75% of the well differentiated OSCC patients whereas low SOX2 expression was noticed in 100% of the poorly differentiated OSCC patients. Concerning clinical TNM staging, there was also significant strong inverse association between clinical stages of OSCC patients and SOX2 expression ( $p=0.007$ ,  $r= -0.850$ ), high SOX2 expression was detected in 91.5% of stage I OSCC patients whereas low SOX2 expression was noticed in all patients in the stage IV OSCC (Table 2). Lastly, SOX2 expression demonstrated significant difference with distant metastases of OSCC patients ( $p=0.03$ ), 51.5% of the patients that revealed no distant metastases had high SOX2 expression whereas entire patients presented with distant metastases had low SOX2 expression (\$).



**Fig. 1:** Hematoxylin and Eosin of OSCC, variable histological grades: Photomicrograph of well differentiated OSCC showing cell nests and keratin pearls (x100) (1). Photomicrograph of moderately differentiated OSCC showing cell nests, keratin pearls, forming cords and strands with nuclear hyperchromatism and pleomorphism (x 100) (2). Photomicrograph of moderately differentiated oral SCC showing area of necrosis within the cell nest, moderate degree of nuclear pleomorphism and hyperchromatism ( $\times 200$ ) (3). Photomicrograph of poorly differentiated OSCC forming cords and strands, with predominant hyperchromatism, pleomorphism and mitosis (x400) (4).

#### 4. Discussion

Despite advances in our knowledge of the epidemiology and pathogenesis of head and neck SCC and its treatment modalities, survival rates of patients have not improved over the past four decades.<sup>1</sup> So, detailed understanding of the biology of this tumor is needed because of the considerable clinicopathological heterogeneity among tumors. The tumor heterogeneity and complexity of oral cancer can be comprehensible successfully by a close examination of molecular markers, events and pathways occurring in the



**Fig. 2:** IHC of SOX2 in OSCC: Photomicrograph of well differentiated OSCC showing high SOX2 expression (x400) (1). Photomicrograph of moderately differentiated OSCC showing high SOX2 expression (x400)(2). Photomicrograph of moderately differentiated OSCC with moderate SOX2 expression (x400) (3). Photomicrograph of poorly differentiated OSCC showing low SOX2 expression (x400) (4).

tumor tissue.<sup>3</sup>

Recently, it has been anticipated that tumors contain a small population of cells CSCs that have genomic signatures similar to embryonic stem cells, which drive cancer development and spread. SOX2 is considered one of the key transcription factors that keep self-renewal and pluripotency of embryonic stem cells.<sup>12</sup>

It has been found that SOX-2 assists as a link between malignancy and “stemness”.<sup>13</sup> Overexpression of SOX2 in SCCs of different organ sites is due to amplification of the gene at 3q26.33 region, suggesting that SOX2 was involved in SCC carcinogenesis. It was mainly expressed in the stratum basal, co-localizing with the region that contained stem cells.<sup>14</sup>

SOX2 activity was organized by several microRNAs, thus particular microRNAs might be controlled by SOX2, such as microRNA-145<sup>15</sup> and microRNA-302.<sup>16</sup> Also, it has a role in oncogenesis in OSCC by driving the epithelial-mesenchymal transition (EMT) an important factor in metastasis.<sup>17</sup>

Studies performed to date have shown that ectopic expression and amplification of SOX2 are associated with the development of cancers, such as lung and breast cancers; however, the role of SOX2 in cancer is still controversial.<sup>18</sup>

Various prognostic factors are recognized in OSCC patients such as TNM clinical stage, regional LNM, tumor

**Table 1:** Comparison between SOX2 expression and various clinical factors of the forty OSCC patients.

	Low SOX2 expression (n=13)	Moderate SOX2 expression (n=8)	High SOX2 expression (n=19)	P
Age				
Less than 50 years (10)	2(20%)	1(10%)	7(70%)	0.255
More than 50 years (30)	11(36.7%)	7(23.3%)	12(40%)	
Sex :				
Male (20)	5(25%)	5(25%)	10(50%)	0.535
Female (20)	8(40%)	3(15%)	9(45%)	
Site				
Tongue				
Others (cheek, mandible, maxilla, Floor of the mouth and Hard palate)	6 (37%) 7 (29.1%)	3(18.75%) 5 (20.8%)	7 (43.75) 12(50%)	0.489 0.85
Clinical presentation:				
Ulcer (22)	6(27.3%)	3(13.7%)	13(59%)	0.25
Mass (18)	7(38.9%)	5(27.8%)	6(33.3%)	
LNM				
Present (16)	11(68.7%)	5(31.3%)	0(0%)	0.0001*
Non (24)	2(8.3%)	3(12.5%)	19(79.2%)	
Tumor recurrence				
Present (10)	5(50%)	2(20%)	3(30%)	0.35
Non (30)	8(26.7%)	6(20%)	16 (53.3%)	
Distant metastases				
Present (3)	3(100%)	0(0%)	Zero%	0.035*
Non(37)	10(27%)	8(21.6%)	19(51.4%)	

\*: Significant statistically &lt; 0.05.

**Table 2:** Pearson correlation between SOX2 expression clinical TNM staging and various histologic grades among the patients.

	Total N=40	SOX2 expression			r	P
		Low expression (n=13)	Moderate expression (n=8)	High Expression (n=19)		
TNM staging						
Stage I	12	Zero%	1(8.5%)	11(91.5%)		
Stage II	8	0 (0%)	1(12.5%)	7(87.5%)		
Stage III	12	5 (41.5%)	6 (50%)	1(8.5%)	-0.850**	0.007*
Stage IV	8	8 (100%)	Zero%	Zero%		
Histological grades						
Well differentiation	20	3 (15 %)	2 (10%)	15 (75 %)		
Moderate Differentiation	14	4 (28.6 %)	6 (42.8 %)	4 (28.6 %)	-0.62**	0.001*
Poor differentiation	6	6(100 %)	Zero%	Zero%		

Significant statistically &lt; 0.05.

differentiation, tumor site, tumor invasion and therapeutic options.<sup>19</sup> Regarding the immunohistochemical findings, the current study demonstrated that there was no significant association among SOX2 expression and age, sex, site, clinical presentation and tumor recurrence of the OSCC patients. On the other hand, there was significant association among SOX2 expression and the existence of LNM, SOX2 expression was substantially high with lack of LNM but had low expression with the existence of LNM. This came in accordance with many preceding researches.<sup>12,20</sup>

On the other hand, Qiao and his colleagues.<sup>21</sup> recommended that, higher SOX2 expression had a statistically significant association with LNM; In addition, they considered that CSCs may be responsible for metastasis and associated with oral mucosa carcinogenesis. Also, Schröck et al.<sup>22</sup> suggested that SOX2 amplification is associated with poor prognosis of patients with OSCC (including patients with advanced LN metastasis), and increases resistance to chemotherapy. However, Züllig et al.<sup>20</sup> indicated that the heterogeneity of primary tumors may be one of the reasons for these controversial results and

recommended SOX2 to be a possible predictive marker for the absence of metastasis to the sentinel lymph nodes of the neck in early stages of OSCC.

Although, underlying association between the expression of SOX2 and LNM in OSCC remains unclear and still in need to be clarified.<sup>8</sup> So, additional studies underlying this association is required.

The present study demonstrated high significant and strong negative association between SOX2 expression and clinical tumor staging, high SOX2 expression was detected in the initial stages (I & II) of OSCC patients whereas low SOX2 expression was accompanied with advanced stages (III & IV). Both Fu et al.<sup>12</sup> and Züllig et al.<sup>20</sup> showed comparable results and confirmed that SOX2 expression was significantly accompanied with initial OSCC stages and was low in progressive stages.

Fu et al.<sup>12</sup> noticed that SOX2 expression level in oral malignant tissues showed significant reduction in comparison with normal tissues, they noticed the down-regulation of SOX2 expression in progressive stages of OSCC, and recommended that the initial high SOX2 expression may be reduced throughout OSCC advancement in a gradual manner.

On the other hand, Bhayekar et al.<sup>23</sup> results were against the current study, they demonstrated that SOX2 displayed a significant higher expression in advanced stages of OSCC. It was confirmed that SOX2 role in the tumorigenesis is related to its features included its action in the regulation of cell differentiation, proliferation, and survival in many important processes.<sup>16</sup>

SOX2 expression demonstrated statistically significant variation ( $p=0.001$ ) with various histologic grades of the OSCC patients, comparable to Michifuri et al.<sup>24</sup> They recommended that the SOX2 expression in the basal layers of intact epithelium, and at the tumor periphery might represent a more differentiated cellular phenotype than the less differentiated cells with more diffuse SOX2 staining pattern throughout the tumor. They also supposed that, SOX2 overexpression may occur early during OSCC carcinogenesis and may be lost as the disease progresses because of genetic inactivation. In contrast, Du and his colleagues<sup>25</sup> revealed that higher SOX2 expression has a significant correlation with higher histologic grade. They recommended that the SOX2 expression might have a role in conferring a less-differentiated tumor or inhibiting the capability for differentiation. Therefore, further studies are required to elucidate the function of SOX2. In addition, there were significant differences among SOX2 expression and distant metastases. In the same line, Bayo et al.<sup>26</sup> reported in their study on head and neck SCC that SOX2 inhibits tumor cell motility, invasive property of tumor cells for metastasis and supposed that low SOX2 expression serves as a predictor of treatment failure and poor survival. An association between SOX2 and a favorable prognosis has still not been demonstrated conclusively as, in contrast,

Yoshihama et al.<sup>27</sup> documented that high sox2 expression was associated with the presence of distant metastases and explain this by the role of SOX2 in stem cell maintenance and promotion of tumorigenesis.

Therefore, based on high SOX2 expression in initial stage of OSCC and the lack of LNM, SOX2 in our study might be utilized as a prognostic predictor for OSCC and might help in establishment of the diagnosis as well as appropriate selection of therapeutic modality for cancer. Moreover, additional researches with large numbers of patients are needed to identify the conflicting issues, as regards SOX2 role in OSCC advancement.

## 5. Source of Funding

None.

## 6. Conflict of Interest

None.

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