Immunohistochemical Expression of Antioxidants CypA in Oral Squamous Cell Carcinoma compared to Normal Oral Mucosa in Relation to Clinicopathological Parameters

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Abstract

Background: Cyclophilin A antioxidant protein (CypA) has been reported in several cancers including oral squamous cell carcinoma (OSCC) regarded the highest incidence cancer of oral cavity. However, the function of CypA in OSCC are far from being understood.

Objective: To evaluates the current research estimate the immunohistochemical expression of CypA in OSCC and normal corresponding mucosa and compare the results with clinicopathological parameters.

Patients and Methods: Forty OSCC cases and fifteen normal mucosae of formalin-fixed, paraffin-embedded tissue blocks were used and the sections samples collected during the period 0f 2016. Data concerning patient's age, gender, site, clinical presentation, clinical staging and histopathological grading were obtained and reviewed by two pathologists. Representative paraffin blocks were selected and section samples immunohistochemically evaluated using CypA marker.

Results: Females affected more than males and the tongue was the most site. CypA expression was high in OSCC than normal (p=0.001) with mean±Sd (55±24.8) (22±10.8). Significant relation found with tumor stage (p=0.03) and no relation observed with age, gender, site and tumor grade.

Conclusion: CypA expression was clearly present in OSCC, it increases with clinical stage of tumor and can be used as prognostic marker to diagnose and evaluate OSCC cases from normal.

Key words: Oxidative stress, Cyclophilin A, Squamous cell carcinoma.

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Introduction

Regarding malignant head and neck tumors, squamous cell carcinoma of the head and neck (HNSCC) is the most common epithelial neoplasia. It is highly incidence rate about of 500,000 and represent about 90% of all oralmalignancies [Salian *et al.*, 2016] , usually worse prognosis in cases. Each year, about 575000 new cases and 320000 deaths occur world-wide [Bhargava *et al.*, 2010]. Lesions in the oral cavity, larynx, and pharynx characterized as HNSCC. The survival of

HNSCC patients has not significantly improved in spite of development of several markers [Molinolo *et al*., 2009]. The clinicopathological characteristics are very important to traat the patients. In spite of that some people share the same features but variation still [Thomas *et al.*, 2005]

So, the biological behavior of the disease need to be clarify to prevent the tumorigenesis, progression and recurrence of the cancer. This study explains the expression of PRDX6 which was found previously highly expressed in various cancers [Qian *et al.*, 2012].

Sies in (1985, 1986) determine the term Oxidative stress by the imbalance between oxidation and antioxidants, "a disturbance in the prooxidant–antioxidant balance in favor of the former, leading to potential damage." The meaning appeared simple; however, it builds on descriptions about oxidation, antioxidants, and balance [Sies, 2015].

The simple explanation oxidation definition was not difficult: the species act to loss electrons, or oxygen gain , or loss of hydrogen. So when the one oxidized, other reduced.

An antioxidant is extra difficult to define. A general definition was put onward by Halliwell in 2004 : An antioxidant is any ingredient that, when present at low intensities as related with those of an oxidizable substrate, significantly delays or prevents the oxidation of that substrate [Halliwell, 2004] [Azzi *et al.*, 2004] [Levonen *et al.*, 2014]. As claimed above, the chemical terms are oxidation and reduction, and an antioxidant is evidently dissimilar from a reducing agent. A reducing agent may equal be a prooxidant if it reduces oxygen to free radicals or changes transition metal ions to lower oxidation states that react more readily with peroxides. Numerous biological reducing agents are Janus-faced (having two faces)

They can be anti- or prooxidants , depending on the levels of O2 and evolution metal ions around [Sies, 2015].

The peptidylprolyl isomerase A (PPIA), also acknowledged as cyclophilin A (CypA) , is an enzyme that is encoded by the PPIA gene on chromosome [7]. As a member of the peptidyl-prolyl cis-trans isomerase (PPIase) lineage, this protein catalyzes the cis-trans isomerization of proline imidic peptide bonds, which allows it to control many biological procedures, comprising intracellular signaling, transcription, inflammation, and apoptosis , [Wei *et al*., 2013] , [Hoffmann *et al*., 2014]. Because its various functions, PPIA has been concerned in a wide range of inflammatory diseases, including atherosclerosis and arthritis, and viral infections [Wei *et al.*, 2013] [Hoffmann *et al*., 2014].

In the past few years, PPIA expression is highly correlated with cancer pathogenesis, but the specific mechanisms remain to be elucidated. PPIA overexpression has been related with several malignancies [Huang *et al.*, 2013].

Several reports explain the role of CypA in cancer and shown that CypA is up regulated in malignances and is a key factor for malignant transformation and metastasis [Yang *et al*., 2007] [Qi *et al*., 2008].

In small cell lung cancer, overexpressed CypA stimulates cancer cell growth, whereas CypA knockdown slows down cancer cell growth [Howard *et al.*, 2005] .

CypA is complicated in assorted pathological processes of tumors development. Specifically, it has been reported that overexpressed CypA in many cancers: (1) associated with cancer proliferation, (2) control cell cycle progression, (3) prevents apoptosis, and (4) allow cell migration/invasion [Choi *et al*., 2007].

Patients and Methods

Fifty-five cases of formalin-fixed, paraffin- embedded (FFPE) tissue blocks (forty squamous cell carcinoma and fifteen normal oral mucosa) obtained from the achieves of department of oral pathology / college of Dentistry- Baghdad University, and some private laboratories were included in this study. Data concerning patient's age, gender, site, clinical presentation, clinical staging and histopathological grading were obtained from the associated reports. Tumor slides were reviewed by two pathologists, and the representative paraffin blocks were selected. Sections of 4-µm thickness was cut from each tissue block and mounted on positively charged slides (Esco, USA) to be stained with monoclonal antibodies to CypA antioxidant marker (Abcam ab126738). Positive plus negative tissue controls were involved into all immunohistochemical runs.

The slides were baked in hot air oven at 65°C overnight. Pieces were consecutively de waxed through a series of xylene, graded alcohol and water immersion steps. Drops of hydrogen peroxide block were added to slides were in a organized to use package (ab126738); All slides were followed by the submission of the primary antibodies with a dilution of 1:250. The slides were placed in the incubator for 1 h at 37°C and then kept at 4°C in a humid chamber overnight. Next day, after washing with PBS (Phosphate Bupher Solution), biotinylated antimouse IgG were applied to the segments, incubated and washed with a stream of PBS. Conjugated antibodies were imagined with DAB chromogen. Sections were counterstained with Mayer's hematoxylin for 1–2 min, dehydrated and mounted, all this laboratory procedure done the college of dentistry/ Laboratory of department of oral pathology.

Estimation of the Immunohistochemical result: The immunostaining grades were sightlessly understood using microscope by couple pathologists at power 400. Using Kinnuna and Lehtonen et al [Kinnula *et al*, 2002; Nordfors *et al*, 2007] criteria , the stain The slides were baked in hot air oven at 65°C overnight. Pieces were consecutively de waxed through a series of xylene, graded alcohol and water immersion steps. Drops of hydrogen peroxide block were added to slides were in a organized to use package (ab126738); All slides were followed by the submission of the primary antibodies with a dilution of 1:250. The slides were placed in the incubator for 1 h at 37°C and then kept at 4°C in a humid chamber overnight. Next day, after washing with PBS (Phosphate Bupher Solution), biotinylated antimouse IgG were applied to the segments, incubated and washed with a stream of PBS. Conjugated antibodies were imagined with DAB chromogen. Sections were counterstained with Mayer's hematoxylin for 1–2 min, dehydrated and mounted, all this laboratory procedure done the college of dentistry/ Laboratory of department of oral pathology.

Was evaluated. A semi quantitative scoring system was used to determine the amount of positive staining cells in cytoplasm. The percent of positive immunostained cells was categorized as follows: 0 = no stained cells; 1 = 1–25% positive cells; 2 = 26–50% positive cells; 3 = 51–75% positive cells; and 4 = more than 75% positive cells [Huang *et al*., 2011].

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences Version 23 (SPSS Inc) .

Results

As shown in table (1), males were slightly more frequent among healthy controls group 9 (60%). In addition, the highest proportion of controls were 40-59 years of age (66.7%).

The age of healthy controls ranged between 25 to 68 years of age and a mean +/- SD of 49 +/- 11 years of age.

As shown in table (2), females were slightly more frequent among cases group 29 (72.5%). In addition, the highest proportion of this study group were 40-59 years of age (42.5%). The age of cases group ranged between 19 to 81 years of age and a mean +/- SD of 54 +/- 15 years of age.

According to site distribution, Tongue was the most frequently reported site of tumor 16(40.0%), while maxillary alveolar ridge was the least frequently reported site 1(2.5%) figure(1).

The tumor size was less than 2 cm in 14(35%) of cases table (3), while it was exceptionally large (>4 cm) in 11(27.5%) of cases and invasive into adjacent area in 2(5%) of cases only. No lymph node involvement was observed in 19(47.5%) of cases, while it reached to the stage of N2 (single ipsilateral lymph node involvement 3 to 6 cm) in 5(12.5%) of cases. In about a quarter of cases 11(27.5%) the tumor was at Stage-I, while it reached to stage-IV in 6(15%) of cases only.

More than half 22(55%) of cases group had a well differentiated tumor,11(27.5%) were moderate, while 7(17.5%) of cases had a poorly differentiated tumor, (Figure 2).

The antioxidant tissue marker Cyclophilin A monoclonal was present in Cytoplasm (Figure 3,4,5,6). The mean percentage of positively stained cells with Cycilophilin A was significantly higher (p= 0.001) in OSCC group than healthy control group with mean±Sd (55±24.8) (22±10.8) respectively figure (7). In the same line, the median score of Cycilophilin A was significantly higher (p= 0.001) with (strong stain score 51-74%) in OSCC group than control group (weak stain score 1-25%) Table (4A and 4B).

As shown in table (5), there was no statistically significant difference in median score of CypA among the 3 age groups (<40, 40-59 and 60+ years of age) among subjects with oral SCC.

In addition, all the observed linear correlations between age and CypA was very weak and not significant statistically.

Similarly, the differences observed between males and females in median score of the CypA was too marginal and small in magnitude to be meaningful or statistically significant table (6).

In this study there was no statistical significant relation found regarding site distribution and the tongue was the most affected site (p= 0.48) table(7).

The observed difference in median cyclophilin A marker score, which was statistically significant between the tumor stages showed a weak negative (inverse) linear correlation which failed to show a statistically significant trend table (8).

As shown in table 9, cyclophilin A tissue marker scores showed no any obvious or statistically significant difference or trend with the degree of tumor differentiation (grade).

Validity of tested parameters in diagnosis of OSCC: The optimum cut-off value for cyclophilin A when used as a test to diagnose OSCC differentiating it from healthy controls is moderate or higher score, since it was associated with the highest accuracy (81.7%). In addition, this cut-off value is also the one associated with highest sensitivity (85%). Testing negative at this highly sensitive cut-off value (obtaining a marker score in the low category) would excluded a possible diagnosis of OSCC with 97.8% confidence in a clinical situation where the presence of the tumor is of low probability on clinical evidence (10% pretest probability). Testing positive at this cut-off value (obtaining a score of moderate or higher) would establish a possible diagnosis of OSCC with 76.1% confidence level in a clinical context with equal odds of having Vs not having the tumor (pretest probability of 50%, which is the case for a lab person dealing with a specimen for which he has no

clinical data about). The confidence in a positive diagnosis (real presence of OSCC) would increase to 96.6% in a clinical context where having the tumor is highly probable on other clinical evidence (pretest probability = 90%). Raising the cut-off value to the strong score or higher provides a test marker of perfect specificity (100%). Testing positive at this highly specific cut-off value (obtaining a marker score of strong or very strong category) would establish a possible diagnosis of OSCC with 100% confidence in any clinical situation, table 10.

Table (1): Frequency distribution of healthy controls group by selected variables.

		N	%
1	Gender		
	Female	6	40.0
	Male	9	60.0
	Total	15	100.0
2	Age (years)		
	<40	3	20.0
	40-59	10	66.7
	60+	2	13.3
	Total	15	100.0

Table (2): Frequency distribution of cases group (OSCC) by selected variables.

		N	%
1	Gender		
	Female	29	72.5
	Male	11	27.5
	Total	40	100.0
2	Age (years)		
	<40	7	17.5
	40-59	17	42.5
	60+	16	40.0
	Total	40	100.0

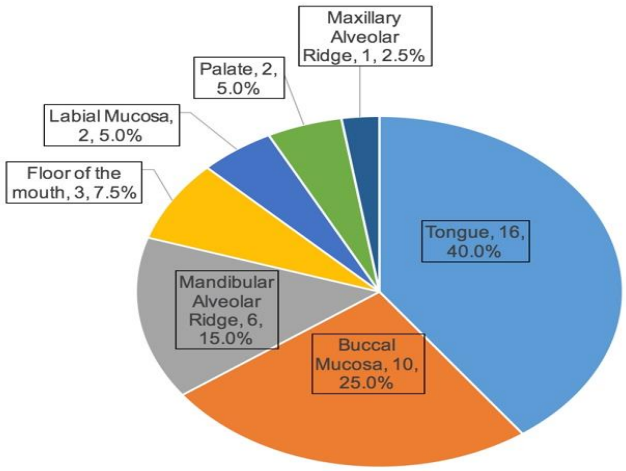

Figure (1): Pie chart showing the relative frequency of selected tumor locations (N=40).

Table (3): Frequency distribution of cases group (OSCC) by selected variables.

		N	%
1	T (Tumor Size)		
	≤ 2 cm	14	35.0
	2 - 4 cm	13	32.5
	> 4 cm	11	27.5
	Invasive to adjacent area	2	5.0
	Total	40	100.0
2	N (lymph Node involvement)		
	No LN involvement	19	47.5
	N1 metastasis to single ipsilateral LN ≤ 3 cm	16	40.0
	N2 metastasis to single ipsilateral LN 3 - 6 cm	5	12.5
	Total	40	100.0
3	Tumor stage		
	Stage-I	11	27.5
	Stage-II	6	15.0
	Stage-III	17	42.5
	Stage-IV	6	15.0
	Total	40	100.0

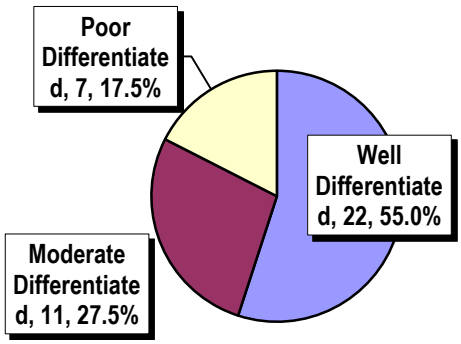

Figure (2): Pie chart showing the relative frequency of cases group by degree of tumor differentiation (N=40).

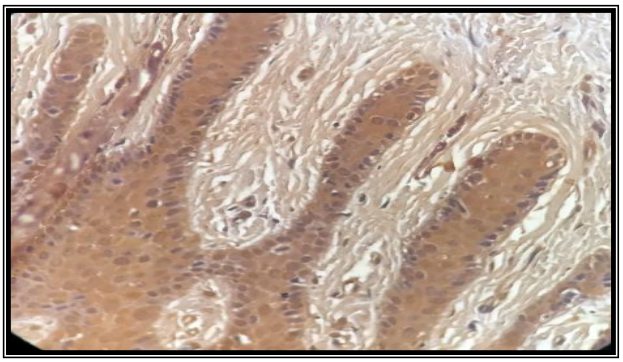

Figure (3): Photomicrograph showing Positive brown cytoplasmic expression of Cycilophilin A in normal oral mucosa (Original magnification X400).

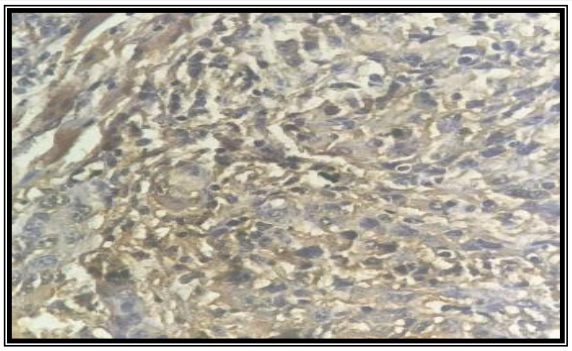

Figure (4): Photomicrograph showing Positive brown cytoplasmic expression of Cycilophilin A in poorly differentiated OSCC (Original magnification X400.

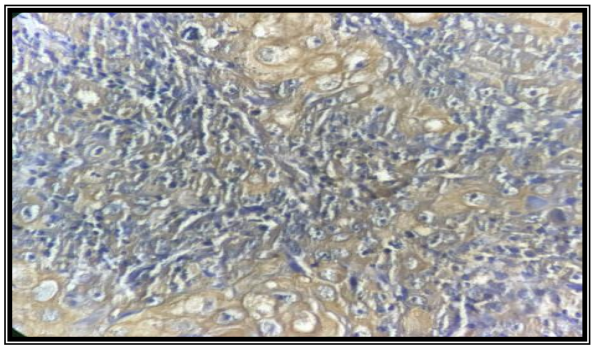

Figure (5): Photomicrograph showing Positive brown cytoplasmic expression of Cycilophilin A in moderately differentiated OSCC (Original magnification X400.

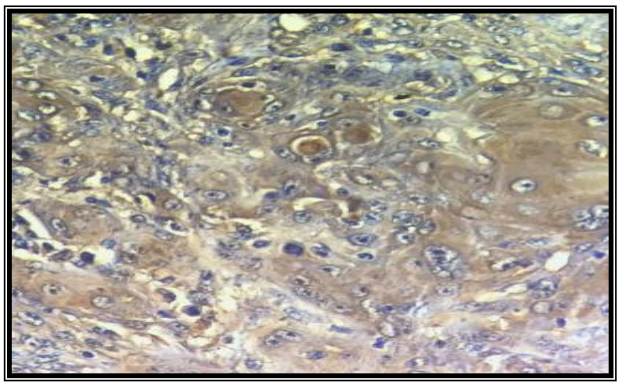

Figure (6): Photomicrograph showing Positive brown cytoplasmic expression of Cycilophilin A in well differentiated OSCC (Original magnification X400 .

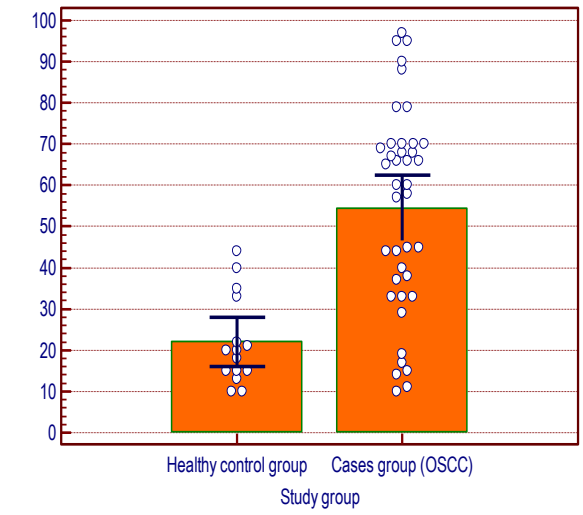

Figure (7): Dot diagram with error bars showing the case-control difference in mean (with its 95% confidence interval) cyclophillin A percent positive cells.

Table (4A): Case-control difference in mean percentage of cells positive for selected markers.

	Study group		
	Healthy control group	Cases group (OSCC)	P
cyclophilin A-percent positive cell			<0.001
Range	(10 to 44)	(10 to 97)	
Mean	22	55	
SD	10.8	24.8	
SE	2.8	3.9	
N	15	40	

Table (4B): Case-control difference in median value of selected marker scores.

	Study group				
	Healthy control group		Cases group (OSCC)		
cyclophilin A-score					<0.001
Negative (0%)	0	0.0	0	0.0	
Weak (1-25%)	11	73.3	6	15.0	
Moderate (26-50%)	4	26.7	11	27.5	
Strong (51-75%)	0	0.0	16	40.0	
Very strong (76-100%)	0	0.0	7	17.5	
Total	15	100.0	40	100.0	
Median	Weak (1-25%)		Strong (51-75%)		
Mean Rank	13.3		33.5		

Table (5): The median value of selected marker scores by age group among OSCC cases group.

	Age (years)						
	<40		40-59		60+		
	N	%	N	%	N	%	P
cyclophilin A-score							0.48[NS]
Negative (0%)	0	0	0	0	0	0	
Weak (1-25%)	2	28.6	3	17.6	1	6.3	
Moderate (26-50%)	2	28.6	2	11.8	7	43.8	
Strong (51-75%)	2	28.6	8	47.1	6	37.5	
Very strong (76-100%)	1	14.3	4	23.5	2	12.5	
Total	7	100	17	100	16	100	
Median	Moderate (26-50%)		Strong (51-75%)		Strong (51-75%)		
Mean Rank	17		22.7		19.7		
r=0.093 P=0.57[NS]							

Table (6): The median value of selected marker scores by gender among OSCC cases.

	Gender				
	Female		Male		
	N	%	N	%	P
cyclophilin A-score					0.45[NS]
Negative (0%)	0	0	0	0	
Weak (1-25%)	6	20.7	0	0	
Moderate (26-50%)	7	24.1	4	36.4	
Strong (51-75%)	11	37.9	5	45.5	
Very strong (76-100%)	5	17.2	2	18.2	
Total	29	100	11	100	
Median	Strong (51-75%)		Strong (51-75%)		
Mean Rank	19.7		22.7		

Table (7): Showing the relative frequency of selected tumor locations (N=40).

	Tumor site														
	Tongue		Mandibular Alveolar Ridge		Floor of the mouth		Buccal Mucosa		Labial Mucosa		Maxillary Alveolar Ridge		Palate		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	P
cyclophilin A-percent positive cell-categories															0.25 [NS]
Weak (1-25%)	2	12.5	1	16.7	1	33.3	2	20.0	0	0.0	0	0.0	0	0.0	
Moderate (26-50%)	1	6.3	3	50.0	1	33.3	3	30.0	1	50.0	1	100.0	1	50.0	
Strong (51-75%)	7	43.8	2	33.3	1	33.3	4	40.0	1	50.0	0	0.0	1	50.0	
Very strong (76-100%)	6	37.5	0	0.0	0	0.0	1	10.0	0	0.0	0	0.0	0	0.0	
Total	16	100.0	6	100.0	3	100.0	10	100.0	2	100.0	1	100.0	2	100.0	
Median	Strong (51-75%)		Moderate (26-50%)		Moderate (26-50%)		Moderate (26-50%)		Moderate (26-50%)		Moderate (26-50%)		Weak (1-25%)		
Mean rank	26.2		15.1		13.7		18.2		18.8		12		18.8		

Table (8): The median value of selected marker scores by tumour stage among OSCC cases group.

	Tumor stage								
	Stage-I		Stage-II		Stage-III		Stage-IV		
cyclophilin A-score									0.018
Negative (0%)	0	0	0	0	0	0	0	0	
Weak (1-25%)	1	9.1	0	0	3	17.6	2	33.3	
Moderate (26-50%)	4	36.4	1	16.7	2	11.8	4	66.7	
Strong (51-75%)	5	45.5	2	33.3	9	52.9	0	0	
Very strong (76-100%)	1	9.1	3	50	3	17.6	0	0	
Total	11	100	6	100	17	100	6	100	
Median	Strong (51-75%)		Very strong (76-100%)		Strong (51-75%)		Moderate (26-50%)		

Table (9): The median value of selected marker scores by degree of tumour differentiation among cases with OSCC.

	Degree of Differentiation (Grade)						
	Well Differentiated		Moderate Differentiated		Poor Differentiated		
	N	%	N	%	N	%	P
cyclophilin A-score							0.95[NS]
Negative (0%)	0	0	0	0	0	0	
Weak (1-25%)	4	18.2	2	18.2	0	0	
Moderate (26-50%)	5	22.7	2	18.2	4	57.1	
Strong (51-75%)	9	40.9	5	45.5	2	28.6	
Very strong (76-100%)	4	18.2	2	18.2	1	14.3	
Total	22	100	11	100	7	100	
Median	Strong (51-75%)		Strong (51-75%)		Moderate (26-50%)		
Mean Rank	20.5		21.1		19.4		
r=-0.017 P=0.92[NS]							

Table (10): Validity parameters for CypA marker when used as test to diagnose OSCC differentiating it from healthy controls.

				PPV at pretest probability=		NPV at pretest probability = 10%
Positive if ≥ cut-off value	Sensitivity	Specificity	Accuracy	50%	90%	
cyclophilin A-Score						
Moderate (26-50%) (Highest sensitivity and optimum cut-off value)	85.0	73.3	81.7	76.1	96.6	97.8
Strong (51-75%) (Highest specificity)	57.5	100.0	69.6	100.0	100.0	95.5

Discussion

CypA expression is highly correlated with cancer pathogenesis, its is suggested to be the key role in treatment of cancer (Feng et al., 2015), but the specific mechanisms remain to be elucidated [Obchoei *et al.*,, 2009].

In the present study, increased the mean of cytoplasmic localization of CypA protein was significantly higher (P= 0.001) in OSCC group than healthy control group, overexpression of CypA were noted with mean±Sd (55±24.8) (22±10.8) respectively .The median score of CypA was significantly higher (p= 0.001) with (strong stain) in OSCC group while control one which (weak stain) , this findings agree with other researches done on OSCC cases [Huang *et al.*, 2013] [Huang *et al.*, 2011] [Feng *et al*, 2015] they found that the cancer cells showed increase the CypA proteins expression compared to the normal corresponding cells and establish to be expressed at strangely high concentrations in several types of malignances including [Campa *et al.*, 2003) [Howard *et al.*, 2004] [Li *et al.*, 2006] [Yang *et al.*, 2005].

In this study, cytoplasmic CypA was stated, nuclear presence some times seen, comparing to neighboring area. CypA was very scarcely expressed within nuclei of some prickle cells, which is in accordance with the findings tongue SCC [Huang *et al*., 2011] , in hepatocellular carcinoma [Gong *et al*., 2017] and in pancreatic malignancy [Li *et al*, 2006b] and endometrial cancer [Li *et al*, 2008], neighboring normal cells within nuclei of some prickle cells and pancreatic tissue composed of acinar cells and ductal epithelial cells with very faint immunostaining of CypA, and normal endometrium showed negative CypA immunostaining in cytoplasm and faintly positive in nuclei. adding, there was no CypA immunostaining in nearby normal lung tissue [Campa *et al*, 2003]. This suggest that OSCC tumorigenesis, the cells act to prevent the apoptosis by removing the oxidative stress through the antioxidant molecules.

Cyclophilin A was labeled to drag to PRDX6, which guard's cells from oxidative stress-induced apoptosis, being consequently as well linked with cancer process. In buccal squamous cell carcinomas, CypA was known by proteomic technology to be a tumor-associated protein that participates in intracellular signaling pathways of buccal tumorigenesis, preventing T-cell receptor-mediated signal transductions, adaptable therefore the T cell activation (Chen et al, 2004). Other study clarifies that the interaction between CypA and SR-25 proteins may be involved in potential cancer functions of CypA in HCC [Jian *et al.*, 2016]. Campa *et a*l [Campa *et al*, 2003)] showed that Cyclophilin A has important role in tumor and this features due to its role or effect like on the cellular growth and differentiation, the transcriptional regulator, cell signaling paths and the immunosuppression [Huang *et al.*, 2011].

This signifying that CypA associated with tumorigenesis in OSCC and more role of it required to clear.

Correlation of CypA expression with the Clinicopathological findings: Regarding age, this study shown no statistically significant difference in median score of CypA OSCC cases in spite of we observed linear correlations between age and CypA marker but was very weak. Similarly, the differences observed between males and females in median score of the CypA were too marginal and small in magnitude to be meaningful or statistically significant in spite of that the expression was strong in both gender. This findings is agree with [Yi *et al*., 2013] who explain the relation of CypA with age and gender in esophageal squamous cell carcinoma. He found that there was no relation with both age and gender.

A statistical non significant relationship of CypA IHC expression with site was found in this study (P= 0.48) in which the tongue was the most affected site, and showed strong staining potential with CypA protein, this is disagreeing with (Huang et al., 2013) in spite of that the tongue was the most affected site in several studies [Zhang *et al.*,, 2004;Hoogsteen *et al.*,, 2007;Kim *et a*l., 2007 and Roh *et al*., 2009].

This study showed that the CypA was failed to reach the level of statistical significance with size , Lymph Node involvement (P= 0.09)for both respectively , such results found in OSCC and agree with our findings [Huang *et al.*, 2013] and Also esophagus SCC cases [Yi *et al.*, 2013]this suggest that more investigation required.

Regarding tumor stage ,The observed difference in median cyclophilin A marker score, which was statistically significant between the tumor stages (stage II was strong stain) showed a weak negative (inverse) linear correlation(r=-0.245) which failed to show a statistically significant trend (P= 0.018), which is disagree with other publications [Huang *et al.*, 2013] in which no relation found .but in line with others such as in hepatocellular carcinoma [Gong *et al*., 2017] .such results may depends on clinical data accuracy that collected with each case.

Regarding the degree of tumour differentiation, the present study showed non significant correlation between expression of CypA and degree of differentiation of OSCC cases, where the P value (0.95) this findings are agree with [Huang *et al*., 2013]. Such results were same as in pancreatic cancer [Lister *et al.*, 2011], [Chang *et al.*, 2013] , it is necessary to enlarge the sample numbers and conduct further research.

During the research conduction, we observe that CypA has no important or statistically significant association with degree of inflammatory reaction, more research is needed to clarify the precise mechanisms involved.

The cyclophilin A optimum cut-off value was (81.7%). SO it can be used as a test to diagnose OSCC differentiating it from healthy controls.

Conclusion: This study demonstrated the expression of CypA in relation to clinicopathological parameters of OSCC High protein expression in OSCC cases was present compared with normal one, probably representing a potentiating effect within the tumorigenesis. Moreover, it was revealed that CypA is considered an independent prognosis factor. This may be contemplated to be biomarkers for the prediction as well as potential targets for molecular treatment strategies in OSCC. Future research, however, is needed to clarify further function and interaction of CypA in OSCC.

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