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The expression of EGFR and clinicopathological parameters in oral squamous cell carcinoma

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Abstract

Background: Oral squamous cell carcinomas (OSCCs) are the most prevalent types of oral cancers. There are a variety of clinicopathological characteristics of these types. The epidermal growth factor receptor (EGFR) is an essential diagnostic, prognostic, and therapeutic marker of OSCCs. The purpose of the research is to analyze the immunohistochemical expression of EGFR in OSCCs and to correlate its expression with clinical measures.

Materials and Methods: The present research included 44 histopathologically confirmed oral squamous cell carcinoma lesions. EGFR expression was determined by using immunohistochemical technique. The spss program version (20.0) was used to correlate the expressions EGFR with the clinical and histopathological parameters.

Results: 25 (57%) were men, while 19 (43%) were women. Most lesions 14(31%) cases were on the buccal mucosa. The palate had the lowest incidence rate 3(6.8%) cases. The highest frequency of OSCC was in well-differentiated samples with 23 (52.3) cases. 15 (34.1%) instances had a poor EGFR score (+1), 17 (38.6%) cases had a moderate score (+2), and 8 (18.2%) had a high score (+3). Except for tumor grade (P = 0.001), none of the studied factors were correlated with EGFR expression.

Conclusion: EGFR has prognostic value and is a good target for therapeutic applications in these tumors. More research needs to be done to see if EGFR levels can be used as a marker of prognosis and a predictor of tumor recurrence in other ways.

Keywords: Oral Cancer; EGFR; Clinical Factors; Prognosis; Immunohistochemistry

1. Introduction

Squamous cell carcinoma (SCC) seems to be the most frequent malignant tumor of the oral mucosa, and oral squamous cell carcinoma (OSCC) is now one of the top 10 most prevalent malignancies in the entire globe [1]. Those tumors are aggressive cancers that account for nearly 600,000 cases reported each year. It is the world's sixth most common malignant tumor [2].

Oral cancer is anticipated to be detected in 300,000 people worldwide each year. Oral cancers with squamous cell carcinoma are the most commonly diagnosed histopathological type. Despite advancements in screening and treatment technology, the 5-year survival rate for individuals with OSCC has remained stable at around 60% over the last two decades [3]. Early detection can increase the five-year survival rate by up to 80%; however, late detection can reduce the five-year survival rate to 19% [4].

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OSCC carcinogenesis is a series of complex processes involving various genetic events that affect oncogenes and tumor suppressor genes' normal activity. Cancerous cells, like normal cells, require stimulation signals to grow, differentiate, and proliferate, and growth factors are involved in this process [5]. Mechanisms underlying alterations that result in disease help the development of techniques for prevention, early detection, and therapeutic targets [6].

The epidermal growth factor receptor (EGFR) is a membrane tyrosine kinase receptor that plays a critical role in the growth and survival of epithelial cells [6]. It is a cell surface protein belonging to the ErbB family that is related to a variety of biological processes that include tumor formation, growth progression, differentiation, apoptosis inhibition, and metastasis development [7]**.** Adult tissues, with the exception of hematopoietic components, express EGFR. It is involved in the development of tumors in a variety of organs of the body. Additionally, OCSCC is associated with EGFR [8].

EGFR protein has been discovered in up to 90% of head and neck SCCs, while its overexpression has been reported in up to 80% of SCCs [9]**.** It has been demonstrated that upregulation of EGFR in head and neck SCC is related to a poor prognosis [10, 11]. Whereas there is no conclusive proof of its prognostic significance in OSCC, Additionally, decreased EGFR expression has been associated with an increase in disease-specific survival in oropharyngeal SCC, indicating that EGFR overexpression may be associated with the outcome of surgically treated patients [12]. Over 80% of invasive head and neck squamous cell carcinomas (HNSCCs) express high levels of the epidermal growth factor receptor (EGFR) which is closely correlated with tumor progression and metastasis, enhanced resistance to radiation therapy and chemotherapy, diminished survival rate, and poor prognosis [13].

EGFR has been established as one of the most potential markers for OCSCC in recent decades, not just for diagnosis but also for treatment and prognosis. HNSCC is often treated with anti-EGFR specific antibodies. Cetuximab is one of the most frequently used medications in this class; it interacts with EGFR and suppresses the activity of transcriptional cascades [14].

The main risk factors include smoking, alcohol consumption, and UV radiation exposure (particularly in carcinoma of the lip). Along with certain hereditary variables and dietary inadequacies, infectious pathogens such as the human papilloma virus and Candida species have indeed been involved [15]. The majority of OCSCCs are described as well or moderately differentiated tumors. The location of the neoplasm has a strong correlation with its histological grade. Buccal mucosa and lip tumors are often of lesser grade, while tongue and gingiva tumors are of greater grade and are poorly distinguished [15]. The tongue's border seems to be the most frequently impacted area in North America and Europe [16, 17].

This article describes an investigative study to assess the distribution of several clinicopathological characteristics in oral SCC patients and their associated EGFR amplification. The research also looked for a link between EGFR score and tumor grade. This research aims were to determine the prognostic significance of EGFR expression in oral malignancies and to to see if there was a link between the amounts of EGFR that was expressed in OSCC patients and their clinicopathological characteristics.

2. Material and methods

2.1. Patient and specimen selection

The present research used 44 formalin-fixed, paraffin-embedded tumor samples from patients diagnosed with oral squamous cell carcinoma (OSCC) of the head and neck from the Specialized Surgeries Hospital/Medical City/Baghdad records between 2010 and 2012. Two expert pathologists validated the diagnosis in all instances by studying the hematoxylin and eosin (H&E) segments. Clinical and pathological details of each case were acquired from surgical and pathological documents accompanying tissue specimens, such as the patient's age, sex, tumor location, and grade. The research was conducted in a teaching oncology hospital. In each block, one representative sample was stained with hematoxylin and eosin for reconsideration of histopathological diagnosis, and another section was established on an adherent slide for detection of EGFR expression using immunohistochemistry. The positive control was prepared in accordance with the manufacturer's data sheet for the antibodies. Slides were produced from individual blocks supposed to contain the relevant antigen recognized by the main antibody employed in this investigation. The negative control sections were made from the testing sections in the same way as the specimen, except that the primary antibody was removed and 20ml of phosphate buffer saline was used instead (PBS).

2.2. Principle of test

The labeled streptavidin-biotin (LSAB) approach employs a biotin-conjugated monoclonal antibody that connects the primary antibody's streptavidin-peroxidase conjugation to the chromogen reagent, resulting in a colorimetric response at the antigen binding site. As a colorimetric chromogen, the DAB (3-diaminobenzidine tetrahydrochloride) substrate is the most sensitive in the horse–radish peroxidase reaction system; a brown deposit forms at the antigen–ligand binding.

2.3. Evaluation of EGFR immunostaining

The sections were stained with anti-EGFR antibody and examined under microscopic examination. Tissue samples were inspected extensively and a total of 100 cells were determined. Then, the number of cells that had taken up the dye was calculated among the 100 cells. The degree and brightness of EGFR immunolabeling in tumor cellular membranes were used to assess EGFR overexpression [18].

- Negative: <10% of cells are labeled
- Positive: more than 10% of the cells have been labeled

1+: Poor staining, either homogenous or fragmented, in > 10% of cells.
2+: Moderate staining in > 10% of cancerous cells, either homogenous or patchy.
3+: Intense staining, either homogenous or fragmented, of > 10% of cells.

2.4. Statistical Analysis

A statistician's opinion was requested. SPSS version (20) was used for statistical analysis (Statistical Package for Social Sciences). We began by creating frequency distributions for a number of variables. Statistical significance was defined as a P value of less than 0.05. The factors evaluated were measured and classified as categorical data, which is why they are given as counts and percentages

3. Results

According to the results of this study, the average age of patients with oral squamous cell carcinoma (OSSC) was 58.30 years. The 6th decade age group had the highest frequency, with 13 (29.5%) cases. The age group distribution of the patients studied reveals no significant differences, showing that age group distribution has no bearing on the likelihood of a reported condition. Males made up 25 (57 %) of the 44 cases, while females made up 19 (43%) (Table 1).

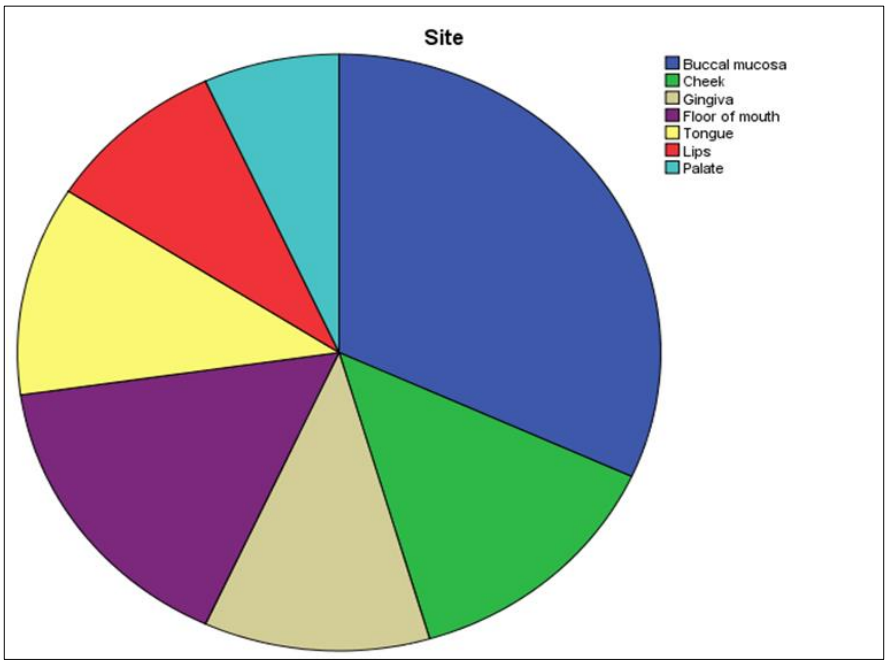

Figure 1 Pie chart shows the distribution of the sites of the studied lesions for the patients with Oral squamous cell carcinoma

Table 1 Frequencies of age groups, gender, site and grade for the patients with OSCC lesions

Parameters	Age groups	Frequencies	(%)	P- Value
Age groups	(20-29)	2	4.5	P= 0.929 Non Sig.
	(30-39)	2	4.5	
	(40-49)	7	15.9	
	(50-59)	9	20.7	
	(60-69)	13	29.5	
	(70-79)	8	18.1	
	(80-89)	3	6.8	
	Mean ± SD	58.30± 14.960		
Gender	Male	25	57	P = 0.366 Non Sig.
	Female	19	43	
Site		Frequency	(%)	P = 0.049 Sig.
	Buccal mucosa	14	31.8	
	Cheek	6	13.6	
	Gingiva	5	11.4	
	Floor of mouth	7	15.9	
	Tongue	5	11.4	
	Lips	4	9.1	
	Palate	3	6.8	
Grade	Grade 1	23	52.3	P = 0.001 Sig.
	Grade 2	18	40.9	
	Grade 3	3	6.8	
	Total	44	100	

NS: Non Sig. at P>0.05; S: Sig. at P<0.05; Testing are based on One Sample Chi Square Test

Table 2 The difference in median EGFR expression scores by gender among cases with Oral Squamous cell carcinoma

Parameters		Gender				Total	%
		Male	%	Female	%		
EGFR Expression	Negative	3	6.8	1	2.3	4	9.1
	Mild	9	20.5	6	13.6	15	34.1
	Moderate	8	18.2	9	20.5	17	38.6
	Sever	5	11.4	3	6.8	8	18.2
Total		25	56.8	19	43.2	44	100
Median		Weak positive		Moderate positive			

Table 3 Relationships of the EGFR expression with age, gender, site and grade of the studied samples with oral squamous cell carcinoma and testing their significant levels**.**

Correlations		**Age**	**Gender**	**Site**	**Grade**
EGFR Expression	Pearson Correlation	0.036	0.077	-0.074	-.368
	Sig. (2-tailed)	0.818	0.618	0.635	0.014
Age	Pearson Correlation	-	0.110	-0.108	-0.223
	Sig. (2-tailed)	-	0.478	0.485	0.145
Gender	Pearson Correlation	-	-	-0.024	-0.101
	Sig. (2-tailed)	-	-	0.878	0.514
Site	Pearson Correlation	-	-	-	0.022
	Sig. (2-tailed)	-	-	-	0.888

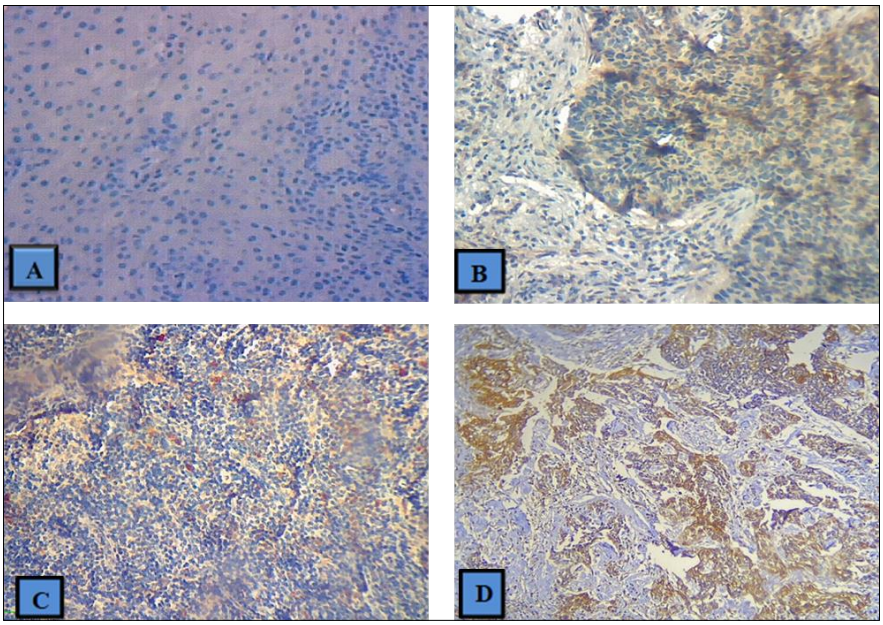

Figure 2 (A) Negative EGFR immunohistochemical expression in Poorly differentiated Oral squamous cell carcinoma(X20), (B) Weak positive EGFR immunohistochemical expression in Oral Squamous cell carcinoma with well differentiated (X20), (C) Moderate positive EGFR immunohistochemical expression in Poorly differentiated Oral squamous cell carcinoma(X20), (D) Strong positive EGFR immunohistochemical expression in colon cancer (X20)

The most common site for lesions was the buccal mucosa, which accounted for 14 (31%) of all cases. With just 3 (6.8%) incidences, the palate had the lowest rate of occurrence. The researched samples show no significant differences, suggesting that the risk of the recorded analyzed disorder is unaffected by the individuals' gender (Fig. 1).

The histological grading of each case was indicated in this study, the highest frequency of OSCC was in well differentiated samples (grade 1) with 23(52.3) cases, then followed with moderately differentiated specimens (grade 2) accounted 18(40.9%) cases, and finally followed with poorly differentiated cases (grade 3) and accounted 3(6.8%) cases and the studied patients has highly significant different at $P<0.01$, and accordance with this result, it could be conclude that probability of recorded studied disordered patients has recorded meaningful differences according to distribution of grade classes (Table 1).

The results of immunohistochemical staining revealed brown cytoplasmic and/or membrane positivity of EGFR in 40 cases of study samples which showed 15 (34.1%) cases with weak score (+1), 17 (38.6%) cases with moderate score (+2) and 8 (18.2%) cases with high score (+3), and there were only 4(9.1%) cases were stained negative (Fig.2).

The distribution of EGFR expression according to gender was weak positive for males and moderate positive for females with no significant correlation (Table 2).

The results of present study showed that regarding to "Spearman's rho Correlations" coefficients and testing significant levels, observing that weak relationships had been obtained, since no significant relationships at P>0.05 are accounted among studied parameters with the expression of EGFR, except only with the grade of tumor, since recorded positive significant relationship at P<0.05(Table 3).

4. Discussion

OCSCC is the most frequent type of head and neck cancer [15]. Because its etiology includes various molecular mechanisms, the molecular alterations driving tumor growth are complicated and have been the topic of countless investigations [19]. A big part of OSCC is the different biological behaviors of people with similar clinical and pathological characteristics. Some cancers have better outcomes than others [20,21].

In the current research, the average age group was 58.3 years old, and the age range was between 22 and 85. This data was consistent with previous research findings that age is a predictor of tumor recurrence, the risk of head and neck cancers rises with age, and the majority of oral cancers occur in those older than 50 years [22,23]. OCSCC often affects adults, most likely as a result of the need for sustained exposure to the carcinogen. OCSCC incidence in individuals under 40 years of age ranges between 0.4% and 6.0% [15].

According to gender, the current investigation revealed a ratio of 1.30:1 between male and female occurrences. This difference may be the consequence of certain male habits or behaviors that are absent in females. This is according to several reports [24,25].

Regarding tumor location, the data indicated that the buccal mucosa was the most prevalent site, followed by others. This conclusion is consistent with a number of studies indicating that there is a substantial difference in the site preference of tumors based on the geographic dispersion of patients. This is a result of the distinct etiologic factors common in various places. In Southeast Asia, the most prevalent place affected is the buccal mucosa due to the popular practice of smokeless tobacco and betel nuts [15]. Other research has observed that the tongue's lateral edge is the most frequent location for tongue cancers. Consistent with previous research, there was a statistically significant difference (P = 0.049) in tumor involvement locations [25,26].

Regarding histological grading of OSCC samples, well-differentiated tumors were more prevalent in our research, which was similar to [26,27], but other studies have shown that moderately differentiated cases were more prevalent than other grades [28,29]. There was a considerable difference between the tumor grades of current lesions.

Cell surface receptor attachment is the mechanism that causes mitogenic activity of EGFR, which is a transmembrane receptor containing an extracellular receptor binding component and an intracellular tyrosine kinase domain (TKD) [29]. Many types of human malignancies overexpress this protein, which means it plays a role in disease etiology. Up to 90% of HNSCC tumors have elevated EGFR expression, as confirmed by IHC [30].

The positive immunoexpression of EGFR was 90.9 percent in the present research, whereas the negative immunoexpression was 9.1 percent. This finding was consistent with another study, which discovered positive EGFR staining in 92.3 percent of their patients [20]. Other studies have shown higher levels of EGFR in OSCC and perioral area malignancies, similar to the findings of this research [29,31].

Although most research reported EGFR positive immunoexpression in the cell membrane [32], the data of this research demonstrated EGFR expression in the cell membrane and cytoplasm of tumor cells, as described in another study [24]. However, the combination of both membrane and cytoplasmic expression has been found to impact the prognosis of patients with oral cancer and other malignancies [33].

Zafar et al. discovered a strong association between patient age and the EGFR scoring system, while the correlation between participant gender, tumor grade, and EGFR activity was statistically irrelevant in their analysis. In contrast, the current study discovered no significant correlation with these clinicopathological factors except that there was a significant correlation with tumor grade (P = 0.014) [25,34]. This conclusion challenged other research, which found no statistically significant relationship between EGFR upregulation and cell differentiation grade [34].

Elevated EGFR expression has been linked to much more serious clinical progression and has been shown to be a helpful diagnostic tool marker. It has also been identified as a potential target for specific antibody treatment in recent years [35].

Despite the introduction of combination regimens including surgery, medication, and radiation, the prognosis of OCSCC has stayed poor for many decades. It has been stated that barely half of the patients recover completely. As a result, researchers have emphasized the importance of molecular targets in OCSCC patients. EGFR seems to be the best target that has emerged in recent years. Cetuximab and nimotuzumab are two EGFR inhibitors that have been investigated [36]. The use of anti-EGFR antibodies is justified by the high rates of EGFR expression. Furthermore, it has been shown that continuous EGFR activation does not necessarily result in increased EGFR expression. However, an increased EGFR score from an immunohistochemical study suggests that these targeted treatments will work [37].

5. Conclusion

The considerable association between EGFR expression and tumor grade in OSCC patients shows that EGFR immunoexpression has prognostic importance and is a possible target for treatment with targeted therapies in these cancers to appreciate the developing features of diverse OSCCs, particularly with reference to EGFR expression. In this century of focused medicine, the significance of the current findings cannot be overestimated. For further evaluation, this data needs to be checked with a larger sample size, and more research is needed to make sure that EGFR levels can be used as a prognostic marker and a predictor of tumor recurrence in other fields.

Compliance with ethical standards

Author contributions

I not only collected, analyzed, and interpreted the data, but also wrote, analyzed, and put together the paper.

Disclosure of conflict of interest

I declare that there is no possible conflict of interest in the publication of this work. Furthermore, I have personally observed ethical difficulties like plagiarism, consent forms, misconduct, data fabrication and/or deception, multiple publishing and/or submission, and duplication.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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