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ORIGINA ARTICLE

Correlation of EGFR expression with survival rate in patients with oral squamous cell carcinoma

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ABSTRACT

Squamous cell carcinoma (SCC) constitutes 4% of oral malignancies with a mortality rate of about 9000 individuals per year in the United States. It is known that expression of epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR) on the surface of tumor cells is correlated with poor prognosis in some areas of the body; but there is no consensus with regard to carcinomas of the oral cavity in this respect. The aim of this study was to determine the correlation between the expression of EGFR and survival rate in patients with oral SCC and we tried to indicate the role of EGF in proliferation and growth of epithelial tissue. Thirty-eight paraffin blocks diagnosed as SCC were collected and immunohistochemical (IHC) staining was performed using antibodies against EGFR. Total score of stained cells and the correlation between the total score and survival rate of patients were estimated. A significant correlation was found between the expression of EGFR and survival rate; over expression of EGFR correlated with poor prognosis. Epidermal growth factor receptor is probably an independent prognostic factor for assessment of survival rate. A correlation also exists between the grade of tumor and expression of EGFR. Further studies are required to better elucidate the relationship of EGFR with the stage of tumor.

Keywords; *oral squamous cell carcinoma; epithelial growth factor receptor; survival rate*

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INTRODUCTION

Squamous cell carcinoma is the sixth most common neoplasm in the world and by far the most common in oral tissues (94% of SCCs). Early diagnosis can increase the 5-year survival rate by up to 80%; whereas diagnosis in advanced stages can decrease this rate to 19% [1, 2].

As oral SCC develops by means of multiple genetic and biological pathways, recent studies have focused on these aspects. Different biological factors are expressed during the pathogenesis of oral SCC [2]. However, the expression of this marker and its relation to prognosis and clinical signs of oral SCC are still unclear.

Studies have shown a direct correlation between EGFR expression and breast, ovary, lung, colon and stomach cancers [3]. Epidermal growth factor receptor, ErbB, HER1 in humans, is a type of tyrosine

kinase receptor and a member of the ERbB/HER family of signalling receptors. After attachment of the ligand to the EGFR, a dimer forms which activates phosphorylation of internal tyrosine continuum. After this procedure, JAK-protein kinase, STAT, Ras/Raf and phosphatydylinosin 3 kinase P13K-AKT cascades are activated which lead to aggressive proliferation of cells, metastasis, angiogenesis and inhibition of apoptosis [4-6].

In a recent study, 87.5% of oral SCC specimens showed positive EGFR immunostaining and investigators stated that EGFR expression was displayed in all epithelial layers while in normal tissue we see this expression only in the basal layer [7]. In advanced stages of oral SCC, over-expression of EGFR occurs and based on a study by Carbareia there is a relation between over-expression of EGFR in lip SCC and poor prognostic indices (i.e. size of the tumor and ulcers) [8]. Also, in oropharyngeal SCC patients, lower rates of EGFR expression were accompanied by improvement of prognostic factors which indicates that EGFR expression can be related to prognosis of surgically treated cases [9]. Increased genetic and molecular changes can be valuable predictors of disease outcomes and some of them can be targets for new therapeutic modalities [10, 11].

Treatment factors such as anti ErbB (a member of EGF receptor family) monoclonal antibody are produced and utilized to cure this kind of neoplasm [2, 12]. Over expression of EGFR in the head and neck SCC has been shown to correlate with poor prognosis [3, 13]; whereas there are no definite data regarding its prognostic role in oral SCC [10]. This study sought to assess the relationship of this factor with the stage and grade of oral SCC, its survival rate and recurrence.

MATERIALS AND METHODS

Patient selection:

This descriptive study collected samples based on the inclusion criteria such as definite diagnosis of SCC, excisional biopsy of SCC, complete manifestation and recognition of signs and symptoms, history of smoking and alcohol consumption and recurrence; 38 oral SCC patients were chosen from the Pathology and Oncology Departments of Shohada-E-Tajrish Hospital and excisional biopsies of the tumor were performed, (table: 1). Avidin-biotin IHC staining of the samples was performed. One skin tissue sample was used as the positive control.

Immunohistochemistry procedure:

Five µm sections of the paraffin embedded blocks were made and mounted on special silanized slides. Slides were kept at 37ºC overnight and then at 60ºC for 1 hour and were deparaffinised and dehydrated sequentially. Specimens were placed in xylene for five times and each time for four minutes and immersed in 100, 96 and 70% graded ethanol and then rinsed with phosphate buffered saline (PBS) solution and water. Slides were immersed in 100% graded methanol for 2-3 minutes and in 3% hydrogen peroxide –containing methanol for 30 minutes afterwards; then they were incubated under the effect of proteinase in plastic dishes containing Tris buffer with a pH of 7.5 for 20 minutes. Block protein was shredded over the samples and after five minutes primary monoclonal antibodies (EGFR/DAKO) diluted 1/40 were decanted over the slides. Slides were incubated in a cold room for one hour and then at room temperature for another hour. Next, they were rinsed with PBS solution and secondary Ab was added for 10 minutes and rinsed again.

Afterwards, one-two drops of DAB (3, 3'-diaminobenzidine) were added, rinsing with water was performed and samples were stained with hematoxylin for 30 seconds. Specimens were then rinsed with water and immersed in graded alcohol and xylene for five minutes sequentially. Slides were then mounted.

Immunochemistry method:

For assessing the expression of EGFR, the total score (which is the result of multiplying the intensity score by the proportion score) was taken into account. For calculation of the intensity score, each slide was scored on the basis of intensity of the marker staining in membrane, cytoplasm and nucleus of tumoral cells as follows:

0- No staining
1- Weak staining
2- Intermediate staining
3- Intense staining

The proportion staining score was the ratio of stained cells to unstained cells and was scored as follows:

0- None of the cells were stained.
1- Less than 10% were stained.
2- 10-50 % were stained.

3- 50-80% were stained.
4- More than 80% were stained.
The total score was a number in the range of 0-12, which was classified as mentioned below:
0: Without expression, score 1
1-3: Low expression, score 2
4-8: Intermediate expression, score 3
8-12: High expression, score 4
After indicating the degree of marker expression, patients were recalled and their existing condition was examined. The time between the end of the treatment and the recurrence of the disease or death due to it was the period used for evaluation of survival rate of patients in this study?
At the end, obtained data were analysed by Kaplan-Meier, Spearman and the log rank tests using SPSS software. Descriptive indices (log rank) were used to evaluate major and minor goals. To determine the mean survival time, the Kaplan Meyer analysis was used. Comparison of the mean survival time in different groups (grade, EGRF scale) was done using the log rank test. The correlation of tumor grade with EGRF scale was evaluated using the Spearman's rank correlation coefficient.

RESULTS

In this study, 38 cases were examined. The mean age of patients was 71.8±1.09 years. There were 20 males and 18 females; 23(60.5%) of the patients were smokers; 26 (68.4%) were in stage 3 and 12 (31.5%) were in stage 4.From 38 cases, four (10%) had well grade histopathogenesis; three (7%) had a total score of two and one (2.6%) had a total score of three. Thirteen cases (34.2%) had moderate grade histopathogenesis; one (2.6%) had a total score of two, seven (18%) had a total score of three and five (13%) had a total score of four. Twenty-one cases (55.2%) had poor grade histopathogenesis; one (2.6%) of them had a total score of two, 11 cases (29%) had a total score of three and nine cases (23.6%) had a total score of four.
Of all cases, five (13.15%) had a total score of two, 19 (50%) had a total score of three and 14 (36.8%) had a total score of four. Among 38 cases, 25 (65.7%) had tongue lesions, 11 (28.9%) had floor of the mouth lesions and two (5.2%) had gingival lesions. Twenty-six cases (68.4%) were in stage three; of whom, four (10.5%) had a total score of two, 13 (34.2%) had a total score of three and nine (23.6%) had a total score of four. Twelve cases (31.5%) were in stage four; of whom, one (2.6%) had a total score of two, six (15.7%) had a total score of three and five (13.1%) had a total score of four. Among all cases, five (13.15%) had a total score of two, 19 (50%) had a total score of three and 14 (36.8%) had a total score of four. (Table: 2).

Table 1: Clinicopathological characteristics of 38 OSCC patients

	N (%)
Total patient material	38
gender	
females	18 (47%)
males	20 (53%)
Tumor site	
tongue	25 (65.7%)
Gingiva	11 (28.9%)
Floor of mouth	2 (5.2%)
smoking	
smokers	23 (59.5%)
Non-smoker	15 (39.5%)
grade	
well	4 (10.5%)
moderate	13 (34%)
poor	21 (55.5%)

Regarding the expression of EGFR, five (13.1%) cases had a total score of two; of whom, three cases (7.8%) were well grade, one (2.6%) was moderate grade and one (2.6%) was poor grade. Also, 19 cases had a total score of three; of whom, one (2.6%) was well grade, seven (18.4%) were moderate grade and 11 (28.9%) were poor grade. Also, 14 (36.8%) cases had a total score of four; of whom, none were well grade, five (13.1%) were moderate grade and nine (23.6%) were poor grade (Figures 1-3).
Of all cases, four (10.5%) had well grade histopathogenesis, 13 cases (34.2%) had moderate grade and 21 (55.2%) had poor grade.

For assessment of analytical indices, we used the log rank test.In general, death or recurrence occurred in 50% (n=19) of 38 cases. The mean survival time was 32.75±3.9 months in the poor grade group and 32.8±9.39 months in the moderate grade group. The survival time for the well-grade group could not be calculated due to small sample size. The log-rank test showed no significant difference in the mean survival time between the moderate and poor grade groups (P=0.862). Also, the mean survival time was 51±9.32 months for score three EGFR and 28.64±4.1 months for score four EGFR; this difference was statistically significant (P=0.002).

The Spearman's correlation test showed a linear moderately significant correlation between the grade of tumor and EGFR scale (P=0.049, R=0.318). Only 10% of the changes in grade and EGFR were in the same direction and the remaining was influenced by other factors.

Table 2: EGRF expression in relation with location, smoking and grade of oral squamous cell carcinoma

		EGRF expression			
		Score 2	Score 3	Score 4	Total
Location	Tongue	3	15	7	25
	Floor of the mouth	0	4	7	11
	Gingiva	2	0	0	2
	Total	5	19	14	38
Smoking	Yes	1	12	10	23
	No	4	7	4	15
	Total	5	19	14	38
Grade	Well	3	1	0	4
	Moderate	1	7	5	13
	Poor	1	11	9	21
	Total	5	19	14	38

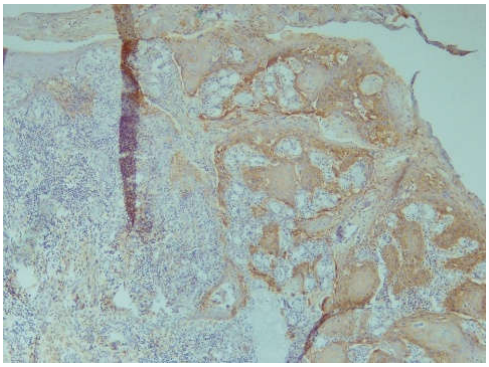

Fig 1: total score 2 of EGFR expression in oral squamous cell carcinoma

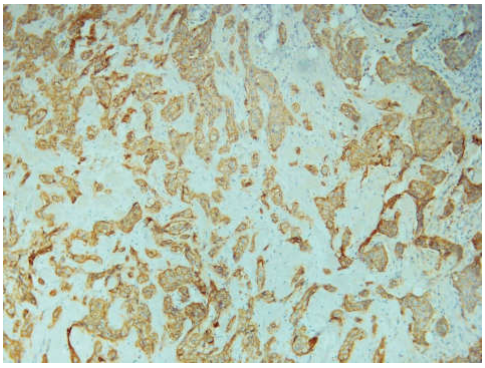

Fig 2: total score 3 of EGFR expression in oral squamous cell carcinoma

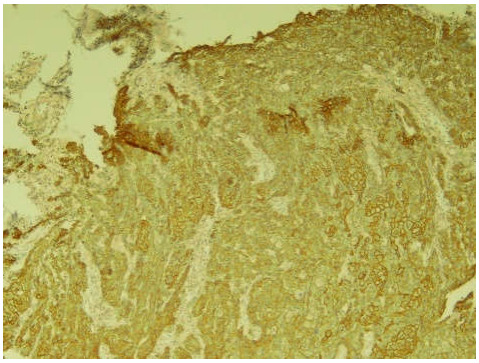

fig.3: total score 4 of EGFR expression in oral squamous cell carcinoma

DISCUSSION

The expression of EGFR gene has been assessed in different kinds of neoplasms and researchers have found a significant correlation between the expression of this receptor and stimulation of migration and division of normal epithelial cells in breast, kidneys and prostate [14, 15]. Similar studies have evaluated the role of EGFR expression in oral SCC. A study performed in Iraq noted EGFR as one of the main causes of rapid growth of oral SCC (7). Another study done by Mohammad Taoudi et al. concluded that EGFR gene copy number is an early sign of tumor progression and contributes to oral SCC risk [16].

In the current study, our aim was to evaluate the correlation of EGFR expression with the grade and stage of the disease and survival rate of patients. As mentioned before, this research was done on 38 paraffin embedded incisional biopsy specimens of oral SCC patients. By studying all the biopsy samples of patients and statistical analysis, it was concluded that there was no significant correlation between EGFR over-expression and oral SCC stage ($P>0.05$). This finding was similar to the result of most previous studies [17, 18].

YokihiroHirashi also reported the same results as ours and it was noted that even though 92% of studied samples showed EGFR expression and 63% of them showed high expression of EGFR, there was no correlation between this expression and tumor stage [19]. Conversely, another study stated that EGFR expression was higher in advanced stages of oral SCC and non-homogenous leukoplakia. Such discrepancies in results can be justified by differences in sample size (19 cases in the latter study) and the initial stage of the biopsies evaluated. In our study, all of the biopsies were done in primary phase while this matter may have been overlooked in other studies [20].

Regarding the correlation between EGFR over-expression and the grade of cell differentiation, we did not find a significant correlation ($P>0.05$), which is in contrast to the result of Ulvanski *et al*. They declared that by increasing the EGFR expression, the differentiation of oral SCC cells significantly diminished [21]. The common point of their research and ours was the method of staining of samples but the differences were the place from which, the biopsies were taken (tongue only) and the time passed from the onset of the disease. In another research on EGFR expression in oral SCC patients' saliva before and after tumor surgery, it was seen that salivary level of EGFR increased after removal of the tumor but no correlation was found between receptor salivary levels and clinicopathological features of the tumor [22]. It is obvious that the main reason for different results compared to ours was the nature of the specimens (saliva).

In our study, the relationship of EGFR over-expression and survival rate was significant ($P=0.0162$), which means that patients with higher rate of EGFR expression had a worse prognosis. Oral SCC patients who did not die because of the disease or had no recurrence in the period between the end of the treatment and the last follow up (which was 25-86 months) were considered as the positive group. Our results were similar to those of AngKee *et al*. who mentioned that EGFR is an independent and strong prognostic factor for evaluating the survival rate and disease relapse [23]. Keren *et al.* performed a meta–analysis on the prognostic role of EGFR in head and neck squamous cell carcinoma (HNSCC) and concluded that EGFR over-expression was associated with shortened overall survival [24]. Another meta-analysis highlighted the role of EGFR over-expression as a prognostic factor in nasopharyngeal carcinoma [25]. On the other hand, a study stated that over-expression of EGFR cannot be a prognostic factor per se [26]. This study had a sample size of 113 cases and its duration was nine years. They included oropharyngeal biopsies in their research which may explain different outcomes.

A recent study evaluating phosphorylated EGFR (pEGFR) expression in oral SCC as a prognostic factor concluded that the independent value of pEGFR expression in cause-specific survival of oral SCC can be a reliable marker for indicating the prognosis of different cases [27]. The main difference of this study with

ours was that they evaluated the rate of pEGFR rather than EGFR itself. Actually, the expression of this marker depends on many known and unknown factors. For example, in a study by Ericsson et al, EGFR expression in the initial stage of tumor invasion was more than that in advanced stages, and after metastasis another rise in EGFR expression was seen [28]. Regarding the fact that our study was performed on paraffin- embedded incisional biopsies and precise information about the onset of neoplastic changes and invasion of the tumor was not available, discrepancies in the result of our study compared to the others seem justifiable. The main difference in these studies is the evaluation process of this factor. For example, in 2005 Heras and Giralt showed the correlation of EGFR over-expression and GI tract malignancies [29]. In their study, the proportion of stained cells to non-stained ones was evaluated and the intensity of staining was not taken into account. This method is not useful in oral SCC because of formation of the cells. In our study, this ratio was 1 or close to 1. In a study by Yamada et al, only the intensity of the staining was examined and it was reported that staining intensity increased in higher grades [30]. Also, there are many studies about EGFR expression changes during chemotherapy and radiotherapy periods [31]; to omit this intervening factor we used the biopsies which were taken prior to the chemotherapy or radiotherapy procedures in order to assess EGFR expression based on the primary characteristic of the tumor.

Finally the strength of this study was the accurate method of assessment of EGFR expression and the attention to the exact date of follow up visits and the main limitation was related to the specimens which were not uniform in staining; we saw that staining intensity was often more in the margins of the tumor compared to the central zone.

Although we did not see any significant correlations between EGFR over-expression and stage and grade of the biopsies, we can use the data regarding the survival rate. However, more studies are needed to better elucidate this subject.

CONCLUSION

Although we did not see any significant correlations between EGFR over-expression and stage and grade of the biopsies, we can use the data regarding the survival rate. However, more studies are needed to better elucidate this subject.

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