Original Article

Assessment of epidermal growth factor receptor in histological, clinical and pathological staging of oral squamous cell carcinoma

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Abstract

Background: Oral squamous cell carcinoma is an invasive epithelial neoplasm with varying degrees of squamous differentiation that arises from the following anatomic sites: the oral cavity, particularly oral soft tissues including the gingival and alveolar mucosa, floor of the mouth, tongue, soft and hard palate, tonsils and oropharynx. In normal epithelium EGFR is localized to basal cell layer, while its expression beyond basal localization in cancerous tissue suggest that correlation of EGFR and tumor progression might exist. The present study aimed to assess epidermal growth factor receptor in histological, clinical and pathological staging of oral squamous cell carcinoma.

Materials and Methods: The current study was performed on subject with confirmed histological diagnosis of oral squamous cell carcinoma of age group between 35 and 70 years reported to Kempe-Gowda Institute of Medical Science and Hospital, Department of Oral and Maxillofacial Surgery, Vokkaligara Sangha Dental College and Hospital Bangalore and KIDWAI Memorial Institute of Oncology, Bangalore between December 2019 and March 2021.Total of 30 subjects included in the study of age group between 35 and 70 years. In the selected subject for the study, tumor was resected and preserved in 10% formalin, which was sent to department of pathology for analysis and PTNM was recorded. Immunohistochemical evaluation of EGFR was done. Total score of EGFR of each subject was co-related with pathological prognostic factor.

Results: Correlation of EGFR with adjuvant therapy and histological grading, *P* values were 0.001 and 0.005, respectively. The obtained results were tabulated statistically using Chi square test and significance was set at $P < 0.05$.

Conclusion: A preventive approach and assessment of EGFR in early stage of SCC provide better results. Subjects with higher EGFR value have poor prognosis and have to undergo postsurgical adjuvant therapy for long term-survival.

Keywords: EGFR, Immunohistochemistry, OSCC, TNM staging

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INTRODUCTION

Oral cancer is a worldwide problem with prevalence in morbidity and mortality. In India, the incidence of oral cancer is 30--50% of whole-body tumor. The prevalence of oral cancer is higher reaching around 45% in India. Worldwide, oral cancer accounts for 2--4% of all cancer cases. The percentage of 5-year survival for patients with OSCC varies from 40--50%. Oral squamous cell carcinoma is usually diagnosed in advanced stages.

Prognostic evaluation for oral squamous cell carcinoma is mainly based on clinical TNM classification but this staging system is not sufficient for optimal prognostication, must be supplemented with other reliable methods.[1]

Recent studies proved that "EGFR" plays a pivotal role in the molecular alteration in carcinogenesis. Overexpression of EGFR has been documented in 80% SCC.

In normal epithelium EGFR is localized to basal cell layer, while its expression beyond basal localization in cancerous tissue suggest that correlation of EGFR and tumor progression might exist.

Epidermal growth factor (EGF) promotes tumorigenesis and tissue repair of epithelial and mesenchymal cells and has a role in chemotaxis, mitogenesis, cell motility, and cyto-protection. It also enhances the growth of cancers. EGF may therefore have a role in the initiation or promotion of oral carcinogenesis.[2]

The anatomic extent described by size of the primary tumor (T classification), by the lymphatic spread (N classification) and by distant metastases (M classification) is still considered as the most important prognostic factor.[2]

Tumors must be classified before treatment (clinical staging, c-TNM) and after resection (pathologic staging, p-TNM). The pretherapeutic anatomic extent (c-TNM) of the tumor is derived from clinical and radiologic examinations such as MRI and CT and determines the choice of primary treatment. The decision for adjuvant radiotherapy (RT) or radio chemotherapy is based on the p-TNM, which is determined by histologic analysis of the resected tumor and the neck dissection specimen.[2]

SUBJECTS AND METHODS

The present (Immunohistochemistry) study includes archival samples of Histopathological diagnosed confirmed cases of oral squamous cell carcinoma (n = 30) reported to Kempe Gowda Institute of Medical Science and Hospital, Department of Oral and Maxillofacial Surgery, Vokkaligara Sangha Dental College and Hospital Bangalore and KIDWAI Memorial Institute of Oncology, Bangalore.

A total number of 30 subjects were included in the current study from the period of December 2019 to March 2021.

Subjects of age between 35 and 70 years with Confirmed Histological diagnosis of Oral Squamous Cell Carcinoma and who required Surgical procedure with postoperative prosthesis were included in the study. Patient with previous history of chemotherapy or radiotherapy treatment done for cancer and have high chance for developing recurrent lesions or Metastatic tumor which has spread from other parts of the body to the oral cavity and Advanced stage of oral squamous cell carcinoma were excluded from the study.

Following histological examination, clinical examination and radiological investigations (CT/MRI) clinical TNM classification was recorded. The selected subjects were planned for surgery under general anesthesia, the tumor was resected and preserved in 10% formalin, which was sent to department of pathology to be analyzed, PTNM and EGFR was recorded.

Formalin-fixed and paraffin-embedded tissue sections were stained immunohistochemically for the expression of EGFR using primary antibodies and the antigen--antibody complex was visualized using the DAB detection kit (k3368; Dako).

Immunohistochemical evaluation of EGFR was done by calculating Intensity Score, Proportional score followed by total score [Table 1].

DISCUSSION

An immunohistochemical assessment using multiple prognostic molecular biomarkers can provide useful information for the identification of high-risk OSCC patients.[3]

The current study is designed to assess EGF Receptor in Histological, Clinical and Pathological Staging of Oral Squamous Cell Carcinoma.

Table 1: The total score will be classified as

0	No expression	Score 1
1-3	Low expression	Score 2
4-7	Intermediate expression	Score 3
8-12	High expression	Score 4

The present study consists of a total of 30 patients.

The mean age group value is 55.1. 43.31% of the total cases were between 51 and 55 years.

63.3% of the total cases belonged to male gender whereas 36.7% belonged to female gender.

The commonest site of the tumor was found to be gingiva-buccal sulcus with a total of 13 cases amongst the total cases.

On comparison of clinical staging with pathological staging the *P* value is 0.138 which is not statistically significant, the tumor size between the two has a *P* value of 0.006 which is statistically significant whereas lymph node status between the two has a *P* value of 0.240 which is not statistically significant. On the other hand, there were no cases with metastasis.

When EGF receptor was co related with the age group, total of 7 cases had EGFR score of 4 and were under the age group between 51 and 55 years. *P* Value is 0.019 which is statistically significant.

When EGF receptor was co related with the adjuvant therapy a total of 10 cases underwent adjuvant therapy postsurgery out of which eight cases had EGFR score of 4. *P* Value is 0.001 which is statistically significant.

When EGF receptor is corelated with the habitual status, all the cases included in the study have a habitual history among them 8 cases have EGFR score of 4. *P* Value is 0.233 which is not statistically significant.

When EGFR score is corelated with the histological grading 8 cases have EGFR score of 4 among them 3 are poorly differentiated, 4 cases and 1 case moderately and well differentiated. *P* Value is 0.005 which is statistically significant.

On corelating EGFR with clinical and pathological staging it is found that most of the cases which have clinical and pathological stage as 1 and 2 have EGFR score of 1 and 2 respectively except of two cases which have clinical and pathological stage 2 and EGFR score of 3. Further in clinical and pathological stage 3 and 4 most of the cases have EGFR score of 3 and 4 and very few cases have EGFR score of 1 and 2.

Immunohistochemical expression of EGFR in head and neck squamous cell carcinoma and its association with prognostic clinicopathological features has been studied and significant association of EGFR expression was found with tumor stage and disease-free survivals which are the most important prognostic factor in head and neck squamous cell carcinoma. EGFR expression aid in prognostic biomarker in head and neck squamous cell carcinoma.

Disease free survival was defined as time from surgical resection till first recurrence, patient death or last medical follow up.

Overexpression of EGFR correlates with aggressive tumor behavior and decreased life expectancy. It is widely accepted that only Immunohistochemical examination of EGFR expression is not enough for patient selection, that may benefit from EGFR directed therapy. The reason behind that is Immunohistochemical examination of EGFR does not necessarily correlate with underlying gene amplification.

Molecular studies should be performed in squamous cell carcinoma to identify patient that can benefit from anti EGFR therapy.

Epidermal growth factor receptor (EGFR), a ubiquitously expressed transmembrane glycoprotein belonging to the Ebb/HER family of receptor tyrosine kinases (TK), is composed of an extracellular ligand-binding domain, a hydrophobic transmembrane segment, and an intracellular TK domain. Upon ligand binding to EGFR, the latter undergoes a conformational change that promotes homo- or heterodimerization with other members of the ErbB/HER family of receptors, followed by autophosphorylation and activation of the TK domain. Activation of EGFR leads to activation of intracellular signaling pathways that regulate cell proliferation, invasion, angiogenesis, and metastasis.[4]

EGFR is expressed at high levels in the majority of epithelial malignancies including HNSCC. Elevated expression of EGFR in HNSCC correlates with poor prognosis, and EGFR has been a target of anticancer treatments due to its critical roles in cell survival and proliferation. Among the tyrosine kinase inhibitors targeting EGFR that have been approved by the US FDA are gefitinib, erlotinib, and lapatinib. These molecules are reversible competitors, competing with adenosine triphosphate (ATP) for the tyrosine kinase binding domain of EGFR. Inhibition of receptor activation inhibits downstream signaling pathways, resulting in decreased cell proliferation and survival.[4]

Rationale for targeting P_{13K}/AKT pathway-EGFR signaling activates a number of downstream effectors including

the phosphatidylinositol-3-kinase (PI3K)/Akt pathway. Immunohistochemical studies using antibodies that recognize Akt phosphorylated at S473 have demonstrated that activated Akt is detectable in cancers including head and neck cancers. Any of the alterations in individual components of the PI3 kinase/Akt pathway would result in its activation, and activation of this pathway has been reported to be among the most frequent molecular alterations in tumors.[4]

EGF promotes tumorigenesis and tissue repair of epithelial and mesenchymal cells and has a role in chemotaxis, mitogenesis, cell motility, and cyto-protection. It also enhances the growth of cancers. EGF may therefore have a role in the initiation or promotion of oral carcinogenesis.[2]

Biomarkers of OSCC such as DNA microarrays and proteomics have contributed to molecular and cellular mechanisms of pathogenesis of OSCC. Early detection of OSCC plays a significant role in successful clinical treatment and the identification of prognostic factors allows the selection of the optimal therapy. Additional serum biomarkers are still needed to improve diagnosis, for prognostic evaluations, and for follow-up.[2]

EGFR appears to have no prognostic value when chemoradiotherapy is used. The parameters used to evaluate EGFR staining and the cut-off considered can strongly impact on the percentage of positive cases. Technical aspects pertaining to the IHC procedure are also probably involved: it is well known that IHC techniques are not perfectly reproducible, and a strong bias could derive from different modalities of sample handling or from the heterogeneity of EGFR expression in different areas of the tumor. Tumors showing the strongest EGFR expression retain some degree of radio-resistance, although this finding should be confirmed in larger trials.[5]

SUMMARY AND CONCLUSION

EGF receptor overexpression is found in the majority of oral squamous cell carcinoma (OSCC) tumors and associations have been made between increased expression levels and an aggressive phenotype, poor prognosis and resistance to anticancer therapy.

The anatomic extent described by size of the primary tumor (T classification), by the lymphatic spread (N classification) and by distant metastases (M classification) is still considered as the most important prognostic factor.

Tumors must be classified before treatment (clinical staging, c-TNM) and after resection (pathologic staging, p-TNM). The pretherapeutic anatomic extent (c-TNM) of the tumor is derived from clinical and radiologic examinations such as MRI and CT and determines the choice of primary treatment. The decision for adjuvant radiotherapy (RT) or radio chemotherapy is based on the p-TNM, which is determined by histologic analysis of the resected tumor and the neck dissection specimen.

The present study has shown that EGFR score is higher in clinical and pathological stage 3 and 4. It is found that *P* value for correlation of EGFR with adjuvant therapy was 0.001 which is statistically significant which suggests that cases with higher EGFR value have poor prognosis and have to undergo postsurgical adjuvant therapy for long term survival. Larger, prospective randomized controlled trials are required to better assess the nature and the effect of EGFR.

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Conflicts of interest
There are no conflicts of interest.

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