Section: Surgical Oncology

Original Research Article

PREVALENCE AND SPECTRUM OF EGFR MUTATIONS IN ORAL CAVITY AND OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Background: The Epidermal Growth Factor Receptor (EGFR) plays a pivotal role in the pathogenesis of several epithelial malignancies. While EGFR overexpression has been widely documented in head and neck squamous cell carcinoma (HNSCC), the occurrence and impact of specific EGFR mutations remain underexplored, especially in oral cavity and oropharyngeal squamous cell carcinoma (OCSCC and OPSCC). This study evaluates the prevalence and mutation spectrum of EGFR in a cohort of 41 patients diagnosed with OCSCC and OPSCC using RT-PCR-based genotyping. Our findings reveal a strikingly high prevalence of EGFR mutations in this cohort, including both activating and resistance mutations, underscoring the potential for personalized EGFR-targeted therapy in this subset of HNSCC patients. **Objective:** To investigate the frequency and mutation profile of EGFR gene alterations in patients diagnosed with OCSCC and OPSCC. **Materials and Methods:** Forty-one patients with histologically confirmed oral cavity and OPSCC were analyzed for EGFR mutations using PCR-based sequencing targeting exons 18 to 21. **Result:** EGFR mutations were detected in a significant portion of the cohort. The most frequent mutations were exon 21 L858R (95.1%)) and L861Q (92.7%). Other alterations included Exon 20 T790M (90.2%), Exon 20 Insertions (90.2%) Exon 20 S768I (85.4%) and Exon 19 deletion (85.4%) Least number was found in G716X mutations (22%). About 97.6% were found to have at least one EGFR mutation. Approximately 90% of mutations were sensitizing alterations responsive to EGFR tyrosine kinase inhibitors (TKIs), while 82.9% had at least one resistance mutation, indicating a potential challenge in frontline EGFR-targeted therapy. **Conclusion:** Sensitizing EGFR mutations are present in a notable subset of oral cavity and OPSCC patients, suggesting a potential role for EGFR-targeted therapies. Further studies with larger sample sizes and clinical correlation are warranted.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) represents a significant global health burden, with the oral cavity and oropharynx being among the most commonly affected anatomical subsites. Despite advancements in surgical, radiation, and chemotherapeutic strategies, overall survival rates for advanced-stage disease remain suboptimal. In recent years, molecular characterization of tumors has unveiled critical insights into the oncogenic drivers of various cancers, paving the way for targeted therapies.

EGFR, a member of the ErbB family of receptor tyrosine kinases, is frequently overexpressed in HNSCC and contributes to tumor growth, angiogenesis, metastasis, and resistance to therapy. However, unlike in non-small cell lung cancer (NSCLC), where EGFR mutations are routinely screened and targeted therapies are widely used, the role of EGFR mutations in OCSCC and OPSCC is less clearly defined. This gap in knowledge necessitates further exploration to understand the therapeutic implications of EGFR mutations in these cancers.

The objective of this study was to determine the prevalence and spectrum of EGFR mutations in

patients with OCSCC and OPSCC and assess their potential impact on treatment strategies.

MATERIALS AND METHODS

This Prospective study analyzed EGFR mutation profiles in 41 patients with histologically confirmed squamous cell carcinoma of the oral cavity and oropharynx. Blood samples were collected and tested using a standardized reverse transcription-polymerase chain reaction (RT-PCR) assay specific for EGFR mutations. The assay detected mutations across the following exons:

- Exon 18: G716X
- Exon 19: Deletions (19D)
- Exon 20: T790M, S768I, and three insertions
- Exon 21: L858R and L861Q

Data on patient age, sex, and clinical details were also collected for correlation with mutation profiles.

RESULTS

Among the 41 patients tested, 40 (97.6%) were found to have at least one EGFR mutation. One patient tested negative across all exons. The most frequent mutations were Exon 21 L858R (95.1%) and L861Q (92.7%), followed by Exon 20 T790M (90.2%), Exon 20 Insertions (90.2%), Exon 20 S768I (85.4%), and Exon 19 Deletion (85.4%), with G716X mutations (22%) being the least common. About 97.6% were found to have at least one EGFR mutation. Approximately 90% of the mutations were sensitizing alterations responsive to EGFR tyrosine kinase inhibitors (TKIs), while 82.9% had at least one resistance mutation, indicating a potential challenge in frontline EGFR-targeted therapy.[2] Figure 1 depicts the distribution of mutation types among patients. Multiple concurrent mutations were common, with a significant proportion of patients exhibiting a combination of activating mutations (L858R, L861Q, 19D) along with resistance mutations (T790M, Exon 20 insertions, and S768I). Multiple concurrent mutations were common. A significant proportion of patients exhibited a combination of activating mutations (L858R, L861Q, 19D) along with resistance mutations (T790M, exon 20 insertions, and S768I). Notably, 34 patients (82.9%) had at least one resistance mutation, indicating a potential challenge in frontline EGFR-targeted therapy. [Figure 1]

The study involved a total of 41 patients, with a majority being male. The age of participants ranged from 40 to 70 years, with the largest group falling between 51 and 60 years. There was a significant prevalence of tobacco use among the patient. Additionally, most tumors were classified as moderately differentiated in terms of grade. [Figure 2]

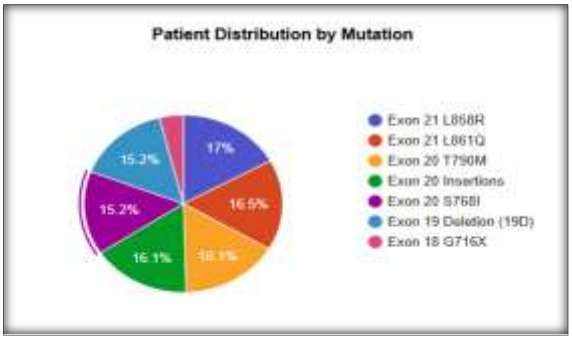

Figure 1: Patient distribution by Mutation

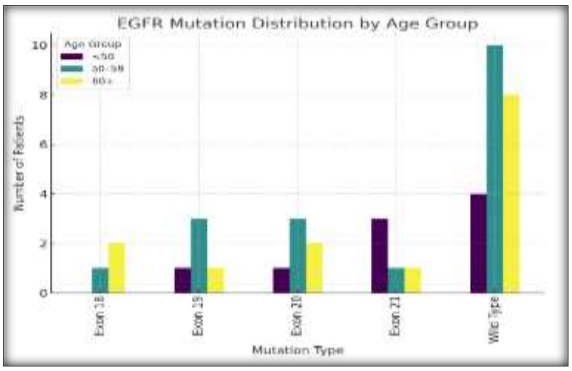

Figure 2: Mutation positivity by Age group

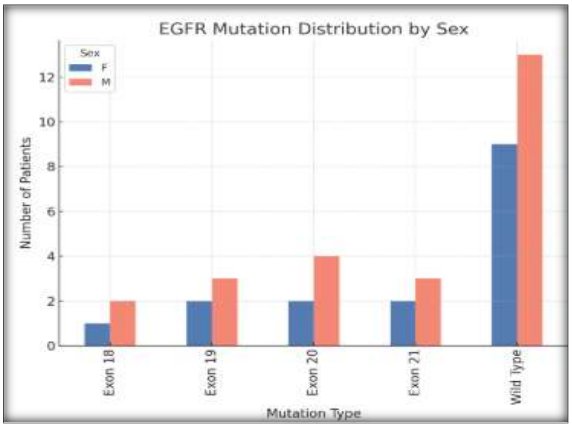

Figure 3: Mutation positively counts between sexes

Correlation by Sex (Mutation positivity count)

Table 1

Sex	T790M	S768I	L858R	L861Q	G716X	Exon 20 Insertions	Exon 19 Deletion
F	4	2	5	5	1	4	3
M	21	17	21	21	7	23	22

Male patients have significantly higher positivity across all exon mutations compared to females.

Correlation by Histopathological Diagnosis:

Well-differentiated squamous cell carcinoma (WDSCC) consistently showed the highest frequency across most exon mutations, followed by moderately differentiated SCC. Mild and low-grade dysplasia

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cases also demonstrated some positivity, notably in Exon 21 mutations (L858R, L861Q) and Exon 20 insertions.

DISCUSSION

The high prevalence of EGFR mutations observed in this study contrasts sharply with previous reports on HNSCC, where EGFR mutations are typically considered rare.[3] This discrepancy may be attributed to geographic, ethnic, or methodological differences. The predominance of mutations like L858R and L861Q, known sensitizing mutations, suggests that a majority of patients could benefit from first- or second-generation EGFR TKIs such as erlotinib, gefitinib, or afatinib.[4] However, the co-occurrence of resistance mutations such as T790M and Exon 20 insertions presents a clinical conundrum. In NSCLC, T790M typically emerges after TKI therapy, but its presence as a primary mutation in treatment-naive patients, as observed here, could necessitate the upfront use of third-generation inhibitors like osimertinib.[5]

Exon 20 insertions and S768I mutations, which mediate resistance to standard TKIs, further complicate the therapeutic landscape. While targeted therapies such as mobocertinib and amivantamab have shown promise against exon 20 insertions, their use in HNSCC remains off-label and investigational.[6] The detection of these mutations in a substantial number of patients highlights the need for clinical trials to assess efficacy in OCSCC and OPSCC.

Interestingly, G716X, a rare mutation associated with variable TKI response, was identified in 22% of patients. Its clinical significance in HNSCC is not well established, but its presence underscores the diversity of the EGFR mutational landscape.[7] These findings reinforce the heterogeneity of EGFR mutations in OCSCC and OPSCC. Comprehensive mutation testing should become routine to facilitate personalized therapy. Future studies should correlate mutation profiles with treatment response, progression-free survival, and overall survival.

Significance of EGFR Exon Mutations in Oropharyngeal Squamous Cell Carcinoma

Mutations in the EGFR gene are frequently localized to exons 18–21, encoding the tyrosine kinase domain critical for downstream signaling. Although most research on EGFR mutations has focused on NSCLC, such mutations are increasingly being identified in HNSCC, including OPSCC.[8] Exon 18 mutations such as G719X (G719S, G719A, G719C) are activating mutations leading to ligand-independent activation of EGFR and are sensitive to second-generation TKIs like afatinib and neratinib. Exon 19 deletions (E746_A750) are among the most common sensitizing mutations and are associated with high sensitivity to first- and second-generation TKIs and better prognosis. Exon 20 mutations, including T790M and insertions, confer resistance to standard TKIs, necessitating third-generation agents like osimertinib. Exon 21 L858R, a classic activating mutation, is highly sensitive to TKIs and suggests potential for cross-applicability of lung cancer strategies in OPSCC patients.

Clinical Implications

Given the high frequency of activating mutations, patients with OCSCC and OPSCC may benefit from EGFR-targeted therapies, particularly in the adjuvant or metastatic setting. However, the presence of resistance mutations necessitates a tailored approach. Sequential or combination therapy involving both first-line and third-generation TKIs may offer improved outcomes. Molecular profiling should also be revisited upon disease progression to detect acquired mutations.

Additionally, the integration of next-generation sequencing (NGS) platforms could provide a more comprehensive view of the mutational burden, including co-occurring mutations in other actionable genes such as PIK3CA, ALK, or MET.

CONCLUSION

This study demonstrates a remarkably high prevalence of EGFR mutations (97.6%) in patients with oral cavity and oropharyngeal squamous cell carcinoma, encompassing both activating and resistance-associated variants. Sensitizing mutations such as L858R and L861Q were highly frequent, suggesting a substantial potential for EGFR-targeted therapies in this population. However, the concurrent detection of resistance mutations like T790M and exon 20 insertions in a significant subset (82.9%) highlights the complexity of treatment strategies and the need for tailored approaches using first-line and third-generation tyrosine kinase inhibitors.

The findings contrast with earlier reports of rare EGFR mutations in head and neck cancers, possibly reflecting geographic, ethnic, or methodological differences. These results underline the importance of routine EGFR mutation testing using sensitive platforms such as RT-PCR or next-generation sequencing (NGS) to guide personalized therapy decisions. Further large-scale, multicenter studies are essential to validate these observations and to develop standardized clinical guidelines for the use of EGFR-targeted therapies in head and neck squamous cell carcinoma.

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