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The Prognostic Value of EGFR Amplifications in Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Objective: The epidermal growth factor receptor (EGFR) pathway plays a crucial role in head and neck squamous cell carcinoma (HNSCC) carcinogenesis, and alterations in this pathway have been explored as potential prognostic biomarkers. This study aimed to evaluate the prognostic role of next-generation sequencing (NGS)-defined EGFR amplification in HNSCC by analyzing data from large public datasets.

Material and Methods: Individual patient-level data from two publicly available datasets (HNSC_TCGA and HNSC_MDAnderson_2013) were extracted from the cBioPortal database. A total of 567 HNSCC patients were included, with data on age, sex, primary tumor location, EGFR amplification status, TNM stage, surgical margins, extracapsular spread, and survival outcomes. Descriptive statistics and Kaplan-Meier survival analyses were conducted to evaluate the association between EGFR amplification and overall survival (OS).

Results: EGFR amplification was present in 9.7% of the patients. Univariate analysis showed that patients with EGFR amplification had a significantly shorter OS (median OS 28.3 vs. 57.4 months, p=0.014). However, in multivariate analysis, EGFR amplification was not a significant predictor of OS after adjusting for other clinical factors (hazard ratio: 1.35, p=0.20). Other significant prognostic factors included extracapsular spread, age, stage, and surgical margin status.

Conclusion: While our findings suggest a trend toward shorter OS in patients with EGFR amplification, this association did not reach statistical significance after adjusting for other clinical factors in multivariate analysis. Further research with larger cohorts is needed to clarify the role of NGS-defined EGFR amplification as a prognostic biomarker and improve treatment strategies in HNSCC.

Keywords: Head and neck squamous cell carcinoma; EGFR amplification; cBioPortal; molecular biomarkers

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is among the most common cancers worldwide, with nearly a million new cases and over 250,000 deaths yearly.[1] While the disease is curable in earlier stages with surgery or radiotherapy, multimodal therapy incorporating surgery, radiotherapy, and chemotherapy is required in advanced settings. However, over half of the patients recur within the first five years following the definitive treatment.[2,3] The prognosis in advanced and metastatic disease is abysmal, with most clinical trials reporting less than 12 months of overall survival (OS) with systemic treatments.[4] Both the frequent recurrences in the earlier stage and the advanced stage with a dismal prognosis require novel individualized approaches for treatment. The development of novel prognostic biomarkers aiding treatment decisions in this regard could aid treatment selection and optimization.

The epidermal growth factor receptor (EGFR) pathway is instrumental for HNSCC carcinogenesis and alterations of this pathway are among the earliest events.[5] Therefore, evaluating EGFR alterations has emerged as a promising prognostic biomarker in HNSCC for over two decades.[6] However, the best method to ascertain the effect of EGFR aberrations on prognosis has yet to be determined. Earlier studies conducted

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by immunohistochemistry (IHC) demonstrated that EGFR overexpression was associated with an increased risk of recurrence, radiotherapy resistance, and treatment failure, although the cut-offs for EGFR overexpression (median, 50%, quartile) were not uniform.[7,8] Additionally, most studies did not show the association between EGFR overexpression and systemic therapy benefit.[9] Similarly, using fluorescence *in situ* hybridization-detected EGFR amplification as a prognostic biomarker was evaluated for different disease stages and treatment modalities, and this approach created inconsistent results.[10] These issues highlight the need for further research on the role of EGFR alterations in HNSCC prognosis via different methods.

Next-generation sequencing (NGS) has become an integral part of cancer care and is widely used in clinical practice, particularly in advanced non-small cell lung cancer.[11] Several studies evaluated the role of NGS-defined EGFR amplifications in NSCLC and colorectal cancer, suggesting its possible use as a prognostic biomarker.[12,13] However, prospective, well-adjusted NGS-based prognostic data on HNSCC are limited. Therefore, we evaluated the prognostic role of NGS-defined EGFR amplification in HNSCC from the published public datasets.

MATERIAL AND METHODS

Patient Population and Study Extraction

We used published individual patient-level data from the two datasets (HNSC_TCGA and HNSC_MDAnderson_2013) from the cBioPortal database (https://www.cbioportal.org/). We selected HNSCC patients through the HNSC OncoTree cancer type taxonomy. After extracting these data, we excluded patients without EGFR amplification or survival data and duplicate cases. The final cohort included 567 patients with HNSCC.

We extracted the following data from the available dataset: Age, sex, primary tumor location, EGFR amplification, TNM stage, surgical margin, presence or absence of extracapsular spread, overall survival, and disease-free survival follow-up times, and presence of progression or death.

Statistical Analyses

We presented descriptive characteristics with the median and [interquartile range (IQR); 25^{th}-75^{th} percentile], for continuous variables and frequency and percentages for categorical variables. According to the NGS results, the patients were dichotomized into the EGFR amplification and no amplification groups. The baseline characteristics of the patients with or without EGFR amplification were compared with Independent samples t-tests and chi-square tests for continuous and categorical variables, respectively.

The OS time was defined as the period from the diagnosis to the last follow-up and/or death. Survival analyses were conducted using the Kaplan-Meier method, and to compare survival times between prognostic subgroups were made using the log-rank test. Multivariate analyses were conducted using Cox regression, including statistically significant parameters from the univariate survival analyses, and hazard ratios were calculated together with 95% confidence intervals (CI). The statistical analyses were performed with SPSS, version 25.0 (IBM Inc., Armonk, NY, USA). A type-I error level of 5% ($p<0.05$) was considered the threshold limit for statistical significance.

RESULTS

A total of 567 patients were included in the analyses. The median age was 61 (IQR 53-69) and 72.8% of the patients were male. The most frequent primary tumor site was the oropharynx (57.7%), followed by the larynx (22%). In patients with available data (n=296), the median smoking pack year was 40 (IQR 25-60). 51.6% of the patients had node-positive disease and 63% of the patients had T3-T4 disease. The median tumor mutational burden was 3.63 (IQR 2.3-5.83). 32% of the patients had extracapsular invasion in lymph nodes and 24% had close or positive surgical margins. Baseline characteristics of the study population are summarized in Table 1.

The EGFR amplification was present in 55 patients. The patients with EGFR amplification had similar age, sex, stage, nodal status, and surgical margin status compared to patients without EGFR amplification (Table 2). The patients with EGFR amplification had significantly shorter OS compared to patients without EGFR amplification [median OS (mOS) 28.3 vs. 57.4 months, p=0.014] (Figure 1). Similarly, patients with close or positive surgical margins (mOS 32.5 vs. 64.8 months, p=0.002) with extracapsular invasion (mOS 17.4 vs. 76.2 months, $p<0.001$) with advanced stage disease (stage III-IV vs. stages I-II, mOS 49.4 vs. 100.5 months, p=0.002) had significantly inferior OS in univariate analyses. A multivariable analysis model via backward variable selection was constructed, including these five parameters that showed statistical significance in univariate analysis. Only extracapsular invasion (microscopic or macroscopic) retained a statistically significant association with OS in these models (hazard ratio: 2.643, 95% CI: 1.906-3.664, $p<0.001$) and the presence of EGFR amplification did not have a statistically significant association with OS in the multivariable analyses. While there were numerical differences, the association between most other classical clinical parameters and survival did not reach statistical significance (Table 3).

TABLE 1: Baseline characteristics of the study population (n=567).	
Characteristic	**n (%) or median (IQR)**
Age, years	61 (53-69)
Sex	
Male	413 (72.8)
Female	154 (27.2)
Primary tumor site[1]	
Oropharynx	304 (57.7)
Larynx	116 (22.0)
Other	107 (20.3)
Smoking, pack-years[1]	40 (25-60)
Nodal status[1]	
Node positive	259 (51.6)
Node negative	245 (48.4)
T stage[1]	
T1-T2	189 (37.0)
T3-T4	323 (63.0)
Tumor mutational burden	3.63 (2.30-5.83)
Extracapsular invasion[1]	116 (32.0)
Surgical margin[1]	
Close/positive	112 (24.0)
Negative	354 (76.0)
[1]: Data available for fewer patients due to missing values; IQR: Interquartile range.	

TABLE 2: Baseline characteristics by EGFR amplification status.			
Characteristic	**EGFR amplification, [n (%) or median (IQR)]**	**No EGFR amplification [n (%) or median (IQR)]**	**p-value**
Age, years	59 (51-67)	61 (53-69)	0.36
Sex			0.73
Male	39 (70.9)	374 (73.0)	
Female	16 (29.1)	138 (27.0)	
Stage (III-IV)	45 (81.8)	372 (78.8)	0.60
Node negative	23 (43.4)	222 (49)	0.81
Close/positive surgical margin[1]	9 (18)	103 (24.8)	0.29
Extracapsular invasion[1]	15 (37.5)	101 (31.4)	0.43
[1]: Data available for fewer patients due to missing values; EGFR: Epidermal growth factor receptor; IQR: Interquartile range.			

DISCUSSION

In the present analyses of two large cohorts with HNSCC, EGFR amplification was present, in approximately 10% of the patients with HNSCC. The rate of EGFR amplification was independent of stage, sex, age and surgical margin status. Although there was a difference in univariate analyses, we observed similar OS in patients with or without EGFR amplification in multivariable analyses. Our findings question the prognostic role of NGS-defined EGFR amplification in HNSCC and the previous data evaluating the EGFR overexpression defined via IHC.

The EGFR is a pivotal target in HNSCC, and improved OS with EGFR targeting was reported both in the localized and the advanced stage disease over 10 years ago.[14] In the localized stage disease, the OS was almost doubled with the addition of cetuximab, an anti-EGFR monoclonal antibody, to radiotherapy. Moreover, the addition of cetuximab to cisplatin plus 5-FU in the first-line treatment of advanced stage disease was associated with a three-month OS benefit

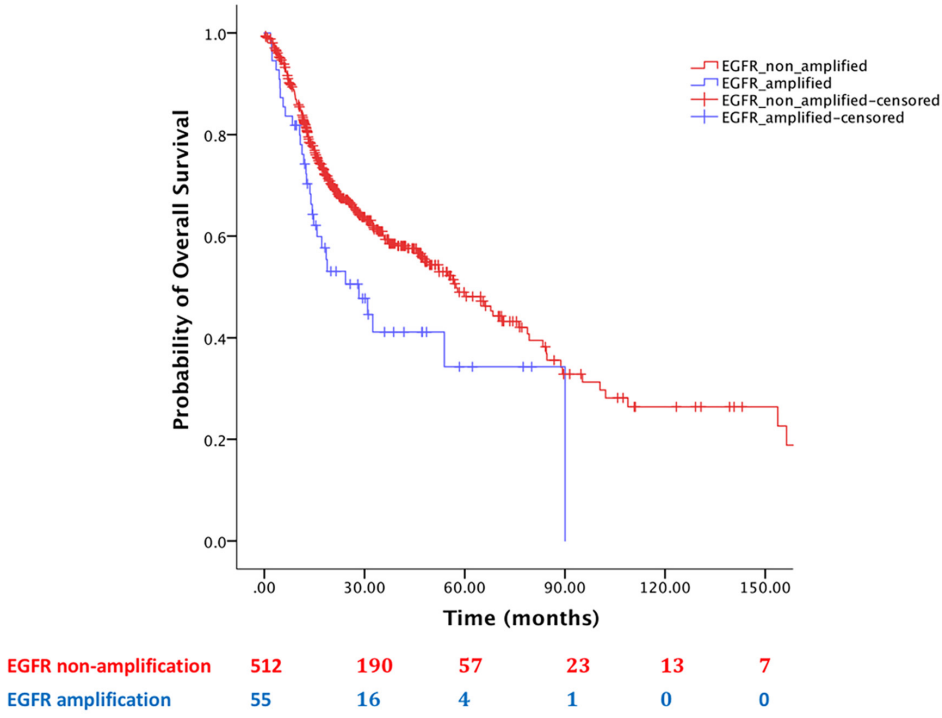

FIGURE 1: Kaplan-Meier curves for overall survival according to EGFR amplification status in patients with head and neck squamous cell carcinoma.

EGFR: Epidermal growth factor receptor

TABLE 3: Multivariate Cox regression analyses for overall survival.

Variable	Multivariate HR (95% CI)	p-value
Presence of EGFR amplification	1.35 (0.85-2.15)	0.20
Close/positive surgical margin	1.18(0.81-1.73)	0.38
Extracapsular invasion	2.64 (1.91-3.66)	<0.001
Stage III-IV	1.39 (0.82-2.34)	0.21

EGFR: Epidermal growth factor receptor; HR: Hazard ratio; CI: Confidence interval.

in the advanced setting.[15,16] While these practices are subject to change in the era of immunotherapy, EGFR targeting is still an indispensiple part of treatment algorithms in cisplatin-ineligible patients in the localized stage disease and in the later lines of treatment in the advanced-stage disease.[17] However, a significant portion of the patients with localized stages and almost all patients with advanced stage disease recur or progress after treatment, necessitating novel biomarkers for treatment individualization.[18] Using EGFR as a prognostic biomarker garnered interest in the past, although the overexpression in up to 80% of the patients and the poorly defined measurement methods limited the clinical utility.[18] We thought that with the more widespread use of NGS, EGFR amplifications could be detected, and we sought to explore the potential of this as a biomarker.

While we observed a numerically shorter OS in patients with the NGS-based EGFR amplification, the difference did not reach statistical significance in the multivariable analyses. There could be several reasons for that. First of all, fewer than 60 patients had EGFR amplification, limiting the power of the analyses. Similar to EGFR amplification status, a robust association in the univariate analyses was not retained in the multivariable analyses, suggesting that limited sample size may be a potential confounder. The rate of EGFR amplification was significantly lower compared to studies evaluating EGFR upregulation via IHC, reporting higher rates of EGFR aberrations.

Study Limitations

The present study has potential limitations. These issues include the retrospective nature of the study and potential

selection bias that may originate from HNSCC datasets included in the cBioPortal. Second, detailed clinical variables such as HPV/p16 status, treatment modality (surgery, radiotherapy, chemotherapy, immunotherapy), primary tumor site, T and N classification, year of diagnosis, and institution were not available.

CONCLUSION

The absence of these factors may have introduced confounding; for example, HPV positivity is a strong prognostic marker in oropharyngeal cancer and may interact with EGFR biology, while differences in treatment modality can substantially alter survival outcomes. Furthermore, the high percentage of missing data on several important variables like ECE and surgical margin status diminished the power of the multivariable analyses. However, despite these limitations, we presented one of the largest bodies of evidence to date on a controversial prognostic parameter in HNSCC. Further prospective studies are warranted to validate our findings in larger cohorts.

Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Y., T.K.Ş., D.C.G., S.A., Concept: B.Y., T.K.Ş., D.C.G., S.A., Design: B.Y., T.K.Ş., D.C.G., S.A., Data Collection or Processing: B.Y., T.K.Ş., D.C.G., S.A., Analysis or Interpretation: B.Y., T.K.Ş., D.C.G., S.A., Literature Search: B.Y., T.K.Ş., D.C.G., S.A., Writing: B.Y., T.K.Ş., D.C.G., S.A.

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