Various Pathways in Aerodigestive Carcinogenesis

Tulunay OE, Tulunay O, Lonardo F, Kucuk O, Sakr W, Jacobs JR
Karmanos Cancer Institute, Detroit Medical Center and Wayne State University, Detroit, MI
Medical School of Ankara University, Ankara, Turkey

ABSTRACT

Objective: Molecular markers that reliably predict outcome of head and neck cancer patients are yet to be identified. The EGFR, as well as the protein adhesion kinase pathways, and their role in the progression of aerodigestive cancer, with particular attention given to the EGFR pathway and various downstream genes was studied.

Design: Immunohistochemical studies with the proliferation marker Ki-67, protein kinase pFak, the growth factor receptor EGFR, as well as its downstream genes pAkt, pStat3 and the nuclear transcription factor kappa B (NFkB) were performed on 27 patient specimens. These were correlated with patient clinical and follow-up data.

RESULTS: Mean age of the patients was 56.6 years (range: 46-74 years) with 6 females and 21 males. The mean follow up was 59.4 mo (range: 11-88 mo). In 77.7 % of the specimens, more than 75% of the cells were stained with Ki-67. While 88.9% were stained strongly for EGFR, 89.3% were positive for pAkt, 3/27 showed strong pFak staining. Only 5/27 was moderate to strongly stained with pAkt, and 15/27 was negative for this marker. 6/27 was positive for NFkB. There was statistically significant correlation between pAkt, NFkB, EGFR and T status, as well as a significant inverse relationship between EGFR and pFak. No significant correlation between recurrence and any of the markers were found.

Conclusion: The EGFR receptor is universally over-expressed in HNSCC, and is correlated with the expression of downstream signaling molecules pAkt and NFkB, which also showed a significant relationship with T status. In contrast, the role for pFak appears to be limited.

INTRODUCTION

HNSCC is the most common histological type in this location, and is one of the leading causes of cancer deaths worldwide.

Most HNSCC patients are diagnosed with advanced disease, i.e. they have locally invasive tumors, tumors with metastasis or recurrent tumors.

Despite improvements in management and extension of the tumor beyond the lymph node capsule have long been known as the most predictive factors for regional recurrence and death from HNSCC, little is known about the biologic basis of tumor progression of HNSCC.

Although current clinicopathological parameters have proven their prognostic significance in primary HNSCC, there is an utmost need of biological predictors for individual tumor behavior with respect to response to treatment, survival rate, and progression to metastasis.

HNSCC, as shown by nuclear Ki-67 expression

EGFR expression in basal and parabasal cells in normal mucosa (A), in SCC, similar to normal mucosa, more differentiated and lower expression (B) and expression is stronger in dysplasia (C).

Nuclear expression of pSTAT3 was graded as none (0), few cells (1), <10% (2), 10-50% (3), >50% (4). The intensity of the immunostaining was semiquantitatively rated as absent (0), weak (1), moderate (2), and strong (3).

EGFR expression in various malignancies correlates significantly with high tumor grade and the development of metastatic disease.

Conclusion: The EGFR receptor is universally over-expressed in HNSCC, and is correlated with the expression of downstream signaling molecules pAkt and NFkB, which also showed a significant relationship with T status. In contrast, the role for pFak appears to be limited.

CONCLUSION

No significant correlation between recurrence and any of the markers were found.

The EGFR receptor is universally over-expressed in HNSCC, and is correlated with the expression of downstream signaling molecules pAkt and NFkB, which also showed a significant relationship with T status.

Further studies with larger series are needed to clearly demonstrate the role of these markers in the progression of HNSCC.