

## INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR (IGF1R) EXPRESSION AND SURVIVAL IN OPERABLE SQUAMOUS-CELL LARYNGEAL CANCER

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### Abstract

#### INTRODUCTION:

Prognosis of patients with operable laryngeal cancer is highly variable and therefore potent prognostic biomarkers are warranted. The insulin-like growth factor receptor (IGFR) signaling pathway plays a critical role in laryngeal carcinogenesis and progression.

#### PATIENTS AND METHODS:

We identified all patients with localized TNM stage I-III laryngeal cancer managed with potentially curative surgery between 1985 and 2008. Immunohistochemical (IHC) expression of IGF1R-alpha, IGF1R-beta and IGF2R was evaluated using the immunoreactive score (IRS) and mRNA levels of important effectors of the IGFR pathway were assessed, including IGF1R, IGF-binding protein 3 (IGFBP3), suppressor of cytokine signaling 2 (SOCS2) and members of the MAP-kinase (MAP2K1, MAPK9) and phosphatidylinositol-3 kinase (PIK3CA, PIK3R1) families. Cox-regression models were applied to assess the predictive value of biomarkers on disease-free survival (DFS) and overall survival (OS).

#### RESULTS:

Among 289 eligible patients, 95.2% were current or ex smokers, 75.4% were alcohol abusers, 15.6% had node-positive disease and 32.2% had received post-operative irradiation. After a median follow-up of 74.5 months, median DFS was 94.5 months and median OS was 106.3 months. Using the median IRS as the pre-defined cut-off, patients whose tumors had increased IGF1R-alpha cytoplasm or membrane expression experienced marginally shorter DFS and significantly shorter OS compared to those whose tumors had low IGF1R-alpha expression (91.1 vs 106.2 months,  $p = 0.0538$  and 100.3 vs 118.6 months,  $p = 0.0157$ , respectively). Increased mRNA levels of MAPK9 were associated with prolonged DFS ( $p = 0.0655$ ) and OS ( $p = 0.0344$ ). In multivariate analysis, IGF1R-alpha overexpression was associated with a 46.6% increase in the probability for relapse ( $p = 0.0374$ ). Independent predictors for poor OS included node-positive disease (HR = 2.569,  $p < 0.0001$ ), subglottic/transglottic localization (HR = 1.756,  $p = 0.0438$ ) and IGF1R-alpha protein overexpression (HR = 1.475,  $p = 0.0504$ ).

#### CONCLUSION:

IGF1R-alpha protein overexpression may serve as an independent predictor of relapse and survival in operable laryngeal cancer. Prospective evaluation of the IGF1R-alpha prognostic utility is warranted.