SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE: STUDIES OF BIOMARKERS CONNECTED TO HUMAN PAPILLOMAVIRUS INFECTION, EPITHELIAL TO MESENCHYMAL TRANSITION AND LOCOREGIONAL METASTASIS

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Betula, byggnad 6M, Fredagen den 2 juni, kl. 09:00. Avhandlingen kommer att förvaras på engelska.

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Abstract

Background: Oral Tongue Squamous Cell Carcinoma (OTSCC) is the most frequent and aggressive carcinoma in the head and neck region. Its incidence has increased during the last decades, especially in young patients (≤ 40 years) mainly female. These young patients have either not been exposed to the traditional risk factors for this disease, or have a much reduced duration of exposure than the typical OTSCC patient. The reasons behind this increasing incidence remain unknown. The aims of this thesis were to analyse the presence and possible role of human papillomavirus (HPV) in oral tongue cancer in correlation with its surrogate marker p16 and its receptor syndecan-1. Other aims were to evaluate expression of EMT (epithelial to mesenchymal transition) - related markers, such as E-cadherin, β-catenin, CK5 and CK19, and to address the potential predictive role of podoplanin in the loco-regional metastatic process. Clinical parameters including age, sex, geographical distribution, relapse, tumour staging and grading were also investigated for a possible correlation with biomarker expression and prediction of survival rate and therapeutic strategy.

Materials and methods: More than one hundred samples of OTSCC coming from two University Hospitals of two different countries (Sweden and Italy) were analysed. HPV presence was evaluated by in situ hybridisation for detection of the high-risk HPV 16 and indirectly by immunohistochemistry (IHC) of its surrogate marker p16. Expression of the HPV receptor syndecan-1 and the EMT biomarkers E-cadherin, β-catenin, CK5, CK19 were also evaluated by immunohistochemistry. Samples were scored using a quick score (QS), taking both number and intensity of cells stained into account. Podoplanin expression was investigated at both protein and RNA level.

Results: Tumour size and lymph node metastasis correlated to both overall and disease-free survival. Despite variable expression of the syndecan-1 receptor, HPV 16 was not detected in any sample analysed, excluding a possible association with p16, which was expressed in 33% of the cases. All EMT-related markers were commonly expressed in tongue cancer. Data showed E-cadherin to be an independent prognostic factor with higher expression associated with poor overall survival. Notably, E-cadherin, β-catenin and CK5 directly correlated to each other. Multivariate analysis of clinical data demonstrated that age of the patient is an independent prognostic factor with younger patients showing a worse survival rate. Patients younger than 40 years also showed significantly higher expression of podoplanin. Data for geographic distribution revealed a difference in expression of E-cadherin between Swedish and Italian patients.

Conclusions: In contrast to SCC of the base of the tongue and the tonsil, HPV is not present in OTSCC, excluding HPV infection as a risk factor. Higher levels of E-cadherin and young age is associated with poor survival in OTSCC patients. The different frequency of EMT markers seen between Swedish and Italian patients suggests an important role for the environment and the geographical area in the onset of different molecular patterns of OTSCC.

Keywords
oral tongue cancer, squamous cell carcinoma, human papillomavirus, p16, syndecan-1, epithelial to mesenchymal transition, E-cadherin, β-catenin, cytokeratins, locoregional metastasis, podoplanin