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Review

Prognostic factors of gingival-alveolar squamous cell carcinoma of the maxilla

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ABSTRACT

Objectives: To determine prognostic factors in gingivo-alveolar squamous cell carcinoma of the maxilla (GA-SCC-M), and particularly the prognostic value of both vertical and antero-posterior tumor spread.
Material and methods: Our retrospective study included all naïve-treatment patients treated in our center between 2006 and 2013 for GA-SCC-M. Posterior involvement was considered when the tumor extended behind the mesial side of the first maxillary molar. Spread posterior to the maxillary tuberosity was defined by the spread to at least one of the following structures: pterygomaxillary fissure, pterygoid muscles, and processes. Involvement of the maxillary sinus floor, nasal fossa, and orbital floor was assessed, concerning the vertical spread.
Results: A radiological tumor spread to the nasal fossa, maxillary sinus floor, and orbital floor were prognostic factors independently of age, cervical lymph node metastasis and positive margins in multivariate analysis ($p < 0.05$). Radiological suggested spread tended to be noticeably more predictive of a poor prognosis than histological proven tumoral spread. The prognosis was not significantly different between clinical tumoral spread anteriorly or posteriorly to the first molar ($p = 0.46$). The prognosis was not worsened, even in case of radiological suggested spread posterior to the maxillary tuberosity ($p = 0.09$).
Conclusion: A vertical radiological spread of GA-SCC-M was a prognostic factor but not the extension posteriorly to the maxillary tuberosity. T4b tumors were mostly resectable, proving that a T4b stage was not predictive of unresectability in GA-SCC-M of the maxilla.

Contents

Abbreviations: GA-SCC-M, Gingival-Alveolar Squamous Cell Carcinoma of the Maxilla; VEGF, Vascular Endothelial Growth Factor; IL1, interleukin 1; TNF, Tumor Necrosis Factor; PDL, Programmed Death Ligand; HIF, Hypoxia Induced Factor.

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1. Introduction

Gingival-alveolar squamous cell carcinoma of the maxilla (GA-SCC-M) is a rare disease, with an incidence around 1 per 100,000 per year [1–3]. As for all rare diseases, establishing a prognostic score for GA-SCC-M is often limited by the small number of patients in retrospective series.

The TNM classification and the UICC cancer staging are widely used in the prognostic evaluation of oral cavity cancers. In oral cavity cancers, according to UICC cancer staging, 5-year overall survival rate varies from 59.8% in stage I to 23.3% in stage IV [4]. However, both TNM and UICC seem to fail in describing the variability of clinical situations in GA-SCC-M.

Öhngren, in 1936, hypothesized that posterosuperior locations of maxillary tumors were associated with poor prognosis [5]. Since then, only Wang et al., in 2010, reported that posterior spread of hard palate and maxillary alveolus SCCs was associated with lower survival rates [6]. Considering the relevant anatomical features of the maxillary bone structure with regards to surgical resectability, both antero-posterior and vertical tumor extensions could worsen the prognosis in GA-SCC-M. Sasaki et al. in 2004 demonstrated that spread to the nasal and maxillary sinus floors was associated with lower survival rates, but the superior spread (i.e. orbital floor and infra orbital nerve canal) was not analyzed [7]. The aim of our study was to determine prognostic factors of GA-SCC-M and particularly the prognostic value of both vertical and antero-posterior spread.

2. Patients and methods

2.1. Patients

Our retrospective study included all patients treated for GA-SCC-M between 2006 and 2013 in our center. Patients whose tumor's primary origin was either the maxillary sinus or the soft palate, and patients previously treated in another center were excluded.

Clinical, radiological, histopathological data, treatment decision of cancer board, event-free survival, number and delay before relapses, and cause of death if occurred were recorded for every patient.

Tumor staging was made according to the sixth edition of UICC TNM classification.

2.2. Radiological assessment

A radiological evaluation of tumor spread was performed after reviewing initial CT scan and Magnetic Resonance Imaging (MRI) with a radiologist. Posterior involvement was considered when the tumor extended behind the mesial side of the first maxillary molar. Spread posterior to the maxillary tuberosity was defined by the spread to at least one of the following structures: pterygomaxillary fissure, pterygoid muscles, and pterygoid processes. Involvement of the maxillary sinus floor, nasal fossa, and orbital floor was assessed, concerning the vertical spread. The spread to the nasal fossa included the invasion of at least one of the following structures: nasal floor, nasal mucosa, and concha. The orbital floor spread was defined by the presence of either orbital floor lysis or infiltration of the infra orbital canal.

2.3. Statistical analysis

In a first stage, the clinical, radiological and histological proven spread to each of the following anatomical structure supposed to be implicated in GA-SCC-M prognosis (clinical spread posterior to the first molar, radiological and histological spread to the nasal fossa, maxillary sinus floor and mucosa, orbital floor, spread posterior to the maxillary tuberosity) were coded as binary variables to conduct a univariate survival analysis following the Kaplan-Meier method. A log-rank test was used to compare the survival curves. We conducted multivariate analyses using Cox's model to take into account various covariates (age, local relapse due to positive surgical margins, pN + stage (histopathological lymph node metastasis), vascular emboli, and perineural spread as categorical factors). We performed a stepwise model selection using the Akaike information criterion. The associated coefficients of the independent factors (HR and corresponding CI at 95%) were calculated from each final Cox model.

Survival analysis for TNM and UICC stages, tobacco and alcohol abuse, narrow margins <5 mm, and positive margins was made to compare our patient sample with the literature.

The primary time variable, whatever the survival analysis process, was the delay between the diagnosis of GA-SCC-M and death when occurred. The test of Schoenfeld residuals was used to verify the hypothesis of proportional risks for each model. The critical significance level (accepted first species error rate) was 0.05.

All analyses were performed using the R version 3.1.0 (2014-04-10) and its associated packages (survival, MASS) and XLSTAT Version 2013.6.01 (Copyright Addinsoft 1995–2013). Kaplan Meier curves were performed with GraphPad Prism 5®.

3. Results

Fourty-seven naïve-treatment patients out of the 60 patients treated for GA-SCC-M in our center between 2006 and 2013 met the inclusion criteria. Three patients previously treated in another center and 10 patients with incomplete radiological data were excluded from the study.

Mean age at diagnosis was 68.6 years (from 29 to 92 years) (Table 1). Age was not significantly different whatever the tumor location, anteriorly or posteriorly to the mesial side of the first molar (70 ± 14 vs 67 ± 15 respectively, $p = 0.61$, Student test). The female/male ratio was 47/53. Alcohol and tobacco abuse was reported in 25% of the cases and didn't influence overall survival ($p = 0.30$ and 0.65 respectively). The most frequent stage was T4 (74%), mainly T4N0 and T4N2 (40% and 28% respectively). T4 stage and UICC stage IV were associated with significantly lower overall survival rates in comparison with T1, T2, and T3 stages ($p < 10^{-2}$) and with UICC stages I, II, and III ($p = 0.01$), respectively. The presence of a pN + stage negatively impacted overall survival ($p < 10^{-2}$). A metastatic stage was present in 2 patients (4%) at the