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The value of histological grading of biopsy and resection specimens in early stage oral squamous cell carcinomas

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ABSTRACT

Introduction: In oral squamous cell carcinoma (OSCC) the differentiation grade of the tumor is determined on the biopsy and the resection specimen. The relation between tumor grade, nodal metastasis and survival is debatable. The aims of this study were to determine the correlation between differentiation grade of the biopsy and the resection specimen. Furthermore, we wanted to correlate tumor differentiation grade with nodal stage and survival.
Patients and methods: One-hundred and forty-five patients with OSCC staged as T1-2, N0 of the tongue, floor of mouth or cheek with primary resection of the tumor were examined. Biopsy and resection specimen were histologically re-assessed with regard to differentiation grade, as well as infiltrative, perineural and vascular invasive growth.
Results: This study showed a poor correlation between differentiation grade in the incisional biopsy and the resection specimen of the same tumor. No significant relation between differentiation grade of the resection specimen and nodal involvement, as well as overall and disease-specific survival was found.
Conclusion: In early OSCC the differentiation grade determined by biopsy is of little predictive value for the grading of the resection specimen. Poor differentiation grade could not be related to the presence of nodal metastasis or survival and seems not to have any prognostic value concerning outcome. Treatment planning must be related to these findings.

1. Introduction

In early stage (I-II) oral squamous cell carcinoma (OSCC) complete surgical removal of the tumor is the treatment of choice (Dik et al., 2014). The management of the clinically negative neck (cN0) is still an issue of debate (D'Cruz et al., 2015; Dik et al., 2016; Iype et al., 2008; Keski-Santti et al., 2008; Melchers et al., 2012; Norling et al., 2012; Yuen et al., 2009). The presence of histological features, such as perineural growth and vascular invasive growth and infiltrative growth, is associated with an increased risk of nodal metastases (Brandwein-Gensler et al., 2005; Dik et al., 2015; Melchers et al., 2012). In some studies, moderate and poor differentiation grade of the OSCC is correlated with a more aggressive tumor behavior and subsequent risk of regional nodal metastases (Akhter et al., 2011; Arduino et al., 2008). Others did not find this association between grade and nodal status (Weijers et al., 2009; Woolgar, 2006). In many head and neck cancer centers, differentiation grade is routinely determined on the biopsy and resection specimen. It is unknown whether the differentiation grade of the preoperative biopsy specimen corresponds to the grade of the subsequent resection specimen and could play a role in the decision making on how to treat the neck. The aims of this study were to determine the correlation between differentiation

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grade of the biopsy and resection specimen in stage I and II OSCC's. Furthermore, we aimed to correlate differentiation grade of the resection specimen with other growth parameters, nodal stage and survival.

2. Materials and methods

2.1. Patients

The prospectively collected database of the Department of Oral and Maxillofacial Surgery of the University Medical Center was queried to identify patients with a pT1-2 cN0, OSCC of the tongue, floor of mouth or cheek (International Classification of Diseases for Oncology. 3rd Edition locations C02.0–C02.3, C04, and C06.0) (A. F, 2000) All patients were staged and treated according to the guideline of the Dutch Society of Head and Neck Cancer and the UICC TNM staging system (A. F, 2000). Patients were treated with primary surgical resection with or without a selective neck dissection between 2004 and 2010. To be included in the study, an incisional biopsy had to be taken before the definitive resection with 10 mm safety margin was performed and histological paraffin sections of all included biopsies had to be present for re-assessment. In total, 226 patients were identified. Twenty-one patients were excluded because of a previous head and neck malignancy in the last five years, 39 patients because a preoperative biopsy was taken elsewhere and not available for reassessment, ten patients due to the inability to assess differentiation grade of the biopsy specimen, and eleven because the resection specimen showed only micro-invasive growth. Postoperatively, all patients were followed up for at least three years with clinical examination (i.e. palpation of the neck) and on indication US examination accompanied by fine needle aspiration cytology if needed. Patients were classified as "node-positive" (N+) if a neck dissection was performed and showed a positive node or if a watchful waiting policy of the neck was performed and the patient was confronted with a nodal metastasis during follow-up. All others were classified as "node-negative" (N−).

2.2. Histological analysis

All preoperative biopsies were taken randomly. A defined protocol on size, volume or location of the biopsy did not exist. Four experienced head and neck surgeons performed tumor resections with macroscopic safety margins of at least 10 mm. The incisional biopsies and surgical resection specimens of the primary tumors were all re-assessed by an experienced head and neck pathologist (SMW) who was blinded for the correlation of histological grade between biopsy and resection specimen. Tumor differentiation grade was determined according to the World Health Organization (WHO) classification system (Broders' grade) (Thompson, 2006) based on the differentiation of the cells. Tumors were scored as well differentiated (<25% of undifferentiated cells), moderately differentiated, (≥25% < 50%) poorly differentiated (≥50% < 75%), or undifferentiated (≥75%) (see Fig. 1) (Kantola et al., 2000; Vasconcelos et al., 2014). Unfavorable growth parameters such as peri-neural growth, vascular invasive growth and infiltrative growth were all re-assessed on biopsy and resection specimen by the same blinded pathologist (SMW) Perineural growth was defined as the presence of malignant cells in the neural space and/or the movement of malignant cells along the nerve (Roh et al., 2015). Vascular invasive growth was defined as the presence of aggregates of tumor cells within endothelial-lined channels or invasion of the media of a vessel with ulceration of the intima. Infiltrative growth was defined based on the presence of non-cohesive tumor cells that form an ill-defined edge with formation of strands with or without isolated tumor islands (Woolgar, 2006).

The results found in the resection specimen were regarded as the true pathological diagnosis.

2.3. Statistical analysis

Diagnostic accuracy of the biopsy comprises sensitivity, specificity and positive predictive value (PPV). Sensitivity (or true positive rate) was defined as the probability of having a positive test, i.e. the finding of a certain differentiation grade in the biopsy, given this specific differentiation grade is present in the resection specimen. Specificity (or true negative rate) is the probability of absence of a particular differentiation grade in the biopsy if the parameter was truly absent in the resection specimen. PPV is defined as the probability of actually having the parameter in those with a certain differentiation grade (Connell and Koepsell, 1985). To calculate these results, the histological parameter in the resection specimen was used as reference standard. P was taken as the pre-test probability.

Differentiation grade in the resection and biopsy specimen was related to N status. Tumor grade in the resection specimen was correlated with unfavorable histological growth parameters (i.e. perineural growth, vascular invasive growth and infiltrative growth) and survival. Hypothesis testing of categorical data was done with Fisher's exact test. Using life table techniques, overall survival and disease-specific survival rates were calculated, illustrated by Kaplan–Meier plots. Overall survival was calculated from date of diagnosis to date of death from any cause. For disease-specific survival, censoring occurred at date of death from causes other than OSCC or at the end of follow-up, whichever came first. Covariates were compared with the log-rank test. Of every histological parameter, prevalence (P) and diagnostic accuracy (point estimate and 95% confidence interval), was determined. All test statistics were two tailed, and the

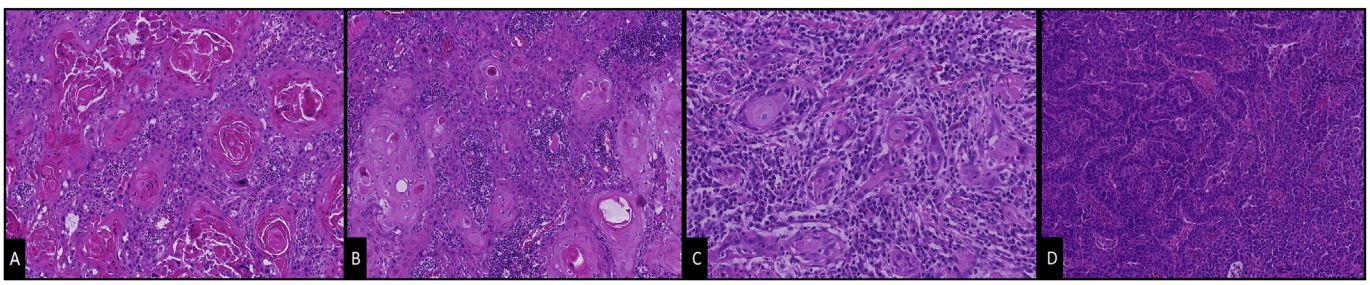

Fig. 1. Differentiation grades in oral squamous cell carcinoma, A. Well differentiated (H&E x 200), B. Moderately differentiated (H&E x 200), C. Poorly differentiated (H&E x 200), D. Undifferentiated (H&E x 200).

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