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Evaluation of bone resection margins of segmental mandibulectomy for oral squamous cell carcinoma

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Abstract. Resection margins are frequently studied in patients with oral squamous cell carcinoma and are accepted as a constant prognostic factor. While most evidence is based on soft tissue margins, reported data for bone resection margins are scarce. The aim of this retrospective study was to evaluate and determine the utility of surgical margins in bone resections for oral cavity squamous cell carcinoma (OCSCC). The status of bone resection margins and their impact on survival was investigated in patients who had undergone segmental mandibulectomy for OCSCC. Medical records were retrieved for the years 2000–2012; 127 patients were identified and included in the study. Tumour-positive bone resection margins were found in 21% of the patients. The 5-year overall survival was significantly lower in this group ($P < 0.005$). Therefore, there is a need for intraoperative feedback on the status of bone resection margins to enable immediate additional resection where necessary. Although the lack of intraoperative methods for the evaluation of bone tissue has been addressed by many authors, there is still no reliable method for widespread use. Future research should focus on an objective, accurate, and rapid method of intraoperative assessment for the entire bone resection margin to optimize patient outcomes.

Key words: oral cancer; oral oncology; segmental mandibulectomy; bone resection margins; intraoperative assessment.

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For oral cavity squamous cell carcinoma (OCSCC), surgery remains the treatment of choice, with the goal of complete removal of the tumour with adequate margins[1,2]. In the case of mandibular invasion by OCSCC, the affected part of the bone is resected. The extent of mandibular resection depends on the degree of bone invasion, but should be as limited as possible in order to preserve function. In general, a segmental mandibulectomy is indicated where there is a large tumour with bone infiltration or where the inferior alveolar nerve (IAN) is involved. Also, in the case where the mandibular resection would result in a remnant that does not have adequate functional strength, a segmental mandibulectomy is preferred over a marginal resection. Moreover, circumferential tumour

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enlargement is also an indication for segmental mandibulectomy. With a segmental mandibulectomy, continuity of the mandible is lost, with negative effects on mastication, speech, swallowing, and aesthetics[3,4]. To limit these adverse effects, it is preferable to perform immediate bone reconstruction, often with a free flap[5–7].

The magnitude of bone resection is based on preoperative imaging and visual inspection. The standard preoperative imaging modalities include magnetic resonance imaging (MRI), computed tomography (CT), and panoramic radiography. Additional positron emission tomography (PET)–CT and single-photon emission CT (SPECT) can improve diagnostic accuracy. However, despite the use of advanced imaging techniques, estimation of the bone involvement by carcinoma can still be inaccurate, possibly leading to inadequate resection margins[8]. Furthermore, preoperative imaging can lead to an overestimation of the extent of bone invasion, leading to the resection of healthy bone.

Ideally there should be intraoperative feedback on bone resection margin status to improve surgical results, but unfortunately there is no routine method to evaluate bone margins during surgery. Frank tumour in the bone marrow or IAN can be established by simple visual inspection and if necessary confirmed by (cyto)histology. However, the cytology method is limited because it does not provide information about the bone cortex. Regarding involvement of the IAN, it is general practice for the surgeon to request a frozen section. Yet a negative frozen section of the IAN does not guarantee completely tumour-negative bone resection margins.

Cases where there is no frank involvement of the bone marrow or IAN and where visual inspection does not provide conclusive information for the surgeon are particularly challenging. Moreover, cortical invasion can be difficult to establish. There is no established method for the intraoperative assessment of the bone resection margins in such cases.

In current practice, the status of the bone resection margins is only known after several weeks, because of the specific requirements for the preparation of bone tissue[9]. If final pathology shows tumour-positive bone resection margins, a re-resection should be considered. However, after a period of several weeks, the surgical defect has healed, making re-resection highly undesirable[5,6,10].

In contrast to soft tissue resection margins, the incidence of inadequate bone resection margins has not often been reported. Moreover, the literature on the effect of inadequate bone resection margins on patient outcomes is limited[11–13].

The aim of this retrospective study was to evaluate and determine the utility of surgical margins in bone resections for oral squamous cell carcinoma. The status of bone resection margins was investigated in patients who had undergone segmental mandibulectomy for OCSCC at Erasmus MC, University Medical Centre, Rotterdam, the Netherlands. In addition, the association between tumour-positive bone resection margins and survival was investigated.

Materials and methods

Retrospective data selection

This study was approved by the institutional medical ethics committee. The pathology reports for all patients who had undergone a segmental mandibulectomy for OCSCC at Erasmus MC, University Medical Centre Rotterdam, the Netherlands, between January 2000 and December 2012, were examined. Patients were selected for further analysis if mandibular invasion of the OCSCC was confirmed on final pathology. The histopathological guidelines of the Royal College of Pathologists are strictly followed at the study institution[1]. Accordingly, for the soft tissues, the exact distance from the invasive carcinoma to the surgical margin is one of the core data items that should be included in the histopathology report. This distance can be subdivided into three groups: clear margins (smallest distance between the tumour and bone resection surface >5 mm), close margins (smallest distance between the tumour and resection surface 1–5 mm), and tumour-positive margins (distance from the tumour to the resection surface <1 mm). With respect to bone resection margins, the guidelines specify that ''if bone invasion is present, the presence or absence of carcinoma at the bone margins should be recorded''.

Using the electronic patient files, a database was created containing entries on age, sex, preoperative imaging, comorbidity, other tumour characteristics (i.e., perineural growth in general (without specification of the IAN), spidery growth, angio-invasion, bone invasion), and bone margin status. The soft tissue resection margin status was also extracted from the pathology reports. Both the clinical TNM (cTNM) and pathological TNM (pTNM) status were recorded[14]. The presence of one or more different comorbid conditions was coded for all patients using the Adult Comorbidity Evaluation-27 (ACE-27) index[15]. The ACE-27 grades specific comorbid conditions occurring in different organ systems into one of three levels of comorbidity. It is commonly used in the head and neck cancer literature. The overall comorbidity score is graded on four levels (none, mild, moderate, or severe), and is based on the highest ranked single ailment. Patients with two or more moderate ailments in different organ systems or disease groupings are graded as severe.

Statistical analysis

The data were analyzed using IBM SPSS Statistics, version 21.0 for Windows (IBM Corp., Armonk, NY, USA). For statistical processing, two variables were converted to dichotomous values: comorbidity and lymph node status. An ACE-27 score of 0 or 1 was recorded as a 'low level of comorbidity', and an ACE-27 score of 2 or 3 was recorded as a 'high level of comorbidity'[16]. Descriptive statistics, Student *t*-tests, and χ^2 tests were used to compare clear versus tumour-positive margins in bone resections with respect to patient characteristics and tumour characteristics. *P*-values of <0.05 were considered to be statistically significant.

Multivariate analysis using logistic regression methods was performed to determine patient characteristics and tumour characteristics that are independently and significantly associated with the presence of clear versus tumour-positive margins in bone resections. For each characteristic, an odds ratio (OR), as a measure of association between exposure and outcome, was calculated. An OR of <1 or 1.0 represents no predictive stratification; a value of >1 reflects an increased risk of tumour-positive bone resection margins. The log rank test and Kaplan–Meier curve were used to compare the survival of patients with tumour-negative bone resection margins and patients with tumour-positive bone resection margins. Furthermore, a Cox proportional hazards regression analysis on all data was done, after checking the proportional hazards assumption for each variable and adjusting the survival analysis for age, sex, N status, soft tissue margin status, comorbidity, and perineural growth.

Results

During the selected study period, 158 patients underwent a segmental mandibulectomy for OCSCC at Erasmus MC. Four cases were excluded because no information was available on mandibular bone involvement and/or bone resection margins. A further 27 cases without histopathologically confirmed bone invasion were also excluded. For the remaining 127

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