Oral Oncology 55 (2016) 49–54

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Margin to tumor thickness ratio – A predictor of local recurrence and survival in oral squamous cell carcinoma

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ARTICLE INFO

Article history:
Received 8 September 2015
Received in revised form 9 January 2016
Accepted 13 January 2016
Available online 6 February 2016

Keywords:
OSCC
Margin
Thickness
Prognostic marker

SUMMARY

Objectives: To assess whether small oral squamous cell carcinomas (OSCC) require the same margin clearance as large tumors. We evaluated the association between the ratio of the closest margin to tumor size (MSR) and tumor thickness (MTR) with local control and survival.
Methods and methods: The clinicopathologic and follow up data were obtained for 501 OSCC patients who had surgical resection with curative intent at our institution. MTR and MSR were computed and their associations with local control and survival were assessed using multivariable Cox-regression model. Survival curves were generated using the Kaplan–Meier method.
Results: MTR was a better predictor of disease control than MSR. MTR was a predictor of local failure ($p = 0.033$) and disease specific death ($p = 0.038$) after adjusting for perineural invasion, lymphovascular involvement, nodal status, and radiotherapy. A threshold MTR value of 0.3 was identified, above which the risk of local recurrence was low.
Conclusion: The ratio of margin to tumor thickness was an independent predictor for local recurrence and disease specific death in this cohort. A MTR > 0.3 can serve as a useful tool for adjuvant therapy planning as it combines tumor thickness and margin clearance, two well established prognostic factors. The minimum safe margin can be calculated by multiplying the tumor thickness by 0.3. Further prospective studies in other institutions are warranted to confirm the prognostic utility of MTR and assess the generalizability of our threshold values.

Introduction

Surgical resection is the mainstay of treatment for oral squamous cell carcinoma (OSCC). Satisfactory oncologic resections require negative and adequate resection margins. A microscopic margin of 5 mm has traditionally been accepted as adequate for various oral cavity sub-sites [1,2]. This definition, however, of adequate surgical resection remains controversial as some authors propose 2 mm to be sufficient [3] while others advocate for more than 7 mm [4]. Ch'ng et al. [5] and Brandwein-Gensler et al. [6] have suggested that the adequacy of surgical resections need to be considered in the context of various pathological characteristics such as differentiation, growth pattern, and perineural invasion (PNI). It is intuitive that larger tumors with an infiltrative growth pattern would require larger margins compared to smaller tumors, particularly those with pushing margins. Thus a ratio that takes into account well established prognostic factors such as tumor size, tumor thickness, and distance to the closest margin may help evaluate whether a certain margin can be considered as safe.

The clinical utility of ratios of two related pathological variables is becoming increasingly recognized in oncology. An important example of this is lymph node ratio (LNR) which is a strong predictor of survival in oral cancer [7–9]. LNR incorporates not only the number of lymph node metastases, but also the total number of nodes counted by the pathologist, which enables information on

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http://dx.doi.org/10.1016/j.oraloncology.2016.01.010
1368-8375/

burden of disease, comprehensiveness of surgical resection, and thoroughness of pathological examination to be combined into a single parameter.

Similar guidelines regarding adequate surgical resections are well established in melanoma based on depth of invasion [10]. Although tumor thickness and depth of invasion have been shown to be important prognostic factors in OSCC, the relation between tumor size or thickness and the resection margins has been not been studied [11–14].

The aim of this study is to evaluate whether a ratio between the resection margin and tumor thickness or tumor size is a predictor of local control or survival in OSCC and whether a clinically useful threshold value that may aid adjuvant therapy planning can be identified.

Methods

Study population

The Sydney Head and Neck Cancer Institute has maintained a prospective database including the clinical, pathologic and follow-up data of all patients treated in the Department of Head and Neck Surgery, Royal Prince Alfred Hospital and Chris O'Brien Lifehouse since October 1987. After obtaining institutional ethics approval, clinico-pathological data for all patients with OSCC treated between October 1987 and December 2014 was extracted from the database.

Histologic variables

Tumor size was defined as the largest dimension of the tumor as measured in millimeters during macroscopic examination and confirmed microscopically for tumors less than 10 mm in maximum dimension. Tumor thickness was measured on formalin fixed paraffin embedded sections stained with haematoxylin and eosin to the nearest 0.1 mm using an ocular micrometer. Multiple sections of the tumor were studied to identify the area with maximum thickness. The tumor thickness was measured from the level of adjacent normal mucosa to the deepest point of tumor invasion as described by Moore et al. [15] and depicted in Fig. 1.

The distance of the tumor from its closest resection margin was measured to the nearest 0.1 mm using an ocular micrometer. The location of the closest margin was not consistently recorded in the database, thus precluding analysis. Other histopathologic factors such as tumor differentiation, patterns of invasion, PNI, and lymphovascular involvement (LVI), lymph node involvement with or without extracapsular spread (ECS) were evaluated as per the College of American Pathologist's criteria [16].

Statistical analysis

Local control (LC) was calculated from the date of surgery to the date of last follow up or local recurrence. Disease specific survival (DSS) was calculated from the date of surgery to the date of last follow up or death from OSCC, with patients dying from other causes being censored at the time of death. Margin to size ratio (MSR) and margin to thickness ratio (MTR) were calculated by dividing the tumor margin in millimeters by tumor diameter (MSR) or tumor thickness (MTR) in millimeters. In cases where the closest margin was greater than 5 mm, a margin of 5.01 mm was imputed because margins more than 5 mm were not routinely recorded. In cases with involved margins, a value of −0.01 mm mm was imputed. The distribution for both MTR and MSR was strongly skewed; hence a natural logarithm transformation was performed. As log (0) cannot be calculated, 1 was added to the margin to allow transformation. Log(MSR) and log(MTR) were analyzed as predictors of

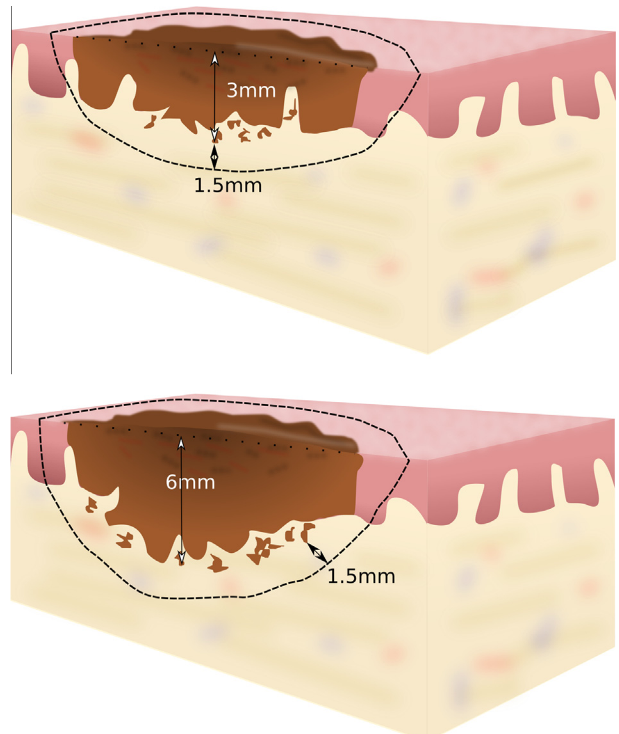

Fig. 1. Two schematized cross sections of OSCC tumors; tumor thickness was measured as the distance from the level of the mucosa (dotted line) to the deepest extent of the tumor. The closest margin in this assumption is between the tumor and the resection (dashed line). In the first example the MTR is 1.5 mm/3 mm = 0.5; in the second example the MTR is 1.5 mm/6 mm = 0.25. Hence, a safe margin for a tumor with a thickness of 4 mm requires 1.2 mm, a safe margin for a tumor with 8 mm thickness would be 2.4 mm and a tumor with a thickness of 15 would require the traditional margin of 5 mm.

LC and survival in isolation and adjusting for the effect of other clinically significant variables such as PNI, LVI, tumor diameter, tumor thickness, lymph node status, ECS, and radiotherapy to ascertain whether log(MSR) and log(MTR) are independent predictors of LC or survival.

Each factor was analyzed in three ways: (1) all patients, (2) excluding patients with involved margins, (3) excluding patients with involved and clear (>5 mm) margins. MSR and MRT were then divided into 10 evenly distributed categories (deciles) in order to identify a clinically useful value that could be used in routine practice.

In order to determine whether MTR/MSR was a better prognostic factor than margin alone, the Akaike information criterion (AIC) was used which takes into account how well the model fits the data and the complexity of the model. Statistical analysis was performed using SPSS version 22.0 (IBM, Armonk, NY).

Results

Cohort characteristics

This cohort includes 539 cases of OSCC from 1987–2014. Of these, 38 were excluded due to insufficient data. The remaining 501 patients were included in the statistical analysis. The baseline characteristics of our study population are depicted in Table 1. Median follow-up was 2.3 years (range 0.1–18.6). The association of various clinicopathologic factors with DSS and LC are summarized in Table 2. There were 55 local failures and 108 total deaths, including 60 deaths due to OSCC. Local failures are further broken down in Table 3.