Oral Oncology 50 (2014) 213–220

Contents lists available at ScienceDirect

Oral Oncology

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

A novel tumor: Specimen index for assessing adequacy of resection in early stage oral tongue cancer ☆

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ARTICLE INFO

Article history:
Received 19 July 2013
Received in revised form 19 November 2013
Accepted 20 November 2013
Available online 12 December 2013

Keywords:
Tumor burden
Tumor volume
Specimen Handling
Head and neck cancer
Outcomes

SUMMARY

Purpose: Surgical margin status frequently affects decisions regarding adjuvant treatment; however, reporting and interpretation of surgical margins is subject to considerable subjectivity because of many factors including the adequacy of resection. We developed a novel measure of the adequacy of surgical resection, the tumor: specimen index (TSI), and tested its utility at predicting clinical outcomes in a retrospective cohort study.

Patients and methods: An institutional database was queried to identify previously untreated patients with T1 and T2 oral tongue cancer who underwent surgery during 1985–2009 ($n = 433$). The TSI, a geometric mean representing the percentage of the surgical specimen that is occupied by the tumor in average single dimension, was calculated from the largest measured lengths, widths, and heights of the tumor in relation to the entire surgical specimen. Multivariate analyses of locoregional recurrence-free probability (LRRFP) and disease-specific survival (DSS) were performed with commonly accepted prognosticators in addition to TSI and surgical margins status.

Results: The mean TSI was 41 (range 11–90; SD 14). Surgical margin status was associated with TSI; margins were negative in 84% of patients with TSI < 45 and in 63% of patients with TSI ⩾ 45 ($p < 0.001$). TSI ⩾ 45 was associated with worse LRRFP (57% vs 76%, $p < 0.001$) and worse DSS (68% vs 85%, $p < 0.001$). In a multivariate analysis that did not include TSI, surgical margin status independently predicted LRRFP ($p = 0.014$) but not DSS. When TSI was included, only TSI, and not surgical margin status, was an independent predictor of both LRRFP ($p = 0.002$) and DSS ($p = 0.011$).

Conclusion: The tumor: specimen index is an easily-calculated metric for estimating the adequacy of 3-dimensional resection in T1 and T2 oral tongue cancer that independently predicts oncologic outcomes.

Introduction

Surgical margin status is a well-established prognostic factor in head and neck cancer and frequently affects decisions regarding adjuvant treatment [1,2]. According to NCCN guidelines, positive surgical margins are an indication to consider adjuvant radiotherapy and/or chemotherapy with radiotherapy, if re-resection is not feasible or is not performed, even for early stage oral cancer [3].

Despite widespread use in decision-making, margin status represents an imperfect assessment of a complex three-dimensional spatial relationship of the tumor to its host. The assessment of margin status is influenced by several factors including anatomic site of a tumor, sampling bias (sampling from the surgical defect vs the specimen), shrinkage of the specimen ex-vivo, variations in specimen processing, variable cutoffs for "positive" and "close" margins, and the inherent difficulty in assessing every interface between malignant and benign cells within a three-dimensional specimen [4–7].

The difficulty in interpreting margin status is compounded in the tongue due to its unique lack of a compartmentalized anatomy. Cancer infiltrates the musculature of the tongue with limited resistance from natural barriers so that microscopic nests are commonly found at varying distances from the gross margin of the tumor [8–10]. Additionally, the tongue musculature retracts when divided, and processing for histopathologic examination causes further shrinkage of the originally mapped margins [7]. This increases the risk that the pathologist will find microscopically visible tumor at or close to one or more surgical margins even though the tumor was not at or close to one or more surgical margins

☆ Presented at the 8th International Meeting of the American Head and Neck Society in Toronto, Canada; July 21-25, 2012.

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http://dx.doi.org/10.1016/j.oraloncology.2013.11.009

in vivo. For these reasons, a positive or close margin may indicate (1) a biologically aggressive tumor; (2) inadequate surgical resection of a tumor that may be amenable to re-resection; or (3) variation in interpretation/orientation of the specimen.

Because the microscopic status of margins at surgical resection is influenced by many confounding variables, positive surgical margins in an adequately resected tumor will likely have different prognostic implications than will positive surgical margins in an inadequately resected tumor. Specifically, the finding of histopathologically involved margins following an adequate surgical resection logically denotes an infiltrative and presumably more biologically aggressive tumor. In current practice, however, all patients with a positive surgical margin are considered high risk and eligible for postoperative chemoradiation therapy, irrespective of the adequacy of surgical resection. This practice is problematic for management of oral cancer in general (and tongue cancer specifically) for at least two reasons. First, a positive or close margin may be re-resected if the initial surgical extirpation was inadequate. Second, providing reflexive adjuvant chemoradiation without interpreting margin status in the context of the adequacy of resection can expose patients to the risk of treatment-related morbidity without defined benefits. It is therefore imperative that decision-making for adjuvant treatment be rationalized to consider margin status relative to the adequacy of surgical resection, so as to estimate the biological aggressiveness of the tumor.

We hypothesized that additional information on the adequacy of resection may be available from a comparison of the estimated volume of the tumor relative to the volume of the surgical resection specimen. Our objective is to introduce this new metric, the tumor: specimen index (TSI), in order to better assess the adequacy of surgical resection and contextualize margin status in early-stage oral tongue cancer.

Patients and methods

We conducted a retrospective cohort study at a tertiary care cancer center. Patients with previously untreated T1 and T2 invasive squamous cell carcinoma of the oral tongue (SCCOT) undergoing surgical extirpation between 1985 and 2009 were included for analysis. The study was approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center (MSKCC). Demographic and clinical data were obtained from a computerized oncologic database and verified via chart abstraction. Tumors were staged in accordance with the American Joint Committee on Cancer seventh edition [11]. Measurements of the specimen and tumor (maximum height, width, and length) were recorded from the pathology report. Margin status was classified as positive (invasive carcinoma or carcinoma in situ at the resected border), close (<5 mm from the resected border), or negative ($\geqslant$5 mm from the resected border or dysplasia at the resected border).

Volumes were calculated based upon the measured maximum dimensions of the tumor and the specimen, assuming an ellipsoid-within-an-ellipsoid configuration (Fig. 1). The ellipsoid, a 3-dimensional analogue of the ellipse, more closely resembles the geometric configuration of a tumor than does a sphere or a cube, and ellipsoidal estimation has been used in the assessment of tumor volume in prostate, renal, and intracranial tumors [12–15].

TSI was calculated as follows:

$$\mathrm{TSI} = \frac{\sqrt[3]{\text{Tumor Volume}}}{\sqrt[3]{\text{Specimen Volume}}} \times 100 = \frac{\sqrt[3]{\frac{4}{3}\pi a_t b_t c_t}}{\sqrt[3]{\frac{4}{3}\pi a_s b_s c_s}} \times 100 \qquad (1)$$

where a_t, b_t, and c_t are height, width, and length of the tumor, and a_s, b_s, and c_s are the corresponding measurements of the specimen.

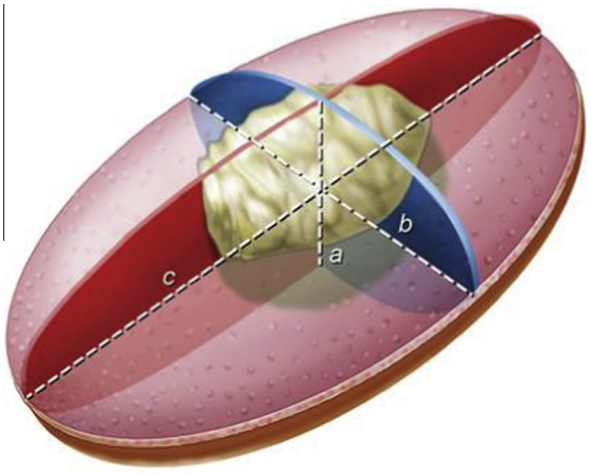

Figure 1. Measurements used in calculating the tumor: specimen index.

The ellipsoidal estimation used to calculate the TSI is analogous to a geometric mean representing the percentage of the surgical specimen that is occupied by the tumor in average single dimension. It is scaled from 0 to 100; a higher TSI indicates that a higher proportion of the specimen is occupied by tumor.

All statistical analyses were conducted using SPSS Version 19. The main outcomes were disease-specific survival (DSS) and locoregional recurrence-free probability (LRRFP), calculated from the date of initial curative surgery using the Kaplan–Meier method.

The event of interest when calculating DSS was death with active SCCOT. Deaths from other causes were considered to be competing risks of DSS as they impeded us from observing the occurrence of DSS. Patients who did not die were censored at the date of last follow-up. Time to event was calculated in months from date of surgery to the date of death or date of last follow-up. DSS represents an individual patient's probability of not dying with active SCCOT within a given time from surgery, assuming he or she does not die of other causes first.

The event of interest when calculating LRRFP was recurrence in the tumor bed and/or neck. Time to event was calculated in months from date of surgery to the date of locoregional recurrence. Patients who did not recur in the tumor bed or neck were censored at the date of last follow up, regardless of distant recurrence or death. LRRFP represents an individual patient's probability of being free from locoregional recurrence within a given time from surgery, assuming he or she does not die first.

Follow-up was calculated to the date of last known follow-up with a member of the head and neck cancer disease management team at our institution. Patients who died of other causes and those who were alive at last follow-up were censored accordingly. Dates and causes of death were abstracted from the medical records and verified via the Social Security Death Index. Locoregional recurrence required confirmatory pathology.

TSI was entered into models as a categorical variable. To choose a TSI cut-point, we plotted receiver operating characteristic (ROC) curves for both LRRFS and DSS at various TSI cut-points and chose the value that maximized sensitivity and specificity for both outcomes. Prognostic variables were identified with univariate analyses using Kaplan–Meier curves and log-rank testing for comparison. A p value of 0.05 or less was considered statistically significant, and all statistically significant factors that were clinically relevant were entered into multivariate analysis employing the Cox proportional hazards model. Parametric and non-parametric comparisons were performed using Pearson's χ^2 test.