SURGICAL MARGIN DETERMINATION IN HEAD AND NECK ONCOLOGY: CURRENT CLINICAL PRACTICE. THE RESULTS OF AN INTERNATIONAL AMERICAN HEAD AND NECK SOCIETY MEMBER SURVEY

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Abstract: Background. Our aim was to investigate the ways in which surgeons who perform head and neck ablative procedures on a regular basis define margins, how they use frozen sections to evaluate margins, and the effect of chemoradiation on determining tumor margins.

Methods. A custom-designed questionnaire was mailed to members of the American Head and Neck Society asking members how they evaluate and define tumor margins.

Results. Of 1500 surveys mailed, 476 completed surveys were received. The most common response for distance of a clear pathologic margin was >5 mm on microscopic evaluation. A margin containing carcinoma in situ was considered a positive margin by most, but most did not consider a margin containing dysplasia a positive margin. When initial frozen section margins are positive for tumor and further resection results in negative frozen section margins, 90% consider the patient's margin negative. Most surgeons sample the frozen section from the surgical bed rather than from the main specimen. Nearly half use wider margins when resecting tumors treated with neoadjuvant therapy. When resecting recurrent or residual tumors treated with previous chemoradiation therapy, most resect to the pretreatment margin.

Conclusions. No uniform criteria to define a clear surgical margin exist among practicing head and neck surgeons. Most head and neck surgeons consider margins clear if resection completed after an initial positive frozen section margin reveals negative margins, but this view is not shared by all. Most surgeons take frozen sections from the surgical bed; however, error may occur when identifying the positive margin within the surgical bed. The definition of a clear tumor margin after chemoradiation is unclear. These questions could be addressed in a multicenter prospective trial.

Keywords: head and neck cancer; surgical margins; frozen sections; chemoradiation

When performing ablative procedures for head and neck cancer, the surgeon's goal is to obtain optimal clearance of the tumor while sparing as much normal tissue as possible, thus preserving function and limiting morbidity. Studies have shown the significance of positive surgical margins. Obtaining a clear margin during resection has been shown to correlate with a lower rate of
local recurrence and, in some studies, a higher rate of survival. In another study, positive surgical margins affected the likelihood of recurrence but did not affect overall survival. However, a third study found no correlation between surgical margins and local recurrence or survival. In each of these studies, the investigators used different criteria to define a positive margin. The acceptable distance of a margin to be free of tumor and, therefore, defined as “clear” varies among surgeons. Also, opinions differ about whether a margin containing dysplasia or carcinoma in situ should be classified as a positive margin. Some of the contradictory literature concerning the prognostic ability of a positive margin may be attributed to the lack of a universally defined clear margin.

No standard guidelines on evaluating margins intraoperatively have been established. If a margin was initially positive on frozen sections, but then on further resection resulted in negative margins, that tumor would be considered by most surgeons to have negative margins. However, some studies have indicated that may not be an accurate assumption. Even though the use of frozen sections to evaluate tumor margins is widely accepted, surgeons’ trends of sampling from the tumor specimen or the surgical bed differ. Also, no guidelines have been outlined to evaluate margins when resecting tumors that have undergone preoperative radiation or chemoradiation. Likewise, the extent of resection necessary in tumor recurrence is not clearly defined.

To evaluate current practice patterns among head and neck surgeons in determining clear tumor margins, we surveyed members of the American Head and Neck Society. This article includes a summary and analysis of the results from this questionnaire.

MATERIALS AND METHODS
This study used a cross-sectional design for the purpose of providing a descriptive analysis of physicians surveyed for practice patterns in evaluating tumor margins. The instrument used was a custom-designed questionnaire. The self-reported survey was mailed to 1500 members of the American Head and Neck Society in October 2003. The survey contained two components, an introductory letter and the survey instrument. A sample form of this questionnaire is available on request from the authors. Twelve items were included in the survey to define three primary objectives (domains). Subjects were asked questions regarding their definition of a clear surgical margin, their use of frozen sections to evaluate margins, and their management of margins in tumors previously treated with chemotherapy or radiation therapy.

Statistical Analysis. Descriptive statistics are presented as frequencies and percentages for all responses to the survey questions. SPSS software was used for all statistical analyses (SPSS 12.0, Chicago, IL).

RESULTS
Of the 1500 surveys mailed to members of the American Head and Neck Society, 86 were ineligible (insufficient or incorrect address \( n = 76 \), not in practice or does not perform head and neck surgery \( n = 9 \), deceased \( n = 1 \)). Of the remaining 1414 surveys, 476 completed surveys
were returned, for a response rate of 34%. However, 60 of the respondents did not answer questions on page 2 of the survey.

**Definition of Clear Margins.** Subjects were asked how they determine their final pathologic margins as clear. Five choices were provided, including no ink on tumor, >5 mm on microscopic evaluation, one high-power field, 1-cm gross margin, or “other.” If the respondents recorded “other,” they were then asked to specify. Figure 1 compares the frequencies (percentages) between the various definitions of a clear margin. The most frequent definition of a clear margin was >5 mm on microscopic examination. The second most common response given was that the definition varied according to the clinical situation or that multiple criteria were used.

Subjects were also asked what they considered to be a close margin. The choices given were <1 high-power field, <5 mm, or “other.” Figure 2 shows that a tumor within 5 mm of the margin on microscopic examination was the most common criteria for a close margin.

The surgeons were asked whether carcinoma in situ or dysplasia at a margin was considered a positive margin. Most indicated they thought a margin containing carcinoma in situ was a positive margin, whereas a minority considered a margin containing dysplasia a positive margin (Figure 3).

**Evaluation of Tumor Margins Using Frozen Sections.** An overwhelming 99% of respondents indicated using frozen sections to evaluate tumor margins. The percentage of surgeons who used frozen sections varied greatly among different anatomic sites, with >90% using frozen sections in the oral cavity and pharynx but approximately 20% to 50% in other areas of the head and neck.
neck (Table 1). When initial frozen sections are positive for tumor and further resection results in negative frozen section margins, most of the respondents consider that patient’s margin negative for tumor (Figure 4). Most respondents reported sampling the frozen section from the surgical bed rather than from the main specimen (Figure 5).

Effect of Neoadjuvant and Adjuvant Therapy on Tumor Margins. The respondents were nearly split on whether to use wider margins when resecting tumors treated with neoadjuvant chemotherapy, radiation, or chemoradiation. When resecting recurrent or residual tumors treated with induction chemotherapy, radiation, or chemoradiation, approximately two thirds resect to the pretreatment margin (Table 2).

DISCUSSION

Definition of Clear Margins. In our survey, the most common definition of a clear margin was >5 mm on microscopic evaluation. However, most of the respondents were divided among other definitions. This variability among the subjects in our study reflects the wide spectrum of definitions used in the literature. In an analysis of 398 patients with oral cavity squamous carcinoma, Loree and Strong2 considered a margin positive if any of the following criteria were met: close (tumor within 0.5 cm), premalignant change at the margin, in situ carcinoma at the margin, and invasive microscopic cancer at the margin. In their study, Loree and Strong found the incidence of local recurrence to be twice as common in patients with positive margins than in those with negative surgical margins (36% to 18%). They also found a significant difference in overall 5-year survival rates; 60% of those with negative margins survived 5 years compared with 52% with positive margins ($p < .025$).

Spiro et al3 studied 150 previously untreated patients who underwent surgery for squamous
carcinoma of the tongue. They found a significant increase in local recurrence in tumors with positive margins (invasive carcinoma at the margin) and close margins (within one high-power field). However, survival was not affected by the status of the margin. In the study by McMahon et al,4 332 patients with previously untreated carcinoma of the mouth or oropharynx were investigated. Using the following criteria, clear margin (≥5 mm from the nearest surgical margin), close (1–5 mm), and involved (<1 mm), their results did not demonstrate that surgical margin status had an independent predictive effect on either local recurrence or disease-specific survival.

These three studies exemplify the confusion within the literature about the effect of margin status on patient prognosis. Our data reflect the wide spectrum of opinions and standards used to define tumor margins. Understandably, a uniform guideline cannot be used for all sites of the head and neck, because margins from carcinomas of the glottis cannot be compared with those from carcinomas of the oral cavity and pharynx.6 However, a declaration of a uniform margin width needed to define a specimen as clear for many specific anatomic sites is warranted. Without such standardization, it is impossible to study the significance of margin status on locoregional control in any prospective multicenter study.

Another dilemma that must be discussed is whether dysplasia or carcinoma in situ at a margin falls under the definition of a positive margin. In the study by Loree and Strong,2 invasive carcinoma at the margin or within 5 mm of the margin, dysplasia at the margin, and in situ carcinoma at the margin all increased the likelihood of local recurrence. However, the 5-year survival rates were drastically different (94% of patients with dysplasia, 71% of those with in situ carcinoma, 51% of those with a close margin, and 43% of those with invasive carcinoma at the margin). With such varied survival rates, we agree with the position of McMahon et al4 that dysplasia and in situ carcinoma at the margin cannot be labeled as positive in the same category as a margin containing invasive carcinoma. Batsakis6 believes carcinoma in situ and severe dysplasia have “equal biologic significance.” Interestingly, those who responded to our survey overwhelmingly (83%) defined carcinoma in situ as a positive margin, whereas a strong majority (76%) categorized a margin as negative if dysplasia was involved.

Recently, focus has been directed toward evaluating margins using molecular techniques. In an effort to explain local recurrences in tumor specimens categorized with negative margins by light microscopy, several studies have investigated the impact of various molecular markers present at tumor margins. Brennan et al7 found an increased risk of local recurrence in patients who had negative histopathologic margins but then contained positive p53 mutations in the margins. In a study investigating the translation initiation factor eIF4E, Franklin et al8 showed a significantly increased risk of local recurrence and decreased survival in patients with this factor present at the resection margin. However, Slootweg et al9 studied 394 patients that underwent resection for a primary head and neck tumor and examined the prognostic ability of histologically determined surgical margins. They concluded that even though some tumor cells may evade histologic detection in surgical margins, the clinical impact of this small group that is missed seems to be negligible, and this leaves little room for improvement from molecular margins. Although not discounting the potential benefits that may be derived from more accurate margins examined by molecular techniques, we agree with Batsakis’s6 viewpoint that we should not ignore establishing uniform definitions of margins by histologic examination, as we look to improve the efficacy of “molecular margins.”

### Evaluation of Tumor Margins Using Frozen Sections.

In his review article, Batsakis6 maintains the position that measurements of margins on formalin-
fixed specimens are inferior to in situ, frozen section samples because of post-removal and post-fixation shrinkage. Similar results were found by Johnson et al\(^{10}\) when studying oral mucosal margins using canine models. These results are significant, especially if one uses the definition of a clear margin as being >5 mm. Then one must ask, should this distance pertain to formalin-fixed tissue or can it apply to frozen sections?

In our survey, nearly all (99\%) of the respondents indicated using frozen sections at some time to intraoperatively assess tumor margins. The reliability and usefulness of frozen sections is well documented.\(^{6,11,12}\) However, frozen sections do have limitations. Ord and Aisner\(^{13}\) examined 307 frozen sections from patients with oral cancer. Although the accuracy rate of frozen sections was 99\%, they concluded that frozen sections were not always helpful in preventing final positive margins. In another article, Gandour-Edwards et al\(^{14}\) divided sources of error during intraoperative frozen section diagnosis into two categories, sampling error and interpretive error. They further described sampling errors as those errors that can occur when a large frozen section specimen is sampled and the diagnostic lesion is not sectioned or when the specimen is inadequately or superficially sectioned and the lesion is missed because it is buried deeper in the block. Interpretative errors occur in such instances when the freezing process distorts the architecture or when previous surgery or radiotherapy causes fibrosis or histologic changes in the specimen.

In another revealing study, Scholl et al\(^{5}\) examined 268 patients with squamous cell carcinoma of the tongue. They found an increase in local recurrence and decreased survival in patients who had an initial positive margin on frozen section that became negative on further resection compared with patients who had initial negative margins on frozen section. These differences decreased when radiotherapy was added to the treatment. This finding is significant in light of the results from our survey, in which 90\% of respondents indicated that they consider a final margin negative if initial frozen section margins are positive but further resection results in negative margins. Many patients may not be receiving potentially beneficial radiotherapy with this popular belief.

Another interesting finding in the Scholl et al\(^{5}\) study was that in those who had initial positive margins and then underwent further resection, 73\% of the repeat margins did not contain any tumor. They attribute this to both the difficult task of performing an accurate microscopic assessment of a three-dimensional organ and the challenge faced by the surgeon to correctly identify intraoperatively the correct margin of involvement. This challenge was studied by Kerawala and Ong\(^{15}\) in which a surgeon was asked to identify certain sites of proposed sampling in 14 cases. After 5 minutes, the surgeon was asked to relocate the site. The mean error was 9 mm at mucosal margins and 12 mm at those deep to the tumor bed when relocating the sample site. In 32\% of cases, the error exceeded 1 cm. In our survey, we asked the subjects to identify whether they sample their frozen sections from the main specimen or the surgical bed; 76\% indicated taking their sample from the surgical bed. It is the authors’ opinion that frozen sections removed from the surgical bed lead to greater sampling error because of increased difficulty in margin relocation. We believe a randomized controlled study is warranted to see whether any differences truly exist.

**Effect of Neoadjuvant and Adjuvant Therapy on Tumor Margins.** The respondents in our survey were nearly split on whether to use wider margins when resecting tumors treated with neoadjuvant chemotherapy, radiation, or chemoradiation. To our knowledge, no prospective trials have investigated whether this is necessary. Also, one fourth of the respondents in our survey resect to the recurrence only, when resecting recurrent or residual tumors treated with induction chemotherapy, radiation, or chemoradiation rather than to the pretreatment margin. Studies have shown that tumors vary significantly in the histologic response to induction therapy.\(^{16,17}\) We need to attempt to define the nature of tumor margin regression in the era of chemoradiation therapy so that a consistent approach to margins may be taken when attempting salvage surgery in this group of patients.

Limitations to our study require consideration when proceeding with a more formal investigation. We realize this study was generalized, and truly all answers cannot apply uniformly to every case encountered by a head and neck surgeon. In addition, the questionnaire has not yet been validated. Other than knowing our respondents are members of the American Head and Neck Society, we did not identify responses by region.
The findings in our survey call attention to the vast spectrum of criteria used to define a clear margin when resecting head and neck tumors. Although realizing that no single definition can apply to all anatomic sites of the head and neck, we believe there does need to be standardization across sites to define what constitutes a clear margin. We believe studies are needed to investigate if it is clinically significant whether the surgeon samples frozen sections from the main specimen or the surgical bed. Finally, how does one define appropriate resection margins when attempting to salvage recurrent tumors in the era of chemoradiation therapy? These questions warrant further research.

REFERENCES