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Accuracy, Utility, and Cost of Frozen Section Margins in Head and Neck Cancer Surgery

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***Objectives:* Intraoperative frozen section analysis of surgical margins is widely used in head and neck cancer surgery. This study evaluates frozen section accuracy relative to permanent controls and final margins from the entire specimen, the rate at which frozen sections impact intraoperative management, and the resultant cost. *Study Design:* Retrospective. *Methods:* From 1997 to 1999 the frozen section results, permanent controls, and final tumor margins from 80 consecutive patients undergoing 420 intraoperative frozen section margins for head and neck malignancy were reviewed. *Results:* A 98.3% accuracy rate (sensitivity, 88.8%; specificity, 98.9%) was found compared with permanent sections of the same tissue. However, 40% (8 of 20) of patients with positive final margins on the resection specimen, and 100% (15 of 15) with close (<5 mm) margins were not detected by frozen section analysis. The overall accuracy of frozen section in the evaluation of close or positive final margins was 71.3% (sensitivity, 34.3%; specificity, 100%). In addition, 5% (4 of 80) of patients potentially benefited from intraoperative frozen section by virtue of immediate margin revision. The estimated cost of intraoperative frozen section averaged as much as $3123 per patient, with a cost-benefit ratio of 20:1. *Conclusions:* Intraoperative frozen section margins are accurate, but they are costly and cannot reliably eradicate positive final margins. Patients with early-stage lesions and those undergoing re-resection for recurrence or salvage surgery after radiation failure derived the greatest potential benefit from frozen section margins. *Key Words:* Frozen section, head and neck cancer, tumor margins.**

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INTRODUCTION

Lower local tumor recurrence rates and improved survival have been reported when tumor-free margins are achieved at the time of surgery.[1–5] Intraoperative frozen section analysis of margins is widely employed to assist in complete tumor extirpation. The technique of frozen section preparation dates to 1818 and has been credited to the work of deRemier.[6] Over time, the quality and accuracy of frozen sections has improved, largely owing to the use of the cryostat.[7] The accuracy of frozen-section diagnosis compared with permanent controls in head and neck surgery has consistently been reported between 96% and 99%.[8–11] The rate at which frozen sections predict final margins from the entire surgical specimen, the frequency with which they alter surgical management, and the resultant cost have not been fully evaluated. This report addresses these issues through a retrospective analysis of 80 consecutive patients with head and neck cancer in whom 420 frozen section margins were used to assess the adequacy of tumor resection.

MATERIALS AND METHODS

Between 1997 and 1999, 80 patients underwent resection of head and neck malignancies utilizing intraoperative frozen section margin analysis. The decision to use frozen sections in each case was based on the surgeon's (L.J.D.) judgment that achieving a 1-cm margin around tumor required frozen section guidance because of ill-defined tumor borders or proximity to vital structures. There were 56 men and 24 women. The mean patient age was 58.5 years (range, 12–84 y). Tumor location included oral cavity in 23 (28.75%), oropharynx in 22 (27.50%), larynx in 17 (21.25%), hypopharynx in 9 (11.25%), sinonasal region in 5 (6.25%), and major salivary gland in 4 (5.00%). Tumor staging was as follows: T1 in 11 (13.75%), T2 in 25 (31.25%), T3 in 21 (26.25%), and T4 in 23 (28.75%). Definitive radiation therapy had failed in 30 patients (37.5%) and an additional 9 patients (11.25%) were undergoing re-resection for recurrence after previous surgery. Tumor histology included squamous cell carcinoma in 69 (86.25%), mucoepidermoid carcinoma in 5 (6.25%), adenoid cystic carcinoma in 2 (2.50%), ameloblastoma in 2 (2.50%), undifferentiated carcinoma in 1 (1.25%), and acinic cell carcinoma in 1 (1.25%).

All intraoperative frozen sections were taken from the surgical bed and included mucosal and deep margins. Frozen section diagnoses were rendered on H&E-stained sections of OCT-embedded, snap-frozen tissue sectioned at 5-μm intervals. Residual tissue was formalin-fixed, paraffin-embedded, sectioned, and stained using H&E. Permanent sections were reviewed for

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corroboration with frozen section slides. Margins of primary resection specimens were determined by the type of specimen, with particular attention to mucosal and bony margins and their relation to tumor. Ink was used to facilitate histological identification of margins. Each case was reviewed by 1 of 3 attending head and neck pathologists.

RESULTS

A total of 420 frozen section margins from 80 patients yielded an average of 5.25 specimens per patient. All frozen section specimens measured 2 cm or less. There were 24 true-positive, 389 true-negative, 4 false-positive, and 3 false-negative frozen section margins compared with permanent sections of the same tissue. The resultant accuracy was 98.39%, sensitivity 88.8%, specificity 98.9%, positive predictive value 95.7%, and negative predictive value 99.2%. Interestingly, all false-positive margins occurred in patients with at least one other true-positive result.

Review of frozen section results collectively by patient and in comparison with permanent tumor margins from the entire specimen revealed that 12 individuals had at least 1 positive frozen section in conjunction with at least 1 positive permanent margin on the resection specimen. This rendered a true-positive rate of 12. Similarly, the false-positive rate was 0, false-negative rate 8, and true-negative rate 60. Thus the accuracy of frozen section in detecting positive final margins was 90.0%, sensitivity 60.0%, specificity 100%, positive predictive value 100%, and negative predictive value 88.2%. Frozen section margins failed to detect 100% (15/15) of close (<5 mm) final margins. The overall accuracy, therefore, of frozen section in the evaluation of close or positive margins was 71.3%, the sensitivity 34.3%, specificity 100%, positive predictive value 100%, and negative predictive value 66.2%.

At every site, a specificity of 100% for the detection of close or positive final margins was achieved by frozen section. Sensitivity (true positive/true positive + false negative) was best for the hypopharynx (100% [3 of 3]), followed by the oral cavity (42.8% [3 of 7]), oropharynx (40.0% [4 of 10]), paranasal sinuses (40.0% [2 of 5]), major salivary glands (0% [0 of 1], and larynx (0% [0 of 7]). Overall, 4 of 12 patients (33%) with positive frozen sections underwent successful margin revision. Oral cavity (1 case) and oropharyngeal (3 cases) tumors accounted for all of these revisions.

Review of frozen section margins compared with permanent tumor margins by T stage also yielded 100% specificity. Sensitivity was best for T1 lesions (100% [1 of 1]), followed by T2 lesions (37.5% [6 of 16]), T4 lesions (37.5% [3 of 8]), and T3 lesions (22.2% [2 of 9]). Successful margin revision occurred with T1 (1 case) and T2 (3 cases) lesions only.

Radiation failures accounted for 37.5% of cases (30 of 80). Once again, the specificity for all patients—irradiated and nonirradiated—was 100%. The sensitivity of frozen section to predict close or positive final margins was 53.3% (8 of 15) for irradiated patients and 20.0% (4 of 20) for nonirradiated patients. In all, 37.5% of irradiated patients with positive frozen section margins (3 of 8) underwent successful revision compared with 25% of nonirradiated patients (1 of 4).

Re-resection for recurrence after previous attempts at tumor extirpation was responsible for 9 (11.25%) of the procedures. This category had a positive frozen section margin rate of 55.5% (5 of 9), with 20% (1 of 5) undergoing successful margin re-resection. Specificity was 100% and sensitivity of frozen section to predict close or positive final margins was 83.3% (5 of 6).

Evaluation by tumor histology revealed 69 patients with squamous cell carcinoma (86.2%) and 11 patients with non–squamous cell tumors (13.7%). In all, 28.9% of patients with squamous cell carcinoma (20 of 69) and 63.6% of patients with non–squamous cell tumors (7 of 11) had close or positive final margins. The sensitivity of frozen section in the detection of close or positive final tumor margins was 28.9% for squamous cell carcinoma and 57.1% for non–squamous cell tumors. Successful margin revision occurred only with squamous cell carcinoma (4 patients).

The estimated cost for intraoperative frozen section margins resulted from pathological evaluation and added operating room expenses. Pathological consultation was divided into a technical component (CPT 88331) of $160 and a professional component of $140 for each frozen section. Each case averaged 5.25 frozen sections for a total average pathology charge of $1575 per patient. Additional operating room time and anesthesia expenses averaged $1548 per patient based on a 15-minute processing time for each margin. The total estimated average charge per patient was $3123 for frozen section margins.

DISCUSSION

It has been noted that two forms of error can occur in frozen section margin evaluation: interpretive and sampling.[12] Interpretive error denotes a failure to correctly identify the tissue present on the frozen section slide. Sampling error refers to evaluation of nonrepresentative tissue. Whereas errors in interpretation are attributable to the pathologist, sampling errors may be the responsibility of the surgeon or the pathologist. When comparing frozen section to permanent section of the same tissue, the accuracy rate is typically between 96% and 99%.[8–11] Spiro et al.[13] reported similar error rates whether margins were taken from the patient or the surgical specimen. Nevertheless, Grandour-Edwards et al.[12] found that most errors (84%) occurring during intraoperative consultation for adequacy of margins were due to incorrect sampling. Because error in this study was limited to the pathologist's evaluation of the tissue submitted for frozen section, the rate at which the surgeon failed to sample an involved tissue margin is unclear. Therefore, although the accuracy rate of frozen section compared with permanent section control in our study was 98%, this figure does not necessarily reflect frozen section accuracy relative to permanent margins for the entire resection specimen.

Several authors have indirectly assessed the accuracy of frozen section margins relative to the adequacy of tumor resection through measurements of local control and tumor-free survival.[11,12,14] Byers et al.[14] reviewed a selected group of 216 patients undergoing surgical treatment of squamous cell carcinoma of the head and neck. Sixty-seven percent of tumors were adequately resected using the surgeon's judgment, as evidenced by negative intraoperative frozen section margins. Ten percent of patients had tumors that could not be completely excised. These two groups did not benefit from the use of frozen section. However, 23% of patients underwent immediate margin revision as a result of positive intraoperative frozen section. The local recurrence rates for free margins, revised margins, and positive margins were 14%, 20%, and 80%, respectively. The authors supported the use of frozen section margin evaluation in all but T4 lesions, owing to poor local control rates in advanced tumors regardless of margin status. Although an association between frozen section margins and local control was evident, cause and effect was not established. In a smaller series of 49 consecutive patients with previously untreated oral carcinoma, Ord and Aisner[11] noted an accuracy rate for frozen section margins of 99% compared with permanent sections of the same tissue. However, 70% of patients (7 of 10) with positive final margins on the resection specimen were not detected by frozen section evaluation. Positive final margins included resection margins containing dysplasia, carcinoma in situ, infiltrating carcinoma, and margins within 5 mm of carcinoma. One patient (2%) had a positive frozen section margin that was re-excised.

In our study, the sensitivity of frozen section in predicting a positive margin on the resection specimen was 60%. The specificity was 100%. When close (<5 mm) margins were included, the sensitivity declined to 34.3% and the specificity remained at 100%. Therefore, a negative frozen section margin did not ensure a tumor free margin on the final specimen, but a positive frozen section margin uniformly reflected an involved permanent margin.

The sensitivity varied by site, and although 100% for hypopharyngeal tumors, it was 0% for laryngeal carcinoma. This finding is explained by the location of frozen section failures at each site. Hypopharyngeal tumor margins were typically from the mucosa of the pyriform sinus. Frozen section margins for laryngeal tumors were often from the tongue base, a large volume margin with a propensity for occult tumor extension.

In consideration of T stage, all successful intraoperative margin revisions occurred with T1 and T2 lesions of the oral cavity or oropharynx. This finding supports Byers' local control data indicating that patients with early-stage lesions derive the most potential benefit from intraoperative frozen section margin evaluation.[14]

The observation that the sensitivity of frozen section to predict close or positive margins in irradiated patients (53.3%) was greater than for nonirradiated individuals (20.0%), although difficult to explain, is of consequence. Combined with the fact that a greater percentage of irradiated patients with positive frozen section margins underwent successful margin revision means that 10% of irradiated as opposed to 2% of nonirradiated patients potentially benefited from the use of frozen section.

Re-resection for recurrence had a high positive frozen section rate (55.5%). Because 20% with positive frozen sections underwent margin revision, frozen section margin analysis was of potential benefit in 11.1% of all re-resection cases.

With regard to tumor histology, the findings were mixed. Although the sensitivity of frozen section in detecting close or positive final margins was greater for non–squamous cell tumors than for squamous cell carcinoma (57.1% vs. 28.9%), only patients with squamous cell carcinoma underwent successful margin revision. This is best explained by the extensive microscopic spread of tumors such as adenoid cystic carcinoma and malignant ameloblastoma, which frequently defy complete excision.

Because the estimated average charge for frozen section margins was $3123 per patient, a total of $249,840 was possibly spent on the entire study group. Four patients potentially benefited from intraoperative margin analysis, utilizing $12,492. This rendered a cost-benefit ratio of 20:1. It is important to note that this analysis assumes that the surgeon was not occupied with a meaningful portion of the procedure while awaiting frozen section results. A similar estimation of charges and cost-benefit ratio was reported by Frable.[15] The author appropriately states, "The dilemma for the physician in all of this is the individual benefit versus group benefit."

Conversely, the elimination of frozen section margin analysis is of consequence. The financial and psychological costs, as well as the additional medical risk for attempted re-resection based on positive margins found on final pathology must be considered. In this study, 12 patients with positive frozen section margins potentially avoided a return to the operating room. Realistically, 6 of the 12 patients would have been candidates for reoperation based on tumor extent and location. Sites included oral cavity (n = 3) oropharynx (n = 2), and paranasal sinuses (n = 1). The estimated average operating room and anesthesia cost for an additional 2-hour procedure would be $1179. Additional pathology expenses are estimated to have been $484 per patient, and a 2-day postoperative hospitalization would cost $1800. The surgeon would bill using a 78 modifier for surgery performed within the global period, resulting in a 20% reduction in fees. The estimated average surgeon's fee would be $800. The total cost avoided for reoperation in six patients by use of frozen section was estimated at $25,580. In comparison, $18,738 was spent on these six individuals for frozen section analysis. Subtracting the cost of reoperation from the estimated $249,840 for frozen sections in this study yields a hypothetical cost of $224,259 for frozen section analysis. Judicious use, not the elimination, of frozen section margins, therefore, seems appropriate.

Several suggestions for improving frozen section margin utilization are apparent. First, they are best used for patients with the highest likelihood of successful margin revision. In this study, patients undergoing tumor re-resection, removal of a T1 or T2 lesion of the oral cavity or oropharynx, or resection after failed radiation therapy, had the highest margin revision rates of 11.1%, 11.0%, and 10.0%, respectively. Individuals with T3 or T4 lesions and non–squamous cell pathology failed to benefit from frozen section guided margin revision. Second, the surgeon should plan to continue to operate while awaiting frozen section results whenever possible because approximately one half of the expense of frozen section is otherwise attributable to increased operating room utilization.

Finally, efforts should be directed toward decreasing sampling error. Close collaboration between the surgeon and the pathologist provides a better understanding of sites of suspected tumor invasion and the limitations of frozen section. Future improvements in margin evaluation through the development of molecular tumor markers may further diminish errors.[16]

CONCLUSION

Frozen section margins, although useful in head and neck surgery, are costly. Frozen section results are highly specific but only moderately sensitive compared with final margins from the resection specimen. Ideally, they should be employed in situations that are most likely to result in immediate margin revision. In this study, patients with T1 and T2 lesions of the oral cavity or oropharynx and patients requiring re-resection for recurrence or salvage surgery after radiation failure received the greatest potential benefit from frozen section margins. The surgeon and pathologist must understand the limitations of frozen section and attempt to minimize cost and sampling error.

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