Frozen Section Evaluation of Margin Status in Primary Squamous Cell Carcinomas of the Head and Neck: A Correlation Study of Frozen Section and Final Diagnoses

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Abstract Frozen section is routinely used for intraoperative margin evaluation in carcinomas of the head and neck. We studied a series of frozen sections performed for margin status of head and neck tumors to determine diagnostic accuracy. All frozen sections for margin control of squamous carcinomas of the head and neck were studied from a 66 month period. Frozen and permanent section diagnoses were classified as negative or malignant. Correlation of diagnoses was performed to determine accuracy. One thousand seven hundred and ninety-six pairs of frozen section and corresponding permanent section diagnoses were obtained. Discordances were found in 55 (3.1%) pairs. In 35 pairs (1.9%), frozen section was reported as benign, but permanent sections disclosed carcinoma. In 21 cases, the discrepancy was due to sampling and in the remaining cases it was an interpretive error. In 20 cases (1.1%), frozen section was malignant, but the permanent section was interpreted as negative. Frozen section is an accurate method for evaluation of operative margins for head and neck carcinomas with concordance between frozen and permanent results of 97%. Most errors are false negative results with the majority of these being due to sampling issues.

Keywords Frozen section · Diagnostic accuracy · Head and neck carcinomas

Introduction

Frozen section evaluation has become a standard of practice for the intraoperative diagnosis of newly discovered lesions as well as confirmation of diagnosis in previously biopsied pathologic processes and to establish the extent of disease. The procedure has been shown to be sufficiently accurate for clinical utilization [1–10]. Frozen section concordance rates with permanent diagnosis average approximately 98% [1]. The concordance rate varies somewhat by site, with the concordance rate for ovary being approximately 93% [2, 3] and somewhat lower at other sites such as the skin [5].

The issue of margin adequacy is critical to the successful management of head and neck cancer patients [11]. Frozen section is commonly utilized for the determination of margin status for resection of head and neck primary carcinomas. A number of review articles have addressed the issues impacting intraoperative consultations for mucosal lesions of the upper aerodigestive tract [11, 12]. Detailed protocols have been published outlining the use of frozen section evaluation in ensuring negative margins for resection of head and neck squamous cell carcinomas [11]. Four studies from the last two decades have presented data useful to assess the concordance rates between frozen section and permanent section diagnoses and the sensitivity and specificity of the technique for recognition of squamous carcinoma at operative margins [13, 14, 18, 19]. Frozen section adequacy has been reported to be approximately 97% (83% sensitivity and 98% specificity) [13]. While variable in reported series it is nonetheless consistently above 90% [14–19] and compares favorably with frozen section margin status evaluation at

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other body sites [20, 21]. While frozen section evaluation of pancreatic margin status is associated with an accuracy as high as 97.8% for specialty pathologists and 87.5% for general pathologists [21], less data is available for the head and neck area. Many of the published series contain fewer than 500 frozen sections for analysis [14, 16, 19, 22]. Only two large series have been published [13, 15]. We reviewed our experience with correlation between frozen and permanent section diagnoses in a series of 1796 pairs of frozen and permanent sections obtained to evaluate margin status in patients with primary head and neck squamous cell carcinomas. Herein we report the results of that study which is the second largest single institution study published to our knowledge in the English language literature.

Materials and Methods

The records of the section of surgical pathology in the Department of Pathology and Anatomical Sciences at the University of Missouri were reviewed for all resections of primary head and neck squamous carcinomas with an associated frozen section diagnosis over a five and a half year period. Each case with documented frozen section analysis was reviewed to determine whether the frozen sections were performed for margin status control and all such cases where margin status was reviewed by frozen section were included in this study. The tissues submitted for frozen section analysis were selected and sent separately by the surgeon. In most cases, the face of the specimen representing the true operative margin was not designated the surgeon. Five different surgeons performed the resections. The specimens were submitted entirely for frozen section evaluation and sampled from the surface designated as representing the “true new margin” when so identified. The tissue site of origin was documented for each specimen. Both frozen and permanent section diagnoses were classified as negative for malignancy or malignant. Correlation of the diagnoses rendered by frozen section and paraffin embedded permanent section review was performed and sensitivity and specificity of the frozen section technique calculated based on the permanent section diagnoses. Positive and negative predictive values were calculated. The nature of the discrepancy when present was noted and its cause was designated as either “sampling” or “interpretation”. “Sampling” errors were those errors where diagnostic malignant tissue was not present in the frozen section slides but appeared in deeper “cuts” prepared for permanent sections. The pathologist signing out the final permanent sections determined if an error was due to sampling. This designation was confirmed for each case by one of the authors (LJL). Interpretive errors were those occurring when diagnostic malignant cells were present in the original frozen sections as identified by the final sign-out

pathologist and confirmed by the study pathologist (LJL) but not recognized by the frozen section pathologist. All pathologists performing the original frozen section evaluations were board certified in Anatomic Pathology but did not have fellowship training in Head and Neck Pathology. Each pathologist was characterized for experience by assigning them to one of two groups (over 10 years’ experience or less than 10 years’ experience). The rates of interpretive error was compared between the two groups. The total number of specimens reviewed and errors made by the two groups were calculated. The number of false positive diagnoses was also calculated for both groups.

Results

One thousand seven hundred and ninety-six individual pairs of frozen and permanent section diagnoses from 288 patients were obtained by the review. The sites of tissue submitted for frozen section analysis are shown in Table 1 and the sites of the frozen sections with diagnostic errors are shown in Table 2. Table 3 lists the sites of origin for the carcinomas studied in this series. All cases were histologically squamous cell carcinomas. Discordances were found in 55 (3.1%) pairs. In 35 pairs (1.9%), the frozen section was reported as benign, but evaluation of the permanent section disclosed a carcinoma. In 21 (60%) of these falsely negative frozen sections, review of the frozen section and corresponding permanent section slides demonstrated that the discrepancy was due to sampling. In the remaining 14 cases, review of the original frozen sections revealed foci of carcinoma and the false negative diagnoses were designated as due to interpretation. In 20 cases (1.1%), the frozen section was positive for malignancy, but the subsequent permanent section was called negative. Secondary review of these cases at the time of re-review for this study showed that the frozen section was falsely positive in 17 cases and the final diagnosis falsely negative in 3 cases. The sensitivity and specificity of frozen section evaluation were 0.889 and 0.986 respectively. The positive predictive value of a positive frozen section diagnosis was 0.933 and the negative predictive value was 0.976. Nine hundred and six frozen sections were performed by the group with less than 10 years’ experience with the remainder performed by the pathologists with 10 or more years’ experience. Thirty-three errors were made by pathologist with less than 10 years’ experience while 22 errors were made by pathologists with 10 or more years’ experience. The less experienced pathologists made 16 of the 20 false positive diagnoses (80%) and 17 of the 35 false negative diagnoses. Table 4 documents the error statistics by experience group. Total errors demonstrated a trend toward higher error rate for less experienced pathologists ($p=0.09$).

Table 1 Sites from which frozen sections were obtained

Site	Number of specimens
Alveolar ridge	21
Arytenoid	8
Auricular nerve	2
Bony mandible	36
Buccal mucosa	69
Carotid sheath	4
Cheek	15
Commissure	9
Cricoid	10
Epiglottis	14
Floor of mouth	133
Facial nerve	13
Gingiva	17
Glottis	12
Hypopharynx	10
Infratemporal fossa	3
Larynx, not otherwise specified	51
Lingual nerve	14
Lip	55
Maxilla, not otherwise specified	6
Maxillary sinus	20
Mandible mucosa	2
Mental nerve	8
Nasal mucosa	2
Oral cavity, not otherwise specified	153
Oral pharynx	51
Orbit	18
Palate, hard	34
Palate, soft	57
Pharynx, not otherwise specified	112
Pterygoid	20
Pyriform sinus	32
Retromolar trigone	10
Skin	118
Skull base	21
Soft tissue, neck	1
Stylomastoid	1
Subglottic	16
Supra glottic	12
Tongue	503
Tonsil	61
Uvula	1
Vallecula	22
Vocal cord	19
Total	1796

Table 2 Sites of frozen section diagnostic errors

Site	Number of specimens
Alveolar mucosa	1
Carotid sheath	1
Cheek	2
Epiglottis	2
Facial nerve	1
Floor of mouth	4
Larynx	5
Lip	3
Lingual nerve	1
Nasal mucosa	1
Oral cavity	3
Orbit	3
Pharynx	8
Pyriform sinus	1
Skin, NOS	1
Soft palate	2
Soft tissue	1
Stylomastoid	1
Tongue	14
Total	55

False positive diagnoses were statistically associated with less experience ($p=0.002$).

Discussion

Intraoperative frozen section evaluation for initial diagnosis or confirmation of prior biopsy diagnosis has become a common procedure [1–10, 23–30]. Discordance rates have been variable ranging from 1.4 to 11.8% with a mean discordance rate of approximately 3.2% [1–10, 23–30]. The discordance rate is in part dependent on type of institution where the frozen section analysis was performed, the tissue type and the pathologic process [27–29]. In the majority of published series, discordant diagnoses were generally due to problems with interpretation [13–25, 29]. Inadequate or inaccurate sampling was the second major cause for frozen section/final diagnosis discrepancies and occurred in approximately one-third of discrepant cases [1]. However, when only series evaluating margin status for squamous cell carcinoma of the head and neck are analyzed, sampling becomes the major cause of diagnostic error [13, 15, 19]. Our results for frozen section analysis of the margin status fall within the reported range for discrepancies with our discordance rate being 3.1% and the mean reported discrepancy rate being 3.2% [1].

While the overall diagnostic accuracy of frozen section evaluation and the discordance rate between intraoperative frozen section diagnosis and final diagnosis have been

Table 3 Sites of origin for squamous cell carcinomas included in this study

Site	Number of Specimens
Alveolar ridge	21
Buccal mucosa	69
Cheek, skin	15
Commissure, vocal cord	9
Epiglottis	14
Floor of mouth	149
Gingiva	17
Glottis, NOS	12
Hypopharynx	11
Infratemporal fossa	3
Larynx, not otherwise specified	61
Lip	55
Maxilla, not otherwise specified	6
Maxillary sinus	38
Mental nerve	8
Nasal mucosa	2
Oral cavity, not otherwise specified	153
Oropharynx	78
Palate, hard	34
Palate, soft	57
Pharynx, not otherwise specified	112
Pyriform sinus	32
Retromolar trigone	10
Skin, including scalp and ear	118
Skull base	21
Subglottic	16
Supra glottic	12
Tongue	545
Tonsil	71
Uvula	1
Vallecula	22
True vocal cord	24
Total	1796

well-studied, less data is available for the utility of frozen section evaluation to determine margin status. Only four recent publications have addressed this issue for head and neck squamous cell carcinomas [13, 14, 18, 19]. The operative characteristics of frozen section evaluation for margin status may be different than those for simple diagnosis of the presence or absence of a pathologic process. Three recent studies have specifically addressed the concordance between frozen section evaluation and final permanent section diagnosis for operative margin status [13, 20, 21]. St. John et al. [20]. Investigated the diagnostic accuracy of intraoperative frozen section evaluation for margin status in breast cancers, while Liu et al. [21] investigated the accuracy of frozen section interpretation of pancreatic margins. Du et al. [13] investigated margin status evaluation by frozen section for head and neck, but did not specifically break down causes of error into interpretive or sampling errors. In a meta-analysis by St. John et al. [20] 838 unique studies were analyzed and revealed 35 studies acceptable for meta-analysis. The pooled sensitivity and specificity for frozen section evaluation of margin status were 86 and 96% respectively. This study suggested that frozen section is a reliable method for assessing margin status in breast cancer specimens. In a study of 77 pancreatic parenchymal resection margins analyzed by frozen section evaluation, Liu et al. [21] demonstrated a specificity and sensitivity of 98 and 61% respectively when pathologists subspecialized in gastrointestinal pathology analyzed the specimens. Specificity and sensitivity were 88 and 67% respectively when general pathologists performed the frozen section analysis. Our data for margin status analysis of head and neck squamous cancers compares favorably with these studies with a sensitivity of 89% and a specificity of approximately 99%. Our results compare favorably with margin status evaluation in the head and neck area as reported by earlier studies [13–19, 22]. Causes of discordant diagnoses may be due to either interpretive or sampling issues. Interpretive issues have been reported as the major cause for discrepancies in some large agreement studies of frozen section/permanent section diagnoses. In our study, most discrepancies were due to interpretative error when all errors were analyzed, but the cause varied between false

Table 4 Error statistics by experience group

Group	<10 years	>10 years	Difference (95% CI)	p value ^a
Cases	906	890		
Total errors	33	22		
False positives	16	4		
False negatives	17	18		
Total error rate	3.6% (2.5–5.1%)	2.5% (1.6–3.7%)	1.1% (–0.5–2.7%)	0.09
FP rate	1.8% (1.0–2.9%)	0.4% (0.1–1.1%)	1.4% (0.4–2.4%)	0.002
FN rate	1.9% (1.1–3.0%)	2.0% (1.2–3.2%)	–0.1% (–1.4–1.2%)	0.56

^aTwo sample test of proportions, one sided

negative and false positive frozen section diagnoses. In 21 of 35 (60%) false negative frozen sections, the cause of the discrepancy was sampling. In the 20 cases where frozen section was falsely positive, all discrepancies were due to interpretive errors. Thus, in 34 of 55 (62%) discrepant pairs, interpretation was the cause of the discrepancy. This is roughly in agreement with the results of most prior non-head and neck studies [1, 20, 21]. Two major studies assessing margin status by frozen section analysis in the head and neck area found that inadequate sampling was the major cause of error rather than interpretation by the pathologist [15, 19].

A potential cause of interpretative error is insufficient experience in interpreting frozen sections. While this would most significantly influence interpretive errors, it might also impact sampling since more experienced pathologists might request additional levels before rendering a diagnosis. Experience did appear to impact diagnostic errors as pathologists with less than 10 years' experience made 50% (33 vs. 22) more errors than the more experienced group even though the number of frozen section "reads" was nearly equal (906 vs. 890). In the less experienced group, 16 of 33 (48%) errors were false positive diagnoses (all interpretive) while in the senior group, 4 of 22 (18%) errors were false positive diagnoses. Thus, pathologists with less experience appear to make a greater number and percentage of interpretive errors than more experienced pathologists but this trend did not reach statistical significance ($p=0.09$). False positive diagnoses were more common in the less experienced group and this relationship did reach statistical significance ($p=0.002$). This appears to support the interpretation that level of experience is a significant factor in the occurrence of diagnostic frozen section error. It appears that false negative diagnoses were more evenly split between the two experience groups indicating that experience did not have as much an impact on sampling error. Du et al. [13] presented considerable information on the impact of patient age, gender, ethnicity and site of carcinoma impact on frozen section accuracy. However, they offered little or no information regarding the impact of the characteristics of the pathologist on frozen section accuracy.

Gandour-Edwards et al. [15] analyzed the cause and nature of frozen section discrepancies and made a series of recommendations to improve frozen section accuracy. They suggested that pathologist-selected specimens may lead to error due to sampling and that several levels (at least three) be taken for frozen section evaluation. They suggested that inconsistent cryostat temperature and dull blades were also causes of error. Gandour-Edwards et al. [15] recommended the use of "diagnosis deferral" when necessary to improve frozen section accuracy. They also suggested that direct orientation of the specimen by the surgeon could reduce errors due to sampling. We concur with the belief that direct orientation of the specimen and

specimen selection by the surgeon might improve frozen section accuracy. Our observation is that many errors are due to insufficient sampling and deeper levels on permanent section reveal carcinoma not present in the frozen sections. Orientation and marking by the surgeon of the true margin side of the specimen may help reduce error. If the true margin side were marked it could be used as the side from which sections are taken. At present, some "sampling" failures may be due to the fact that the frozen section is obtained from the surface nearest the true margin, but deeper permanent levels are further into the block and further from the true margin. Thus, these additional levels would not necessarily represent the true margin. Our study contained only margin specimens selected by the surgeon. This addresses one of the recommendations given by both Gandour-Edwards et al. [15] and Du et al. [13] but our accuracy results were not significantly improved over those reported by Du et al. [13] and Gandour-Edwards et al. [15] putting into question the value of surgeon selection of specimens for margin status evaluation.

Controversy remains as to what is the best method for insuring complete excision of squamous cell carcinomas of the head and neck. Meier et al. [31] and Maxwell et al. [32] documented three methods for controlling and documenting margin status. These are: (1) sampling of main specimen edges without tumor bed sampling; (2) intraoperative evaluation of main specimen margins by a pathologist with additional tissue taken if these samples are positive for carcinoma; and (3) tumor bed sampling only without intraoperative sampling of the main specimen. Maxwell et al. [32] found that the 3-year recurrence-free survival was poorest for the third method. The institution for our study uses the third method. The present study was performed to only evaluate the accuracy of frozen section for determining the status of cavitary margins. Because this investigation only studied the correlation of frozen section diagnoses with final diagnoses, clinical follow-up was unnecessary. The present study was not designed to determine which sampling method is optimal. The relative accuracies of different sampling methods have been discussed by Varvares et al. [33], Maxwell et al. [32], Yahalom R et al. [34] and Amit et al. [35]. Our study documents the discrepancy rate for a large series of frozen sections performed for margin status evaluation of head and neck squamous cell cancers at a single institution. The discrepancy rate, sensitivity and specificity compare favorably with those reported in the previously published literature. Discordant diagnoses are found in approximately 3% of frozen section/permanent section diagnostic pairs and frozen section evaluation of margin status has a sensitivity of approximately 89% and a specificity of approximately 99%. These data indicate that frozen section is a reliable method for the intraoperative evaluation of margin status for head and neck squamous cell carcinomas.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study underwent Institutional Review Board analysis at the University of Missouri and was determined to be exempt. It was determined by the IRB that patient consent was not needed for this study. The study also meets the standards of the Helsinki Protocol.

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