Intraoperative Frozen Section Diagnosis in Skull Base Surgery

Abstract—During January 1990 through June 1992, we performed 39 surgeries for base of skull tumors with extracranial and intracranial involvement on 33 patients. Intraoperative frozen section was requested on 581 of 904 specimens submitted (64%). There was a discrepancy between the frozen section diagnosis and final diagnosis in 15 specimens for an error rate of 3%. There were two false-positive diagnoses of malignancy and 13 false-negative diagnoses. The discrepancies were a result of sampling error in ten cases and of interpretive error in five cases. Four of the five interpretive errors involved intradural tissues. Only two of the discrepancies were clinically significant. One involved the evaluation of adequacy of surgical margins and a second involved the misinterpretation of metastatic renal cell carcinoma for hemangioblastoma. We recommend careful attention to cryostat sectioning and interpretive experience in head and neck pathology and neuropathology. The importance of vigilant communications between surgeon and pathologist before, during, and after surgery cannot be overstated. We are utilizing a video-linked microscopic network that allows the surgeon to view the frozen section histologic sections in the operating room. Future trends may include the use of monoclonal antibodies and morphometry to improve accuracy in frozen section diagnosis. (*Skull Base Surgery*, 3(3):159–163, 1993)

The technique and value of frozen section for intraoperative consultation has been in widespread use for approximately 60 years.^{1–4} Studies concerning the accuracy rate of intraoperative frozen section diagnosis in head and neck surgery average 96 to 97%.^{5–8} In two recent reports, we reviewed our experience with intraoperative frozen section diagnosis in head and neck surgery and found a consistent discrepancy rate of 2%.^{9,10}

In January 1990, we formally inaugurated the University of California Davis Medical Center, Center for Skull Base Surgery. These complex surgeries have resulted in a significant challenge to surgical pathology along with an increase in both the number and difficulty of intraoperative frozen section diagnoses. The intent of this report is to reappraise critically the value and limitations of intraoperative frozen section diagnosis in skull base surgery by examining the indications for the frozen section requests and analyzing the frequency and causes of discrepancies between the frozen section diagnosis and the final pathologic diagnosis.

METHODS AND MATERIALS

During the 2½ year study period, 39 surgeries for base of skull tumors with extracranial and intracranial involvement were performed at the University of California Davis Medical Center. A total of 581 intraoperative frozen section diagnoses were requested. The appropriate tissues were snap frozen in liquid nitrogen, embedded in OCT (polyethylene glycol-based embedding medium) and sectioned on a Tissue-Tek cryostat at –24°C. The specimens were sectioned by resident pathologists at different stages of training under the direction of staff pathologists. Typically, 2 to 4 sections per block were cut and mounted on a single glass slide and stained with standard hematoxylin and eosin solutions. The sections were examined microscopically and diagnoses made by staff pathologists. The diagnostic interpretations were recorded in the frozen section request form and in the patients' chart as well as verbally communicated to the surgeon by an intercom system.

The sectioned tissues were then thawed and submitted in 10% buffered formalin for routine histologic processing. The original cryostat sections were retained. The following working day, all of the microscopic sections were reviewed with careful comparison of the frozen section with the permanent section of each specimen. Any discrepancies between the frozen section diagnosis and final diagnosis were promptly communicated by telephone to the surgeon, as well as discussed in the comment section of the surgical pathology report.

All specimens from these surgeries were analyzed to determine the rate of disagreement between the frozen section diagnosis and final diagnosis as well as to analyze the indications for the frozen section diagnosis requests. We reviewed the cryostat and permanent sections on all cases, including those without noted discrepancies to determine the sources of error. Frozen section diagnosis errors were divided into two major categories: sampling and interpretation. Sampling errors were defined as the lack of the representative lesion on the cryostat section. Interpretive errors involve a failure of the pathologist to diagnose appropriately the tissue present on the cryostat section.

RESULTS

During January 1990 through June 1992, we performed 39 skull base surgeries for tumors with extracranial and intracranial involvement on 33 patients. Fourteen surgeries were anterior fossa resections for eight cases of benign disease and six cases of malignant tumor. Twenty-five surgeries were middle fossa resections for malignant tumors (Table 1).

In most instances, intraoperative frozen sections were requested to ensure tumor-free margins of resection. The presence of a "positive margin" led to further resec-

tion of tissues and an additional frozen section to establish a "new margin." Intraoperative frozen section was requested on 581 of 904 specimens submitted for a request rate of 64%. A discrepancy between the intraoperative frozen section diagnosis and the final diagnosis occurred in 15 specimens for an overall error rate of 3%. Ten of the discrepancies were sampling errors, which occurred at the time of cryostat sectioning, that is, the cryostat sections did not contain tumor but permanent sections revealed tumor hidden deeper in the tissue block. Five discrepancies were due to interpretive errors by the pathologists (Table 2). There were two false-positive and 13 false-negative diagnoses of malignancy.

DISCUSSION

Sources of error during intraoperative frozen section diagnosis can be divided into two major categories, sampling error and interpretive error. There are two kinds of sampling errors. Specimens submitted for frozen section that are greater than 2 cm in diameter are too large for a single cryostat section. These specimens must be subdivided and a representative sample sectioned. The "representative" sample may actually miss the diagnostic lesion. More commonly, however, the specimen is inadequately or superficially sectioned and thus misses the lesion, which is buried deeper in the frozen tissue block. This was our most common reason for sampling errors and accounted for the majority of our false-negative diagnoses. Clinical follow-up has not, however, revealed clinical or radiologic evidence of recurrence at these specific sites in these patients.

The reasons for interpretive errors are more complex to analyze. As is well known, the freezing process produces a degree of distortion of architecture. Variable section thickness and uneven staining can obscure cytologic detail and influence subjective judgment. Specimens taken from the head and neck in sites of previous surgery or radiation are particularly problematic. Fibrosis from previous surgery may distort the architecture of normal vessels and glands and radiation often induces permanent nuclear changes that may resemble malignancy.^{9,10} Although, 12 of our patients had received radiation therapy prior to surgery, none of our interpretive errors were attributable to tissues altered by radiation. An unfamil-

Table 1. Results of 39 Skull Base Surgeries for Tumors

	No.
Benign diagnoses	
Meningioma	6
Juvenile angiofibroma	1
Chromophobe adenoma	1
Fibrous dysplasia	1
Solitary fibrous tumor	1
Hemangiopericytoma	1
Chondroid chordoma	1
Malignant diagnoses	
Squamous cell carcinoma	13
Neuroblastoma	3
Adenoid cystic carcinoma	3
Undifferentiated carcinoma	3
Melanoma	2
Basal cell carcinoma	1
Malignant schwannoma	1
Metastatic carcinoma	1

Table 2. Interpretive Errors

<i>Frozen Section Diagnosis</i>	<i>Final Diagnosis</i>
Adenoid cystic carcinoma	Normal blood vessel
Hemangioblastoma	Metastatic renal cell carcinoma
Undifferentiated carcinoma	Normal pituitary
Inflammation	Neuroblastoma
Inflammation	Squamous cell carcinoma

ilarity with normal neural tissues and their tumors is a particular handicap for the general surgical pathologist. Four of our five interpretive errors involved the misinterpretation of intradural tissues.

The errors were of clinical significance in only two cases. One case involved the misinterpretation of a distorted blood vessel within the brainstem white matter as infiltrating adenoid cystic carcinoma (Fig. 1). On report of a malignant frozen section diagnosis at this site, surgery was discontinued. When the permanent section diagnosis was recognized, a subsequent surgical procedure at a second setting was attempted to complete the resection. A final clear margin at other locations, however, could not be obtained during the second procedure. The patient subsequently underwent radiation therapy. At 2 years post-operation, she is free of local disease and is being treated for distant metastases.

The second case involved pre-resection biopsy specimens from the infratemporal fossa in a 66-year-old woman. The frozen section diagnosis was "neoplasm, favor vascular origin" and the permanent diagnosis "probable heman glioblastoma." This diagnosis was considered improbable by the surgeons because of the tumor location. Unfortunately, all of these initial biopsies were utilized for frozen section, which resulted in suboptimal morphology, equivocal immunohistochemistry, and prohibited the use of electron microscopy for definitive diagnosis. Following definitive resection of the tumor, permanent sections from tissues properly fixed for immunohistochemistry and electron microscopy confirmed a diagnosis of metastatic renal cell carcinoma. Further workup revealed an asymptomatic renal mass that had not been suspected clinically.

A close liaison between the surgeons and pathologist before, during, and after the operative procedure is essential to prevent errors in pathologic diagnosis, which must be reduced to a minimum to provide optimal management of the oncologic patient. To prevent intraoperative frozen section discrepancies, we recommend thorough sampling and technically adequate sections.^{9,10} To reduce interpretive errors, a thorough knowledge of surgical anatomy and expertise in the interpretation of neural tissues is essential. The pathologist, surgeon, and patient should also realize that, infrequently, a definitive diagnosis cannot be rendered and a deferral of diagnosis may be the most prudent interpretation.

The surgeon and pathologist need to maintain vigilant communication throughout the surgery to ensure the most successful outcome during these challenging surgeries. We have recently installed a microscopic video link between the surgical pathology grossing room and surgery. This enables the surgeon to view the frozen section microscopic image on a monitor in the operating room. Future plans include a macro-lens camera in surgery so that an image of the operative field can be transmitted to the pathologists.

There is a tremendous need to improve our ability to identify tumors precisely at the skull base. The biology of tumors with intracranial infiltration are particularly problematic because, often, extensive intradural and perineural extension occurs without clinical symptomatology, radiographic evidence, or gross intraoperative evidence. Intraoperative frozen section diagnosis is currently the most definitive method available to establish the presence or absence of tumor. As may be inferred from our study,

Figure 1. Distorted blood vessel in cranial nerve V, near brainstem interpreted as adenoid cystic carcinoma. (H&E; $\times 400$.)

we utilize intraoperative frozen sections extensively to guide our dissections and believe that this has assisted with tumor extirpation and local control. Future studies will necessarily involve long-term follow-up of our patients to answer the question of the effect of intraoperative frozen section diagnosis on patient outcome. Evolving pathologic technology may involve the application of modalities such as monoclonal antibodies and morphometric analysis to intraoperative histopathologic diagnosis to enhance its clinical utility in skull base surgery.

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REVIEWER'S COMMENTS

The paper by Gandour-Edwards, Donald, and Boggan on "Intraoperative Frozen Section Diagnosis in Skull Base Surgery" is both informative and timely. Over the last several years, there have been enormous advances in and numerous publications pertaining to skull base surgery, especially in the areas of radiologic imaging and innovative operative approaches and reconstruction. This is the first article, however, that I am aware of that retrospectively analyzes the experience with frozen sections in this area of the body.

The authors report in their medical center a 97% concordance between intraoperative frozen and permanent histologic sections of cranial base neoplasms, which is identical to that seen in frozen sections in general. This is a remarkable correlation considering the complex anatomy and vast array of tumors that may occur in this region and the fact that biopsies from this site are often small, crushed, and distorted and frequently obtained from patients who have received preoperative irradiation. They have been able to achieve this degree of accuracy by the two professionals—pathologist and surgeon—developing a close working relationship.

As they indicate, most frozen sections in skull base procedures are concerned with the adequacy of the margins of resections, the diagnosis usually having been established previously. Most errors are due to inadequate sampling but occasionally to misinterpretation of the lesion by the pathologist.

In addition to routine frozen sections, we have found intraoperative imprint (touch) cytology to be useful, especially in small biopsies or where the frozen section diagnosis is equivocal or uncertain. In this procedure, a microscopic slide is pressed against the tissue specimen, then fixed, and examined cytologically.

Perhaps most frustrating to the skull base surgeon is the inability of the pathologist to evaluate intraoperatively bone resection margins. There are only three ways in which this may be accomplished and none is optimal. If the bone is osteoporotic, the medullary cavity can be curetted and examined microscopically. If the bone is firm, then a slide imprint of the margin may be done and examined cytologically. In both instances, the specimens may be bloody and obscure foci of tumor. In addition, pathologists must take care not to confuse normal, immature hematopoietic marrow cells for malignant ones. As a last resort, the resected specimen can be taken to radiology for a specimen radiograph. The radiologist may be able to make some judgment about the adequacy of the osseous margins. The bone saw used in removing the specimen, however, often creates sufficient distortion of the margin to invalidate this approach.

Pathologists must always be aware of the clinical implication of their diagnosis, for few diagnostic procedures can have such an immediate and serious consequence in the treatment of a

patient as a frozen section. Likewise, the surgeon must not fall into a sense of complacency about frozen sections. Errors, although rare, do occur, and the results can be disastrous not only for the patient, but also medicolegally for the surgeon and pathologist. As Gandour-Edwards et al have indicated, the frozen section achieves its highest degree of accuracy when there is mutual respect and good communication between the surgeon and pathologist

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