Approach to the Intraoperative Consultation for Neurosurgical Specimens

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Abstract: Intraoperative consultation remains an invaluable tool in the initial evaluation of surgically excised specimens. Good communication is required between the pathologist and surgeon to obtain the best care for their mutual patient. Intraoperative consultation (frozen section, FS) provides a preliminary diagnosis for the surgeon and aids in guiding his/her subsequent surgical approach. For the pathologist, it serves to assess tissue adequacy in the context of the clinical and imaging features of the patient. FS can guarantee that the surgeon is in the desired anatomic location, but most often serves to ensure that adequate amounts of abnormal, and likely diagnostic, tissue will be available to the pathologist to render a final diagnosis on permanent sections. The preliminary evaluation of tissue at the time of intraoperative FS also guides the pathologist in the ordering of ancillary studies, some of which need to be performed on fresh or frozen tissues and must be sent at the time of the intraoperative consultation. This brief review will specifically focus on the role of the pathologist who is called to perform a FS for a neurosurgical specimen. We will discuss (1) the goals of the neurosurgeon for the intraoperative consultation, (2) how to achieve optimal communication between neurosurgeon and pathologist at the time of the FS, (3) what constitutes reasonable and unreasonable expectations by the neurosurgeon for the FS, (4) choices of techniques that can be used by the pathologist, (5) what tissue should be triaged, and (6) common discrepancies between FS and permanent section diagnoses in central nervous system disorders. The published literature on FS and permanent section discrepancies will be briefly reviewed so that pathologists will understand that some difficulties are inherent in neurosurgical specimens and are not specific to their practice, or to a given pathologist. Hopefully, this knowledge will enhance pathologists' confidence as they negotiate how best to handle this time-sensitive, and sometimes angst-producing, task.

Key Words: intraoperative, consultation, neurosurgical specimens, frozen section, neurosurgeon, neuropathologist, touch preparation, smear/squash preparation

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THE GOAL OF THE NEUROSURGEON IS TO EXPEDITIOUSLY OBTAIN DIAGNOSTIC TISSUE FROM WHAT HE/SHE PERCEIVES TO BE THE OPTIMAL AREA OF NEUROIMAGING ABNORMALITY

Despite advances in neuroimaging including intraoperative neuroimaging techniques, biopsies occasionally collect tissue outside of the lesion. In addition, for stereotactic biopsies, what neurosurgeons consider the optimal target is not always the most informative for pathologists because of known heterogeneity of many tumors and infections. In the event that a first frozen section (FS) specimen fails to capture diagnostic tissue, the pathologist can provide this feedback and offer guidance with regard to acquisition of subsequent specimens. Sometimes a larger specimen or additional stereotactic core biopsies are needed for the diagnosis. Similarly, if a biopsy contains predominantly necrotic material, the neurosurgeon can seek more viable cells at a different depth or location.

Although stereotactic guidance techniques are now commonly used during surgery in most neurosurgical practices, there are limitations. First, the brain may shift during the actual operation because of swelling. Thus, the lesion of interest may be in a slightly different position once the actual operation is underway than it was while the imaging data was being obtained preoperatively. Hence, what seemed to be the "target" for their biopsy can actually be several millimeters, or even centimeters, away from where they obtain the first biopsy specimen they send out to the pathologist. Second, there can also be operator-dependent errors in the neuroimaging guidance calculations. All of this may come as a surprise to the pathologist, who with today's advanced technology, presumes that the neurosurgeon must be in the optimal desired targeted site. In fact, the neurosurgeon often needs the pathologist to confirm that the specimen he/she sent is optimally representative.

What does "optimally representative" actually mean? The most common scenario is when the neuroimaging features are those of a ring-enhancing mass for which the differential diagnosis is bacterial abscess versus a highly necrotic glioblastoma versus metastasis. The pathologist prepares the FS and it appears hypocellular—and he/she is struggling with a diagnosis of gliosis versus normal versus low-grade glioma. Knowing the neuroimaging features, the struggle for the pathologist should cease immediately and additional tissue should be obtained, as the neurosurgeon is not in an optimal area.

In the case of infiltrative primary glial brain tumors, often the most hypercellular and highest grade of tumor is located in the white matter rather than cortical gray matter and the neurosurgeon knows this and attempts to obtain tissue deep to the cortical gray-white junction. However, sulci extend several centimeters deep to the surface of brain and occasionally biopsies aimed for white matter are actually still in gray matter when they are performed along one of these deep sulci. The identification of neurons in the biopsy specimen by the pathologist at the time of FS guides the neurosurgeon in obtaining a deeper white matter specimen. Finally, there are instances where the neurosurgeon is specifically targeting subependymal tissue or some other anatomic location for which he/she needs intraoperative guidance. The pathologist can identify anatomic areas of

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interest under the microscope that may be valuable to include or exclude in the biopsy.

HOW CAN ONE ACHIEVE OPTIMAL COMMUNICATION BETWEEN NEUROSURGEON AND PATHOLOGIST AT THE TIME OF THE FROZEN SECTION?

In the best case scenario, the pathologist and neurosurgeon will talk to each other before, during, and after the surgical procedure to arrive at the best diagnosis for their mutual patient. There is no substitute for direct person-to-person contact, but often the pathology suite location in the hospital or time constraints do not allow for the pathologist to go into the actual operating room, or for the neurosurgeon to visit the FS room. Intercom systems are often used, but the main point is that on complicated cases, the two physicians should speak directly if at all possible, rather than through intermediary operating room personnel.

WHAT CONSTITUTES REASONABLE AND UNREASONABLE EXPECTATIONS BY THE NEUROSURGEON FOR THE FROZEN SECTION?

Both parties usually understand the limitations of FS, but pathologists sometimes need to underscore to neurosurgeons that the FS diagnosis is preliminary. As noted above, pathologists should convey their diagnosis verbatim to avoid any misunderstanding. Neurosurgeons should not expect exact grading of gliomas or meningiomas, assessment of margins for gliomas, determination of infectious organism in an abscess or cerebritis, the cause of a stroke or another ill-defined, nonenhancing white matter lesion, or the exact diagnosis in non-neoplastic samples including vasculitis, collagen vascular diseases, vasculopathy, leukodystrophies, leukoencephalopathies, and histiocytosis. For their part, pathologists need to be cognizant of the few diagnoses that direct the neurosurgeon not to undertake gross total resection. These conditions include primary central nervous system (CNS) lymphoma, acute demyelinating disease, rare leukodystrophies that present with mass effect, systemic inflammatory disorders and lymphocytic hypophysitis.

Much of the communication revolves around making certain that both the neurosurgeon and the pathologist have procured tissue that is appropriately diagnostic for what is anticipated from the clinical and neuroimaging data. Obviously, either direct communication between neurosurgeon and pathologist is necessary to obtain this information, or clinical and neuroimaging data must be readily accessible to the pathologist in the FS room by computer-based medical record information. This assessment of "adequacy" of tissue relies on a cogent differential diagnosis formed from the patient's age and sex, duration and tempo of disease, earlier medical history and surgeries, travel history, earlier treatments, and underlying systemic diseases. Fortunately, this differential has usually already been advanced by the clinical or neuroimaging experts who have seen the patient preoperatively and the pathologist simply needs to read the medical record to obtain this information. Probably the most important consideration when assessing adequacy of the tissue is the neuroimaging features of the case.

SHOULD I USE TOUCH PREPARATION, SMEAR/SQUASH PREPARATION, OR ACTUAL FROZEN SECTION?

Choices of techniques that can be used by the pathologist depend on the experience of the pathologist with the various techniques (often driven by how they were trained during residency), the expected pathology, the quality of actual FS available at that institution, and quantity of tissue. FS offers the best architectural detail and largely preserves the tissue for permanent section; however, freezing takes more time, hampers some subsequent immunohistochemistry and results in loss of tissue volume if not done carefully. Certainly, leveled sections should not be obtained at the time of FS, to maximize the tissue for later permanent sections. In comparison, smear (squash, SP) preparations are more rapid and offer both cytological and architectural detail, but they also exhaust the smeared piece of tissue and preclude permanent sections and any further studies on that exact tissue fragment. If the quantity of tissue is very small, therefore, FSs are preferred, and if the quality of FSs hinders cytologic and architectural detail (e.g., ice crystal artifact), smear preparations may elucidate the needed details. It should be noted that many institutions produce extremely high quality FSs which in some cases are sufficient for the final diagnosis. This is especially true if rapid liquid nitrogen freezing is used.

Touch preparation (TP) supplies a third alternative for intraoperative consultation and TP is fortunately not an either/or choice, as TP does not exhaust tissue and can be used in addition to FS or SP. This method is especially useful for identifying neutrophils, macrophages, nuclear and cytoplasmic details of metastatic tumor, germinomas, lymphomas, or any other high-grade tumor (Fig. 1). TPs in many practices often serve as the sole testing for pituitary adenomas (Fig. 2). A final unique advantage to TP is that it retains the tissue fragment of interest, thereby allowing for corroboration with the final permanent section.

Regardless of the preparation, once the slide is obtained, an orderly and organized, but reasonably rapid, algorithmic thought process and approach to the slide can be helpful when viewing CNS biopsies.[1,2] In brief, pathologists first need to determine the location of the biopsy. Next, they should query whether or not the biopsy represents normal tissue. If not normal, the first decision is whether the process might be one that mimics a neoplasm (e.g., reactive changes, inflammation, vascular malformation, etc.). Pathologists should always consider reactive gliosis. Finally, if all of the above reactive, non-neoplastic conditions do not satisfactorily explain the tissue findings, the lesion should be approached as neoplastic and then effort should be made to determine if it is primary or metastatic to the CNS. Working through this algorithm ensures inclusion of all diagnostic possibilities and helps to avoid overcalling neoplasms or failing to recognize normal tissue as such. It is useful to remember that often determining what a lesion is not may be as clinically helpful in some situations as determining what something is.

WHAT TISSUE SHOULD BE TRIAGED?

Aside from assuring adequacy of the tissue sample and generating a preliminary diagnosis, neuropathologists must also guide the triage of tissue. Some diagnoses necessitate further studies (apart from routine H&E) that require tissue to be stored in a very particular way. Fresh, sterile tissue

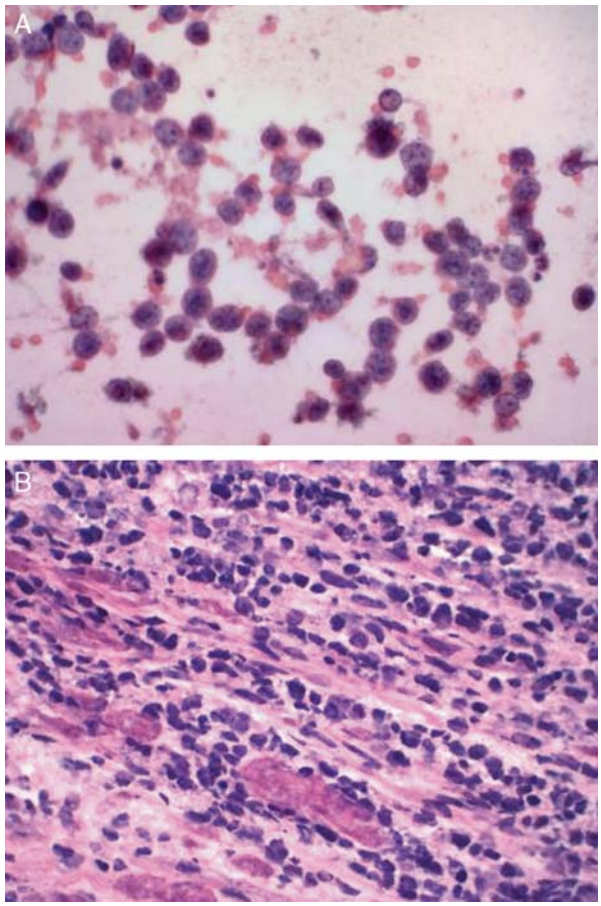

FIGURE 1. Cytological features of some tumors show up much better on touch preparation (top) than on actual frozen section (bottom), as seen in this systemic lymphoma involving peripheral nerve. (Hematoxylin and eosin-stained sections).

may need to be sent to the microbiology laboratory for culture of organisms, by either the neurosurgeon or the pathologist. Frozen tissue is essential for immunohistochemistry for muscle biopsies, Western blot analysis for neurodegenerative diseases such as Creutzfeldt-Jakob disease, enzymatic studies, and certain tissue banking protocols. Optimally, if polymerase chain reaction testing is anticipated, frozen tissue for DNA retrieval should also be set aside (such as in cases of rare CNS infections), as aldehyde fixation can sometimes cause a decreased yield for polymerase chain reaction techniques. For cases requiring cytogenetics or flow cytometry, including suspected systemic lymphomas that involve the dura or epidural spaces, tissue must be placed in culture medium (Roswell Park Memorial Institute); it is prudent not to assume there will be additional tissue from lymph nodes or bone marrow for this purpose. Lastly, tissue should be set aside for electron microscopy in cases of very poorly differentiated neoplasms that are difficult to classify on FS/SP/TP such as sarcoma, pediatric neoplasms, and rare pituitary adenomas (such as acidophil stem cell adenomas). If the surgery yields ample fresh tissue and if there is even a remote chance that the final diagnosis will be served with any of these ancillary studies, it is best practice to operate under the principle "better safe than sorry" and divide tissue accordingly,

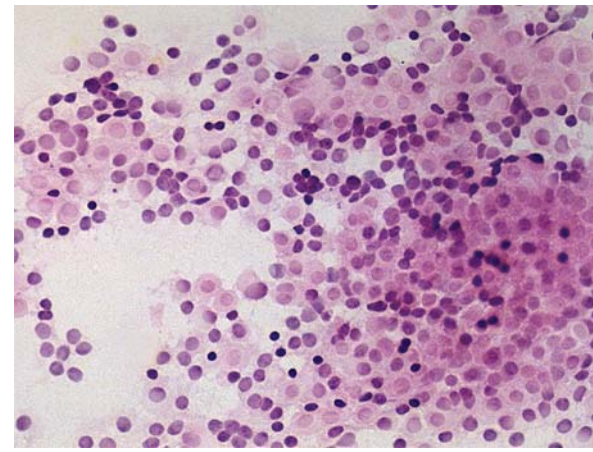

FIGURE 2. Touch preparation may be all that is necessary to diagnose a pituitary adenoma at the time of intraoperative consultation; the abundance of cells that have exfoliated, coupled with their nuclear and cytoplasmic features including monotony, as assessed on hematoxylin and eosin stain, ensure that this is neither normal anterior pituitary gland nor another type of sellar region mass such as craniopharyngioma.

especially as small amounts are necessary for many of these studies.

WHAT IS THE DIAGNOSTIC YIELD FOR STEREOTACTIC BIOPSIES FOR CERTAIN TYPES OF DIAGNOSES FROM THE LITERATURE?

The diagnostic yield of FS diagnoses is relatively high and most diagnoses are achieved with the first biopsy. In a series of 188 biopsies, 73% of tumors and 50% of nontumors (for a total of 67% of all cases) were diagnosed with the first sample.[3] Subsequent biopsies successfully facilitated the diagnosis in an additional subset of cases and errant sampling occurred with only one biopsy.

The rate of discrepant diagnoses in non-neoplastic lesions is consistently higher than that in CNS neoplasms. The notorious heterogeneity of non-neoplastic CNS lesions, coupled with the fact that these lesions are less commonly sampled for FS diagnosis and thus less familiar to most pathologists, form possible explanations for this observation. In a recent study, particularly problematic conditions included the following: inflammatory lesions, malformation of cortical development (cortical dysplasia), gliosis, vascular malformations, demyelination/progressive multifocal leukoencephalopathy, infarct, hemorrhage/blood clot, and no pathologic changes.[4] Discrepant diagnoses were also seen with amyloid angiopathy, nonspecific vasculopathy, vasculitis, and meningioangiomatosis. Examination of FS discrepancies involving CNS tumors also uncovered distinctly challenging categories. These diagnoses usually involved spindle cell lesions, differentiating between astrocytoma versus oligodendroglioma, CNS lymphoma, discerning reactive from neoplastic processes, and (over) grading tumors.[5]

FS evaluation is susceptible to errors from sampling, bias, and misinterpretation like any other area of pathology and medicine. To avoid these problems, it is essential to maintain a focused understanding of the goal of FS—namely, the acquisition of diagnostic tissue for the final diagnosis at the time of permanent section. Similarly,

communication with neurosurgery, familiarity with common diagnostic pitfalls, and adequate preparation of the slide will improve the quality of the intraoperative consultation and ultimate care of the patient. In sum, FS, when performed correctly, guides intraoperative management, confirms adequacy of tissue, and guides triage of the neurosurgically excised specimen for further special studies.

REFERENCES

1. Kleinschmidt-DeMasters BK, Prayson RA. An algorithmic approach to the brain biopsy—part I. *Arch Pathol Lab Med*. 2006;130:1630–1638.
2. Prayson RA, Kleinschmidt-DeMasters BK. An algorithmic approach to the brain biopsy—part II. *Arch Pathol Lab Med*. 2006;130:1639–1648.
3. Brainard JA, Prayson RA, Barnett GH. Frozen section evaluation of stereotactic brain biopsies: diagnostic yield at the stereotactic target position in 188 cases. *Arch Pathol Lab Med*. 1997;121:481–484.
4. Plesec TP, Prayson RA. Frozen section discrepancy in the evaluation of nonneoplastic central nervous system samples. *Ann Diagn Pathol*. 2009;13:359–366.
5. Plesec TP, Prayson RA. Frozen section discrepancy in the evaluation of central nervous system tumors. *Arch Pathol Lab Med*. 2007;131:1532–1540.