PRACTICAL APPROACH TO INTRAOPERATIVE CONSULTATION AND DIAGNOSIS OF CENTRAL NERVOUS SYSTEM TUMORS

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INTRAOPERATIVE CONSULTATION PRINCIPLES

- Do your homework
- Cytologic preparations and frozen tissue sections are complementary – USE BOTH
- Don't freeze all of the tissue if possible
- PLAN FOR TOMORROW!

DO YOUR HOMEWORK

CLINICAL INFORMATION IS CRITICAL!

One point cannot be emphasized enough: Knowledge of the patient's clinical information is absolutely essential to avoid the potentially disastrous consequences of intraoperative consultation misdiagnosis! The key features to know are the patient's age, anatomic location of the lesion (from the preoperative MRI and/or CT scans), the duration and nature of the presenting signs and symptoms, and any relevant clinical history of concurrent disease, previous surgeries, etc. The presenting signs & symptoms can be simplified to "recent onset" versus "long history." In general, a long history, particularly an extended past history of medically intractable seizures, suggests a more indolent disease process or a low-grade neoplasm. Throughout our discussion, the central importance of an awareness of the patient's age, location and MRI features of the lesion, duration and nature of the presenting symptoms, and relevant clinical history will be repeatedly emphasized.

The clinical information facilitates formulation of a highly focused and relevant differential diagnosis. For example, the differential diagnosis of a contrast-enhancing mass in a child is very different from that in a 65-year-old. Whereas the two most common brain tumors in children are pilocytic astrocytoma and medulloblastoma, in an older adult, the principal entities are metastatic carcinoma, glioblastoma and primary CNS lymphoma. The anatomic location of the lesion is equally useful. For example, a solitary mass in the lumbar cistern is most likely one of four tumors: schwannoma, meningioma, myxopapillary ependymoma or paraganglioma of the filum terminale. Similarly, there are

specific tumors that comprise the list of most likely possibilities for a mass in the lateral ventricle or the cerebello-pontine angle. The anatomic relationship to various intracranial structural compartments can also be very helpful. For example, the differential diagnosis for a dura-based mass includes specific mesenchymal and hematopoietic tumors as well as several non-neoplastic entities. Type and duration of symptoms simplifies to acute onset versus long history. The latter tends to indicate a more indolent lesion compared to the first. The relevant clinical history includes information such as a pre-existing or predisposing disease or syndrome, prior surgery, etc.

Pre-IOC Preparation:

Confidant, accurate diagnosis is greatly facilitated by knowledge of the following:

- **AGE** of the patient
- **ANATOMIC LOCATION** of the lesion
- **IMAGING** characteristics of the lesion
- **PAST MEDICAL HISTORY** of the patient
- **TYPE and DURATION** of presenting signs & symptoms
- **WHAT TYPE of SURGICAL PROCEDURE** is being performed?
- **WHAT INFORMATION WILL THE SURGEON <u>NEED</u> TO KNOW?**

INTRAOPERATIVE CYTOLOGIC PREPARATIONS

- Cytologic preparations reveal exquisite nuclear, cytoplasmic and background stroma detail free of freeze artifact; frozen tissue sections reveal lesion architectural relationships; the two procedures each provide some unique information about the pathologic process and are very complementary to each other – USE BOTH!

Cytologic Preparations

- Touch (Imprint)
- Smear (Squash, Crush)
- Scrape
- Drag

Technique	Tissue Consistency	Representative Example
Touch	Soft and discohesive	Pituitary adenoma
Smear	Soft	Glioma
Scrape	Densely fibrous	Dural metastasis
Drag	Necrotic	Necrotic metastasis; Stereotactic radiosurgery site resection

These Different Cytologic Techniques ARE NOT MUTUALLY EXCLUSIVE: FEEL FREE TO USE MORE THAN JUST ONE ON THE SPECIMEN!

Bottom line: use whatever technique(s) you need to in order to get high quality, representative cytologic information on the lesion.

PLAN FOR TOMORROW!

For very small biopsies (e.g., stereotactic bx), you must ensure adequate specimen for IHC:

- unstained touch preps
- unstained sections cut from FS block
- order unstained from paraffin block at the time of frozen section ("biopsy processing") to avoid re-facing of the block (and, hence, loss of valuable tissue) after examining the H&Es

WHAT INFORMATION WILL THE SURGEON NEED TO KNOW?

Answer: Information that will DETERMINE THE SUBSEQUENT COURSE OF THE OPERATION.

Valid indications for IOC:

- Is adequate, representative tissue present?
- Is the disease an infectious process?
- If tumor, is it of a type amenable to gross total resection
- Is viable GBM present? (if so, Gliadel wafer, Gliacyte balloon, other intraoperative treatment can procede)

WHAT INFORMATION DOES THE SURGEON NOT NEED TO KNOW?

Answer: Any information that is not needed to successfully complete the operation.

Prominent Example: whether a diffuse glioma is astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. It is generally sufficient to determine that the pathologic process is a diffuse glioma, and that representative tissue with respect to the preoperative imaging studies has been obtained for grading purposes (contrast-enhancing diffuse gliomas are high-grade) and that a sufficient amount of tissue has been obtained for marker studies to permit definitive subclassification on FFPE sections. A definitive diagnosis, including characterization of the diffuse glioma with respect to major molecular markers that will directly impact treatment (IDH mutation status and 1p/19q codeletion status) **WILL** need to be achieved from appropriate evaluation and testing of the FFPE permanent section tissue, but this degree of diagnostic specificity is not needed (indeed, is not possible) at the time of intraoperative consultation. One of the most common frozen section/permanent section diagnostic discrepancies is the

misdiagnosis of oligodendroglioma as astrocytoma at the time of frozen section (because freezing distorts the nuclei, making them appear astrocytic, and the characteristic “fried egg” artifact of oligodendroglioma is a product of delayed fixation seen only in FFPE tissue, not in frozen sections). Although this error is virtually always corrected prior to the institution of treatment (being obvious once the classic features are seen on the FFPE sections the following day) and would not have altered the operation, it is an embarrassing mistake for the pathologist.

AN IMPORTANT DIGRESSION
NEUROIMAGING 101: NEURORADIOLOGY FOR THE GENRAL SURGICAL PATHOLOGIST

The surgical pathologist is certainly not expected to be a neuroradiologist; however, even a very basic understanding of CNS CT and MRI scans can be extremely helpful in terms of both narrowing the differential diagnosis and thereby helping to point the pathologist in the direction of the correct diagnosis, as well as warning the pathologist when a preliminary impression does not fit with the clinical data! Following is a brief synopsis of basic imaging interpretation.

CT vs MRI

- CT scanning is widely available and much easier and quicker compared to MRI; it is generally the technique of choice for trauma cases in which intracranial / meningeal **bleeding** must be addressed.
- CT scanning is also superior to MRI for detecting **mineralization** and **bone** formation.
- CT scanning is often superior to MRI when detailed anatomy of bony regions is essential, such as with lesions of the skull base, vertebral column and pelvis.
- Clinically useful advanced techniques for CT are available, including colorized three-dimensional reconstruction.

Critical Information Derived from MR Imaging

- Anatomic location of the lesion(s)
- Nature of the interaction of the lesion border with the surrounding brain: sharp margin or diffuse infiltration
- Presence or absence of lesion enhancement following administration of the contrast agent gadolinium
- For contrast-enhancing lesions, the pattern of the enhancement (e.g., smooth ring, ring with dark rim, ragged ring, incomplete ring, solid enhancement, cyst with enhancing nodule, etc.)

Some Common MRI Contrast Enhancement Patterns

Pattern	Disease
Smooth ring	Abscess
Ragged ring	GBM, Metastasis

Ring w/dark rim	Cavernous angioma
Broken ring	Demyelinating pseudotumor
Solid uniform	Primary CNS lymphoma (PCNSL)
Cyst w/ enhancing nodule	JPA, PXA, Ganglioglioma, Hemangioblastoma
Disappearing enhancement	Primary CNS lymphoma (PCNSL)

Imaging Planes

The three standard planes of image presentation are:

- Axial (primary acquisition plane)
- Sagittal
- Coronal

Imaging Sequences

The four general purpose sequences are:

T1-weighted image (T1WI)
• Cerebrospinal fluid (CSF) appears dark (hypointense, black)

T2-weighted image (T2WI)
• Cerebrospinal fluid (CSF) appears bright (hyperintense, white)
• Fluid in tissue (edema) and in tumors appears bright (white)

T2-FLAIR sequence
• Cerebrospinal fluid (CSF) appears dark (black)
• Fluid in tissue (edema) and in tumors appears bright (white)

T1-weighted post-gadolinium (post-contrast administration) image
• Cerebrospinal fluid (CSF) appears dark (black)
• Blood vessels (arterial) appear bright (white)
• Tumors with abnormal blood vessels (e.g., vascular proliferation) appear bright (white)

Three Additional Very Useful Imaging Sequences

- DWI: Diffusion-weighted imaging
- GRE: Gradient Echo Imaging
- SWI: Susceptibility-Weighted Imaging

Diffusion-weighted Imaging (DWI) and the Apparent Diffusion Coefficient (ADC) Map

"Restricted" diffusion appears Hyperintense (bright, white) on the DWI sequence and Hypointense (dark, black) on the ADC map.

DWI is useful for detecting:

- **Early detection of Acute Infarct (within 6 hrs. of stroke – 7d)**
- **Abscess (pyogenic)**
- **Epidermoid cyst**

Gradient Echo Imaging (GRE) and Susceptibility-Weighted Imaging (SWI)

GRE and SWI are T2-based sequences that are especially useful for detecting the presence of:

- **Blood products**
- **Iron**
- **Calcium**

All of these substances appear Hypointense (dark, black) on both GRE and SWI

Susceptibility (SWI) is better than GRE imaging in detecting and visualizing:

- **Iron**
- **Calcium**
- **Small veins**

Advanced Imaging Techniques
(Many are used for Pre-Surgical Planning and Intraoperative Neuronavigation)

- Time of Flight (TOF) MR Arteriography & Venography (TOF MRA and TOF MRV)
- MR Perfusion (for vascular permeability)
- Single & Multivoxel MR Spectroscopy ("Spect")
- Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)
- Functional MR
- Three Dimensional Computed Tomography Reconstruction
- Diffusion Tensor Imaging (DTI): Fiber Tractography Vector Mapping

Putting It All Together: The Interaction of the Neuroimaging Differential Diagnosis With the Histologic Differential Diagnosis

Based on the location and nature of the lesion(s) as revealed by MR imaging, a neuroimaging differential diagnosis is formulated. The imaging differential diagnosis will be modified based on clinical history factors such as the known presence of a systemic malignancy, previous surgery at the site of the lesion, etc. This list is then refined and

narrowed by comparing with the histologic differential diagnosis that is based on the H&E characteristics seen on cytologic and frozen section preparations, yielding the most accurate diagnosis possible.

A Very Important, Update: Practical Molecular Classification of Diffuse Gliomas

Clinically Relevant (Diagnosis, Treatment and Prognosis) Diffuse Glioma Molecular Markers (There are currently only 2)

- **1p/19q Codeletion** Codeletion is a FAVORABLE genetic signature, correlates with classical oligodendroglioma morphology, and directly impacts the patient treatment regimen. 1p/19q codeletion is the "**molecular definition of oligodendroglioma**".

- **Isocitrate Dehydrogenase (IDH) Mutation** Mutation is a FAVORABLE genetic signature, is seen in virtually all 1p/19q codeleted oligodendrogliomas and in approximately 70% of grade II and grade III astrocytomas, in which **IDH mutation status can be used to stratify patients into favorable (mutation present) and unfavorable (mutation absent) groups.** The most common IDH mutation, which encompases approximately 95% of all IDH mutations in diffuse gliomas, is a single point mutation in the IDH1 gene: IDH1(R132H). Antibodies directed against the IDH1(R132H) mutant protein are commercially available for clinical use on routinely prepared FFPE tissue. When present, the mutation results in expression of the mutant protein in 100% of tumor cells.

- **Molecular Classification of the Diffuse Gliomas** for clinical treatment purposes using these two markers is rapidly becoming routine, and constitutes the evolving standard of care for diffuse glioma diagnosis and classification.

- [Parenthetically, IDH mutations have also been reported in a significant percentage of **acute myeloid leukemia (10-15%)**, **central chondrosarcoma and chondromas (55%)**, and, most recently, in **intrahepatic cholangiocarcinoma (25%)**.]