PRACTICAL GUIDE FOR FROZEN SECTIONS IN NEUROPATHOLOGY
CURRENT ISSUES IN ANATOMIC PATHOLOGY 2011

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Outline

- Purpose/goals of intraoperative diagnosis
- Incorporation of clinical-radiologic information
- Tips on performing the intraoperative frozen section/smear
- Interpreting the results
  - Key examples

Purposes of Intraoperative Diagnosis in Neuropathology

- A. Establish adequacy of tissue
- B. Preliminary diagnosis
  - Help define surgical management
  - Allows post-operative planning

Purposes of Intraoperative Frozen Section

- A. Establish adequacy of tissue
  - Is lesional tissue present? – Can we establish a diagnosis on permanent section?
  - Is it representative of expected pathology based on clinical-radiologic impression
  - Is there enough tissue for stains and other studies (IPOX, etc)
Purposes of Intraoperative Frozen Section

- Is the operative procedure a biopsy only or is a resection in progress?
  - The primary purpose of a biopsy is to obtain diagnostic tissue, hence a specific diagnosis is not necessarily required intraoperatively
  - A diagnosis of “lesional tissue present” may suffice in such cases

Purposes of Intraoperative Frozen Section

- B. Preliminary diagnosis
  - Establish a pathologic category
    - Inflammatory/infectious vs Neoplastic
  - Help define surgical management, eg:
    - No resection
    - Gross total resection
      - Infection/inflammatory
      - Lymphoma
      - Germ cell tumors
      - Small cell carcinoma
  - Allow consideration of special studies:
    - Cultures, flow cytometry, electron microscopy

Clinical and radiologic Information

- Procedure: Biopsy only or possible resection?
- Age
- Anatomic Location of lesion
- Other clinical data:
  - Immunodeficiency
  - Prior treatments
- MRI characteristics

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Clinical and radiologic Information

- Age (and common intra-parenchymal neoplasms)
  - Adult
    - Older adult
      - Metastases, lymphoma
      - Infiltrating gliomas, particularly higher grade
    - Young adult
      - Infiltrating gliomas
      - Circumscribed glial or glioneuronal tumors
  - Pediatric
    - Infiltrating gliomas
    - Circumscribed glial or glioneuronal tumors
    - Embryonal tumors

Clinical and radiologic Information

- Location
  - Intra-axial vs Extra-axial (intramedullary vs extra-medullary)
    - Intra- (parenchymal): gliomas, etc (neuroepithelial tumors)
    - Extra-: meningioma, PNST (mesenchymal tumors)

Clinical and radiologic Information

- Location
  - Intra-axial vs Extra-axial (intramedullary vs extra-medullary)
    - Intra- (parenchymal): glioma (neuroepithelial tumors)
    - Extra-: meningioma, PNST tumors
  - Intracranial vs Spinal
Clinical and radiologic Information

Location
- Intra-axial vs Extra-axial (intramedullary vs extra-medullary)
  - Intra- (parenchymal): gliomas, etc (neuroepithelial tumors)
  - Extra-: meningioma, PNST (mesenchymal tumors)
- Intracranial vs Spinal
- Intraventricular

Radiology is essential for obtaining anatomic localization

Highly distinct differential diagnoses

Immunodeficiency
- Lymphoma, infections (eg Fungal, toxoplasma)

Prior treatments
- Radiation
- Corticosteroids

Basic radiologic (MRI) information

Anatomic location
Ill-defined vs discrete mass lesion
Contrast enhancement on MRI:
- Infiltrating gliomas: enhancement indicates high grade (III, IV)
- Circumscribed (low grade) primary tumors usually enhance
- Metastasis, lymphoma
- Inflammatory/infectious lesions
Examples of correlating radiology with intraoperative pathology

A Contrast Enhancing lesion with……
- Minimal pathologic findings
  - Eg gliosis, slight hypercellularity/chronic inflammation
  - Low grade infiltrating glioma
  - Necrosis only

=Not representative of the lesion!

Basic radiologic (MRI) information

- Rim enhancing mass lesions may be……
  - Glioblastoma, lymphoma, metastasis, cystic, abscess, infarct, demyelinating…

Tips on performing the intraoperative frozen section/smear: Tissue sampling

1. Sample for cytologic smear
2. Sample for frozen section
3. Reserve tissue for unfrozen permanents.
   - Keep in mind that subsequent specimens may not be as representative of a lesion

Cytologic smears

- ~ 1 cubic millimeter size of tissue is ideal
  - (1 x 1 x 1 mm)
Cytologic smears

- Immediate immersion in alcohol fixative upon smearing is critical, to avoid air-drying

Some frozen effects/artifacts

- Brain (CNS) tissue is particularly susceptible to freezing artifact – ice crystals
  - Water content may also reflect myxoid tissue or edema
  - Imbed tissue in OCT (completely surround tissue with OCT, rapid freeze using heat sink, avoiding direct contact with tissue.

- cautery

Frozen Section

Cellularity is often underestimated as result of artifact

Permanent Section

10X

Subtract artifactual spaces in assessing cellularity
What to do if tissue received is too small

- Confer with surgeon
  - Is an intraoperative diagnosis really necessary?
    - Consider permanent section only
  - Is more tissue coming?
    - (Don’t depend on it)
- Consider cytologic smear only, or cytologic smear before frozen section

Interpretation: Basic principles of neuropathologic diagnosis
(for parenchymal lesions)

- Is tissue normal or abnormal?
- Abnormal: Neoplastic or non-neoplastic
  - Neoplastic
    - Circumscribed (discrete) vs infiltrating tumor
    - Metastasis vs primary tumor vs lymphoma
      - (high grade lesions)
  - Non-neoplastic: Inflammatory/infectious

Infiltrative vs circumscribed neoplasms

<table>
<thead>
<tr>
<th>Infiltrating Neoplasms</th>
<th>Circumscribed neoplasms</th>
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<tbody>
<tr>
<td>Infiltrating Astrocytomas</td>
<td>Low grade gliomas, glioneuronal tumors:</td>
</tr>
<tr>
<td>• Diffuse Astrocytoma (grade II)</td>
<td>• Ependymoma</td>
</tr>
<tr>
<td>• Anaplastic astrocytoma (grade III)</td>
<td>• Pilocytic astrocytoma*</td>
</tr>
<tr>
<td>• Glioblastoma (grade IV)</td>
<td>• Ganglioglioma*</td>
</tr>
<tr>
<td>Low grade gliomas, glioneuronal tumors:</td>
<td>• Pleomorphic Xanthoastrocytoma</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>• And others</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>* Certain circumscribed tumors frequently have a degree of infiltrative growth, particularly at periphery</td>
</tr>
</tbody>
</table>
Select example of intraoperative neuropathology

- Common scenario:
  Infiltrating astrocytoma vs gliosis

Scenario 1: Infiltrating astrocytoma vs gliosis.

38 year old man with ill-defined non-enhancing lesion and adjacent edema in temporal-parietal lobe

Radiologic impression: Low grade Infiltrating glioma vs reactive/inflammatory

Infiltrating Astrocytoma

- Basic features of a neoplasm:
  - Hypercellularity + cytologic atypia
  - And an infiltrative pattern of neoplasia
    - Individual neoplastic astrocytes intermixed with normal tissue
    - Neuropil, neurons, swollen axons
Infiltrating Astrocytoma

- Basic features of a neoplasm:
  - Hypercellularity + cytologic atypia
    - Verify hypercellularity is *not due to inflammatory* cells (macrophages, lymphocytes)
Infiltrating Astrocytoma

- Basic features of a neoplasm:
  - Hypercellularity + cytologic atypia
    - Verify hypercellularity is not due to inflammatory cells (macrophages, lymphocytes)
    - Ensure that apparent hypercellular and homogeneous cell population is not native oligodendrocytes of white matter
    - Ensure that “atypical cells” are not neurons, or enlarged reactive astrocytes

- Reactive astrocytes may have enlarged nuclei, but show characteristic radiating fibrillary processes and/or gemistocytic cytoplasm
  - Part of heterogeneous cell population
Infiltrating Astrocytoma

- Basic features:
  - Fibrillary processes
  - Naked atypical astrocytic (elongate) nuclei
  - Clusters of atypical cells
    - Uneven cell distribution
  - Ice crystal artifact is common due to edema, myxoid
  - +/- gemistocytes

Smears of Infiltrating Astrocytomas

May show near homogeneous population of tumor cells

Frozen section: Hypercellularity?

Gliosis, white matter

Various examples of cellularity in infiltrating glioma
A conservative approach to intraoperative diagnosis

- Possible terminologies to be used:
  - “Scattered atypical astrocytes”
  - “Hypercellularity”
  - “suggest additional frozen section”
  - “Lesional tissue present”
  - “Infiltrating glioma, no high grade features”