Protocol for the Examination of Specimens from Patients with Tumors of the Brain/Spinal Cord

Protocol applies to all primary neoplasms of the brain/spinal cord/peripheral nerve and pituitary. Metastatic tumors are not included.

No AJCC/UICC TNM Staging System
Protocol web posting date: June 2008
Protocol effective date: February 2009

Procedures
• Biopsy/Resection

Authors
Joseph E. Parisi, MD
  Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota
Dylan V. Miller, MD
  Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota
Philip J. Boyer, MD, PhD
  Department of Pathology, University of Colorado Health Sciences Center, Denver, Colorado
Daniel J. Brat, MD, PhD
  Department of Pathology and Laboratory Medicine, Emory University Hospital, Atlanta, Georgia
Elizabeth J. Cochran, MD
  Department of Pathology and Neurologic Science, Rush University Medical Center, Chicago, Illinois
Mark L. Cohen, MD
  Department of Pathology, Case Western Reserve University, Cleveland, Ohio
Bette K. DeMasters, MD
  Department of Pathology, University of Colorado Health Sciences Center, Denver, Colorado
David Dolinak, MD
  Travis County Medical Examiner Office, Austin, Texas
Rodney D. McComb, MD
  Department of Pathology, University of Nebraska Medical Center, Omaha, Nebraska
Roger E. McLendon, MD
  Department of Pathology, Duke University Medical Center, Durham, North Carolina
Suzanne Z. Powell, MD
  Department of Pathology, The Methodist Hospital, Houston, Texas
Richard A. Prayson, MD
  Department of Pathology, Cleveland Clinic Foundation, Cleveland, Ohio
Harry V. Vinters, MD
  Department of Pathology and Laboratory Medicine, University of California Los Angeles, Los Angeles, California
Anthony T. Yachnis, MD
  Department of Pathology, Shands Hospital at University of Florida, Gainsville, Florida

For the Members of the Cancer Committee, College of American Pathologists

Previous contributors: Gary S. Pearl, MD, PhD; Saeid Movahedi-Lankarani, MD; Nancy C. Karpinski, MD; Kyung-Whan Min, MD; Steven C. Bauserman, MD; Lawrence A. Hansen, MD; Charles Kerber, MD
Central Nervous System • Brain/Spinal Cord

© 2008 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the Protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from CAP. Applications for such a license should be addressed to the SNOMED Terminology Solutions division of the CAP.

Any public dissemination of the original or modified Protocols is prohibited without a written license from the CAP.

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product of service to be construed as disapproval.
Important Note

This protocol should be applied to all primary neoplasms of the brain/spinal cord/peripheral nerve and pituitary, and it should be applied at initial biopsy/resection. Metastatic tumors are not included. There is no American Joint Committee on Cancer / International Union Against Cancer TNM classification system for primary nervous system neoplasms. The World Health Organization (WHO) grading system is recommended.
**Surgical Pathology Cancer Case Summary (Checklist)**

Protocol web posting date: June 2008  
Protocol effective date: February 2009

**BRAIN/SPINAL CORD: Biopsy/Resection**

Check 1 Response Unless Otherwise Indicated

*History of Previous Tumor/Familial Syndrome (Note A)*  
* ___ None known  
* ___ Known (specify, if known: _______________________)  
* ___ Not specified

**Specimen Type/Procedure (Note B)**  
___ Open biopsy  
___ Resection  
___ Stereotactic biopsy  
___ Other (specify): _____________________  
___ Not specified

**Specimen Handling (check all that apply) (Note C)**  
___ Squash/smear/touch preparation  
___ Frozen section  
___ Tissue for electron microscopy  
___ Frozen tissue  
___ Unfrozen for routine permanent paraffin sections  
___ Other (specify): _____________________  
___ Not specified

*Specimen Size (Note D)*  
* ___ Greatest dimension: ___ cm  
* ___ Additional dimensions: ___ x ___ cm (for fragmented tissue, an aggregate size may be given)  
* ___ Cannot be determined (see Comment)

**Laterality**  
___ Right  
___ Left  
___ Bilateral  
___ Not specified  
___ Not applicable

* Data elements with asterisks are not required for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
<table>
<thead>
<tr>
<th>Tumor Site (check all that apply) (Note E)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skull</strong></td>
</tr>
<tr>
<td>*Specify further (eg, frontal, parietal, temporal, occipital), if known: ___________________</td>
</tr>
<tr>
<td><strong>Dura</strong></td>
</tr>
<tr>
<td>*Specify further (eg, cerebral [convexity/lobe, falx, tentorium, sphenoid wing, skull base, other], spinal or other), if known: ___________________</td>
</tr>
<tr>
<td><strong>Leptomeninges</strong></td>
</tr>
<tr>
<td>*Specify further (eg, cerebral [convexity/lobe], spinal, or other), if known: ___________________</td>
</tr>
<tr>
<td><strong>Brain/cerebrum</strong></td>
</tr>
<tr>
<td>*Specify lobe(s) (eg, frontal, temporal, parietal, occipital), if known: ___________________</td>
</tr>
<tr>
<td><strong>Brain, other:</strong></td>
</tr>
<tr>
<td>____ Basal ganglia</td>
</tr>
<tr>
<td>____ Thalamus</td>
</tr>
<tr>
<td>____ Hypothalamus</td>
</tr>
<tr>
<td>____ Pineal</td>
</tr>
<tr>
<td>____ Cerebellum</td>
</tr>
<tr>
<td>____ Cerebellopontine angle</td>
</tr>
<tr>
<td>____ Suprasellar</td>
</tr>
<tr>
<td>____ Sella</td>
</tr>
<tr>
<td>____ Other (specify, if known: __________)</td>
</tr>
<tr>
<td><strong>Cranial nerve</strong></td>
</tr>
<tr>
<td>*Specify I-XII, if known: _______________</td>
</tr>
<tr>
<td><strong>Ventricle</strong></td>
</tr>
<tr>
<td>*Specify lateral, third, fourth, cerebral aqueduct, if known: ___________________</td>
</tr>
<tr>
<td><strong>Brainstem</strong></td>
</tr>
<tr>
<td>*Specify midbrain, pons, or medulla, if known: ___________________</td>
</tr>
<tr>
<td><strong>Spine (vertebral column)</strong></td>
</tr>
<tr>
<td>*Specify bony level (eg, C5, T2, L3), if known: ___________________</td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
</tr>
<tr>
<td>*Specify bony level (eg, C5, T2, L3), if known: ___________________</td>
</tr>
<tr>
<td>*Specify spinal location (eg, extradural, intradural-extramedullary, intramedullary, conus medullaris, filum terminale), if known: ___________________</td>
</tr>
<tr>
<td><strong>Spinal nerve root(s)</strong></td>
</tr>
<tr>
<td>*Specify bony level (eg, C5, T2, L3), if known: ___________________</td>
</tr>
<tr>
<td>*Specify location (eg, intradural, foramen), if known: ___________________</td>
</tr>
<tr>
<td><strong>Cranial or peripheral nerve</strong></td>
</tr>
<tr>
<td>*Specify site, if known: _______________</td>
</tr>
<tr>
<td><strong>Ganglion</strong></td>
</tr>
<tr>
<td>*Specify site, if known: _______________</td>
</tr>
<tr>
<td>**Other (specify):_______________________</td>
</tr>
<tr>
<td><strong>Not specified</strong></td>
</tr>
</tbody>
</table>

* Data elements *with asterisks* are not required for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
Histologic Type and Grade (applicable World Health Organization [WHO] classification and grade) (check all that apply) (Note F, Note G)

Astrocytic Tumors
___ Pilocytic astrocytoma (WHO grade I)
___ Pilomyxoid astrocytoma (WHO grade II)
___ Subependymal giant cell astrocytoma (WHO grade I)
___ Pleomorphic xanthoastrocytoma (WHO grade II)
___ Pleomorphic xanthoastrocytoma with anaplastic features (WHO grade not assigned)
___ Diffuse astrocytoma (WHO grade II)
   ___ Fibrillary astrocytoma (WHO grade II)
   ___ Protoplasmic astrocytoma (WHO grade II)
   ___ Gemistocytic astrocytoma (WHO grade II)
___ Anaplastic astrocytoma (WHO grade III)
___ Glioblastoma (WHO grade IV)
   ___ Giant cell glioblastoma (WHO grade IV)
   ___ Gliosarcoma (WHO grade IV)
___ Gliomatosis cerebri (usually WHO grade III; diagnosis requires clinical-pathological correlation)
___ Astrocytoma, not otherwise characterized (WHO grades I-IV)

Oligodendroglial Tumors
___ Oligodendroglioma (WHO grade II)
___ Anaplastic oligodendroglioma (WHO grade III)

Oligoastrocytic Tumors (mixed glioma)
___ Oligoastrocytoma (WHO grade II)
___ Anaplastic oligoastrocytoma (WHO grade III)

Ependymal Tumors
___ Subependymoma (WHO grade I)
___ Myxopapillary ependymoma (WHO grade I)
___ Ependymoma (WHO grade II)
   ___ Cellular ependymoma (WHO grade II)
   ___ Papillary ependymoma (WHO grade II)
   ___ Clear cell ependymoma (WHO grade II)
   ___ Tanyctic ependymoma (WHO grade II)
___ Anaplastic ependymoma (WHO grade III)

Choroid Plexus Tumors
___ Choroid plexus papilloma (WHO grade I)
___ Atypical choroid plexus papilloma (WHO grade II)
___ Choroid plexus carcinoma (WHO grade III)

* Data elements with asterisks are not required for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
Other Neuroepithelial Tumors
____ Astroblastoma (WHO grade not assigned)
____ Chordoid glioma of the third ventricle (WHO grade II)
____ Angiocentric glioma (WHO grade I)

Neuronal and Mixed Neuronal-Glial Tumors
____ Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos) (WHO grade I)
____ Desmoplastic infantile astrocytoma/ganglioglioma (WHO grade I)
____ Dysembryoplastic neuroepithelial tumor (WHO grade I)
____ Gangliocytoma (WHO grade I)
____ Ganglioglioma (WHO grade I)
____ Anaplastic ganglioglioma (WHO grade III)
____ Central neurocytoma (WHO grade II)
____ Extraventricular neurocytoma (WHO grade II)
____ Cerebellar liponeurocytoma (WHO grade II)
____ Papillary glioneuronal tumor (PGNT) (WHO grade I)
____ Rosette-forming glioneuronal tumor of the fourth ventricle (RGNT) (WHO grade I)
____ Paraganglioma of the spinal cord (WHO grade I)

Tumors of the Pineal Region
Pineal parenchymal tumors
____ Pineocytoma (WHO grade I)
____ Pineal parenchymal tumor of intermediate differentiation (WHO II-III)
____ Pineoblastoma (WHO grade IV)
____ Papillary tumor of the pineal region (WHO grade II-III)

Embryonal Tumors
____ Medulloblastoma, not otherwise characterized (WHO grade IV)
____ Desmoplastic/nodular medulloblastoma (WHO grade IV)
____ Medulloblastoma with extensive nodularity (WHO grade IV)
____ Anaplastic medulloblastoma (WHO grade IV)
____ Large cell medulloblastoma (WHO grade IV)
____ Central nervous system (CNS) primitive neuroectodermal tumor (PNET) (WHO grade IV)
____ Medulloepithelioma (WHO grade IV)
____ Neuroblastoma (WHO grade IV)
____ Ganglioneuroblastoma (WHO grade IV)
____ Ependymoblastoma (WHO grade IV)
____ Atypical teratoid/rhabdoid tumor (WHO grade IV)

* Data elements with asterisks are not required for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
Tumors of Cranial and Paraspinal Nerves
___ Schwannoma (WHO grade I)
     ___ Cellular (WHO grade I)
     ___ Plexiform (WHO grade I)
     ___ Melanotic (WHO grade I)
___ Neurofibroma (WHO grade I)
     ___ Plexiform (WHO grade I)
___ Perineurioma (WHO grade I)
     ___ Intraneural perineurioma (WHO grade I)
     ___ Soft tissue perineurioma (WHO grade I)
___ Ganglioneuroma (WHO grade I)
___ Malignant peripheral nerve sheath tumor (MPNST) (WHO grade II-IV)
     (Note H, Note I)
     ___ Epithelioid (WHO grade II-IV)
     ___ MPNST with divergent mesenchymal and/or epithelial differentiation
        (WHO grade II-IV)

Tumors of the Meninges/Meningothelial Cells
___ Meningioma (WHO grade I)
     ___ Meningothelial (WHO grade I)
     ___ Fibrous (fibroblastic) (WHO grade I)
     ___ Transitional (mixed) (WHO grade I)
     ___ Psammomatous (WHO grade I)
     ___ Angiomatous (WHO grade I)
     ___ Microcystic (WHO grade I)
     ___ Secretory (WHO grade I)
     ___ Lymphoplasmacyte-rich (lymphoplasmacytic) (WHO grade I)
     ___ Metaplastic (WHO grade I)
___ Atypical meningioma (WHO grade II)
___ Clear cell meningioma (WHO grade II)
___ Chordoid meningioma (WHO grade II)
___ Anaplastic meningioma (WHO grade III)
___ Papillary meningioma (WHO grade III)
___ Rhabdoid meningioma (WHO grade III)
___ Other (specify): ________________________

* Data elements with asterisks are not required for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
Mesenchymal (Nonmeningothelial) Tumors

- Lipoma
- Angiolipoma
- Hibernoma
- Liposarcoma (intracranial)
- Solitary fibrous tumor
- Fibrosarcoma
- Malignant fibrous histiocytoma
- Leiomyoma
- Leiomyosarcoma
- Rhabdomyoma
- Rhabdomyosarcoma
- Chordroma
- Chondrosarcoma
- Osteosarcoma
- Osteochondroma
- Hemangioma
- Epithelioid hemangioendothelioma
- Hemangiopericytoma
- Angiosarcoma
- Kaposi sarcoma
- Chordoma
- Mesenchymal, nonmeningothelial tumor, other (specify type, if possible): _______________________
- Sarcoma, primary CNS (specify type, if possible): _______________________

Primary Melanotic Tumors

- Diffuse melanocytosis
- Melanocytoma
- Malignant melanoma
- Meningeal melanomatosis

Tumors of Uncertain Histogenesis

- Hemangioblastoma (WHO grade I)

Lymphoma and Hematopoietic Tumors

- Malignant lymphoma (specify type, if possible): _______________________
- Plasmacytoma
- Granulocytic sarcoma
- Hematopoietic neoplasm, other (specify type, if possible): _______________________

* Data elements with *asterisks* are not required* for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
**Germ Cell Tumors**

- Germinoma
- Embryonal carcinoma
- Yolk sac tumor
- Choriocarcinoma
- Teratoma, mature
- Teratoma, immature
- Teratoma with malignant transformation
- Malignant mixed germ cell tumor (specify components, eg, germinoma, embryonal, yolk sac, choriocarcinoma, teratoma): __________________________

**Tumors of the Sellar Region**

- Craniopharyngioma, adamantinomatous (WHO grade I)
- Craniopharyngioma, papillary (WHO grade I)
- Granular cell tumor (WHO grade I)
- Pituicytoma (WHO grade I)
- Spindle cell oncocytoma (WHO grade I)
- Pituitary adenoma (specify nonfunctional or hormone expression, if known):
- Pituitary carcinoma
- Pituitary hyperplasia
- Other (specify): __________________________

**Other/Nonclassifiable**

- Other(s) (specify): _________________________
- Malignant neoplasm, type cannot be determined

**Histologic Grade (WHO histologic grade) (Note G)**

- Not applicable
- Cannot be determined
- WHO grade I
- WHO grade II
- WHO grade III
- WHO grade IV
- WHO grade not assigned
- Other (specify): __________________________

**Margins (for resections of malignant peripheral nerve sheath tumors only) (Note H)**

- Cannot be assessed
- Margins not involved by tumor
- Margins involved by tumor
  * Specify, if possible: _______________________

* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
*Ancillary Studies (check all that apply)
* ___ None performed
* ___ Immunohistochemistry (specify): _________________________
* ___ Electron microscopy
* ___ Molecular genetic studies (specify): _________________________ (Note J)
  * ___ 1p deletion identified
  * ___ 1p deletion not identified
  * ___ 19q deletion identified
  * ___ 19q deletion not identified
  * ___ Other (specify): _________________________
* ___ Other (specify): _________________________

*Additional Pathologic Findings
*Specify: _________________________

*Comment(s): _________________________
Explanatory Notes

A. Relevant History

Patient Age
Patient age may be critically important for predicting tumor behavior. For example, patient age is predictive of survival in many malignant CNS neoplasms. For diffusely infiltrating astrocytomas, age and histologic grade are the two strongest predictors of patient outcome, with patient age greater than 50 years and high-grade histologic features serving as negative indicators. 1-4

Duration of Symptoms
A long clinical history of CNS symptoms or seizures prior to the diagnosis of a CNS tumor is suggestive of origin from a slowly growing neoplasm. Alternatively, a sudden onset of clinical symptoms or a rapidly progressive neurological deficit may be indicative of a high-grade tumor, hemorrhage, infarct, active demyelinating disease, or edema associated with some other benign or low-grade lesion.

Previous Diagnoses or CNS Biopsies
Knowledge of the presence or absence of previous intracranial or extracranial disease (eg, immunosuppression, previous CNS or other primary neoplasm) is essential for specimen interpretation. If a previous tumor is included in the differential diagnosis, it is useful to have microscopic slides of the lesion available for review and comparison.

Preoperative Treatment
Knowledge of preoperative treatment, including radiation therapy, corticosteroid therapy, chemotherapy, and other therapy, is helpful for specimen interpretation. In particular, prior radiation therapy or radiosurgery may alter the interpretation of specimens in which there are increased cellular atypia, decreased proliferative activity, or large areas of radiation-induced change (eg, coagulative [nonpalisading] necrosis, vascular hyalinization, and gliosis).

Family History of Cancer or Primary CNS Tumors
Several genetic conditions/syndromes are associated with an increased predisposition to the development of certain brain neoplasms (eg, neurofibromatosis types 1 and 2, Turcot/Lynch, tuberous sclerosis, von Hippel-Lindau, Cowden, Li-Fraumeni, and Gorlin syndromes).

Relevant Radiographic Imaging Features
Knowledge of neuroimaging features is extremely helpful in specimen interpretation. A differential diagnosis may be generated based on patient age, tumor location, and neuroimaging features. Neuroimaging also can be helpful in providing correlation with or highlighting discrepancy with pathologic diagnosis (eg, contrast enhancement with hypocellularity). A close collaboration with the neuroradiologist and neurosurgeon is essential.

B. Specimen Type/Procedure
It is useful to know if the specimen was procured by open craniotomy or stereotactic biopsy. Since tumors may be heterogeneous, adequate sampling is an issue. The reliability of the prognostic information derived from such specimens may vary depending on how the specimen was obtained.
C. Specimen Handling, Triage, and Special Procedures
It may be necessary to divide biopsy/resection tissue into portions for the following procedures:
- Squash/smear/touch preparations
- Frozen sections
- Unfrozen routine permanent paraffin sections (essential to avoid artifacts)
- Electron microscopy (retain a small portion in glutaraldehyde, or "embed and hold" for electron microscopy, if necessary)
- Frozen tissue, for possible molecular diagnostic studies (freeze fresh tissue as soon as possible and store)
- Other (microbiology, flow cytometry, cytogenetics, molecular diagnostics)

Since cellular details are very important in interpreting CNS neoplasms, previously frozen tissue with its inherent artifacts is suboptimal, especially for subclassifying and grading gliomas. Recommendations for optimally freezing and cutting frozen sections from tissue from the brain and spinal cord have been published.\(^5\) It is imperative to retain tissue that has not been previously frozen for permanent sections. Avoid using sponges in cassettes because they produce angular defects that resemble vascular/luminal spaces in the final sections. Wrapping small biopsies in lens paper, or placement into agar or into tissue sacs prior to submitting in cassettes, is recommended. If biopsy frozen and permanent sections are nondiagnostic, tissue that was retained in glutaraldehyde may be submitted for additional paraffin sections.

If touch preparations are used, the presence of cells with delicate processes on smear/squash preparations is suggestive of a primary CNS neoplasm. The formation of processes and cytoplasmic fibrillarity may be seen in reactive astrocytosis. The identification of macrophages is important since a macrophage-rich lesion is more likely a subacute infarct or demyelination, rather than a neoplasm.

If an infectious etiology is suspected, the neurosurgeon should be alerted to submit a fresh sample to microbiology to be processed for bacterial, fungal, and/or viral cultures.

If a lymphoproliferative disorder is suspected and sufficient tissue is available, a portion of fresh tissue should be set aside for appropriate workup.

D. Specimen Size
For most CNS tumors, specimen size is of limited significance, with optimal preservation and processing of greater importance. In heterogeneous lesions, issues of tissue sampling may become important.

E. Primary Tumor Location and Size
Since the anatomic site of a neoplasm may correlate with tumor type and prognosis, it should be recorded, if known.

F. Histologic Type
Classification of tumors should be made according to the WHO classification of tumors of the nervous system\(^6,7\) whenever possible.
G. Histologic Grade
The WHO grading\(^6,7\) of some of the more common CNS tumors is shown in Table 1. There is no formal TNM-based classification and staging system for CNS tumors.

### Table 1. WHO Grading System for some of the More Common Tumors of the CNS

<table>
<thead>
<tr>
<th>Tumor Group</th>
<th>Tumor Type</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytic tumors</td>
<td>Diffuse astrocytoma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic astrocytoma</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glioblastoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Pilocytic astrocytoma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pilomyxoid astrocytoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Subependymal giant cell astrocytoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Pleomorphic xanthoastrocytoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>Oligodendroglioma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligodendroglioma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Oligoastrocytomas</td>
<td>Oligoastrocytoma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligoastrocytoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ependymal tumors</td>
<td>Ependymoma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic ependymoma</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subependymoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Myxopapillary ependymoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Choroid plexus tumors</td>
<td>Choroid plexus papilloma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atypical choroid plexus papilloma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Choroid plexus carcinoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Other neuroepithelial tumors</td>
<td>Angiocentric glioma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Choroid glioma of the third ventricle</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neuronal-gial tumors</td>
<td>Gangliocytoma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desmoplastic infantile ganglioglioma/astrocytoma (DIG)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Dysembryoplastic neuroepithelial tumor (DNET)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Ganglioglioma</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic ganglioglioma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Central neurocytoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Extraventricular neurocytoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Cerebellar liponeurocytoma</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Papillary glioneuronal tumor (PGNT)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Rosette-forming glioneuronal tumor of the fourth ventricle (RGNT)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Paraganglioma of the spinal cord</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Tumor Group | Tumor Type | Grade I | Grade II | Grade III | Grade IV
---|---|---|---|---|---
Pineal parenchymal tumors | Pineocytoma | X | | | |
Pineal parenchymal tumor of intermediate differentiation | | X | X | | |
Pineoblastoma | | | X | | |
Papillary tumor of the pineal region | | X | X | | |

Embryonal tumors | Medulloblastoma | | X | | |
CNS primitive neuroectodermal tumor | | | X | | |
Medulloepithelioma | | | X | | |
Neuroblastoma | | | X | | |
Ganglioneuroblastoma | | | X | | |
Ependymoblastoma | | | X | | |
Atypical teratoid/rhabdoid tumor | | | | X |

Cranial and peripheral nerve tumors | Schwannoma | | X | | |
Neurofibroma | | | X | | |
Perineurioma | | X | X | X |
Malignant peripheral nerve sheath tumors (MPNST) | | | X | X | X |

Meningeal tumors | Meningioma | | X | | |
Atypical meningioma | | | X | | |
Clear cell meningioma | | | X | | |
Chordoid meningioma | | | X | | |
Anaplastic meningioma | | | X | | |
Papillary meningioma | | | X | | |
Rhabdoid meningioma | | | X | | |

Mesenchymal tumors\(^8,9\) | (Named as soft tissue counterpart) | X | X | X | X |
Hemangiopericytoma | | X | X | | |

Tumors of uncertain histogenesis | Hemangioblastoma | | X | | |

After patient age, tumor histology and grade have been shown to be the strongest predictors of clinical course in selected CNS astrocytomas. Several grading systems for diffusely infiltrating astrocytomas are based on their ability to define distinct groups with significantly different survivals. The WHO uses a 3-tiered grading system (modified St. Anne-Mayo) for diffuse astrocytomas\(^6,7\) (Table 2).

**Table 2. WHO Grading System for Diffuse Infiltrating Astrocytomas**

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>WHO Designation</th>
<th>Histologic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Diffuse astrocytoma</td>
<td>1 criterion: usually nuclear atypia</td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td>2 criteria: usually nuclear atypia and mitoses</td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma</td>
<td>3 criteria: usually nuclear atypia, mitoses, and endothelial proliferation and/or necrosis</td>
</tr>
</tbody>
</table>
H. Margins
With the exception of malignant peripheral nerve sheath tumors, resection margins provide no prognostic information and generally are not required for most CNS neoplasms.

I. Mesenchymal Tumors
Mesenchymal tumors vary widely in grade, from benign tumors (WHO grade I) to highly malignant sarcomas (WHO grade III to IV). The classification and grading of these lesions is performed as for the corresponding tumor of soft tissue and bone, as detailed in the WHO monograph, *Tumours of Soft Tissue and Bone*, and the College of American Pathologists bone and soft tissue cancer protocol.

J. Molecular Genetic Studies
Recent studies have shown that combined 1p and 19q deletions in oligodendrogliomas are associated with enhanced chemoresponsiveness and improved survival. In addition, several other rapidly emerging molecular markers are providing useful diagnostic and prognostic information. For example, EGFR amplification may be useful in distinguishing high-grade astrocytoma from anaplastic oligodendroglioma; n-Myc amplification has prognostic significance in medulloblastomas; and INI1 studies are useful in the diagnosis of atypical teratoid/rhabdoid tumor.

References