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
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Procedures
• Biopsy/Resection

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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.

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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.

Tumor Site (check all that apply) (Note E)

___ Skull
*Specify further (eg, frontal, parietal, temporal, occipital), if known: _____

___ Dura
*Specify further (eg, cerebral [convexity/lobe, falx, tentorium, sphenoid wing, skull base, other], spinal or other), if known: _____

___ Leptomeninges
*Specify further (eg, cerebral [convexity/lobe], spinal, or other), if known: _____

___ Brain/cerebrum
*Specify lobe(s) (eg, frontal, temporal, parietal, occipital), if known: _____

___ Brain, other:
- ___ Basal ganglia
- ___ Thalamus
- ___ Hypothalamus
- ___ Pineal
- ___ Cerebellum
- ___ Cerebellopontine angle
- ___ Suprasellar
- ___ Sella
- ___Other (specify, if known: _____)

___ Cranial nerve
*Specify I-XII, if known: _____

___ Ventricle
*Specify lateral, third, fourth, cerebral aqueduct, if known: _____

___ Brainstem
*Specify midbrain, pons, or medulla, if known: _____

___ Spine (vertebral column)
*Specify bony level (eg, C5, T2, L3), if known: _____

___ Spinal Cord
*Specify bony level (eg, C5, T2, L3), if known: _____
*Specify spinal location (eg, extradural, intradural-extramedullary, intramedullary, conus medullaris, filum terminale), if known: _____

___ Spinal nerve root(s)
*Specify bony level (eg, C5, T2, L3), if known: _____
*Specify location (eg, intradural, foramen), if known: _____

___ Cranial or peripheral nerve
*Specify site, if known: _____

___ Ganglion
*Specify site, if known: _____

___ Other (specify): _____

___ Not specified

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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)
    ___ Tanycytic 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)

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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)

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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): _____

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Mesenchymal (Nonmeningothelial) Tumors **(Note I)**
___ Lipoma
___ Angiolipoma
___ Hibernoma
___ Liposarcoma (intracranial)
___ Solitary fibrous tumor
___ Fibrosarcoma
___ Malignant fibrous histiocytoma
___ Leiomyoma
___ Leiomyosarcoma
___ Rhabdomyoma
___ Rhabdomyosarcoma
___ Chondroma
___ 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): _____

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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: _____

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***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

Tumor Group	Tumor Type	Grade I	Grade II	Grade III	Grade IV
Astrocytic tumors	Diffuse astrocytoma		X		
	Anaplastic astrocytoma			X	
	Glioblastoma				X
	Pilocytic astrocytoma	X			
	Pilomyxoid astrocytoma		X		
	Subependymal giant cell astrocytoma	X			
	Pleomorphic xanthoastrocytoma		X		
Oligodendrogliomas	Oligodendroglioma		X		
	Anaplastic oligodendroglioma			X	
Oligoastrocytomas	Oligoastrocytoma		X		
	Anaplastic oligoastrocytoma			X	
Ependymal tumors	Ependymoma		X		
	Anaplastic ependymoma			X	
	Subependymoma	X			
	Myxopapillary ependymoma	X			
Choroid plexus tumors	Choroid plexus papilloma	X			
	Atypical choroid plexus papilloma		X		
	Choroid plexus carcinoma			X	
Other neuroepithelial tumors	Angiocentric glioma	X			
	Chordoid glioma of the third ventricle		X		
Neuronal-glial tumors	Gangliocytoma	X			
	Desmoplastic infantile ganglioglioma/ astrocytoma (DIG)	X			
	Dysembryoplastic neuroepithelial tumor (DNET)	X			
	Ganglioglioma	X			
	Anaplastic ganglioglioma			X	
	Central neurocytoma		X		
	Extraventricular neurocytoma		X		
	Cerebellar liponeurocytoma		X		
	Papillary glioneuronal tumor (PGNT)	X			
	Rosette-forming glioneuronal tumor of the fourth ventricle (RGNT)	X			
	Paraganglioma of the spinal cord	X			

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

WHO Grade	WHO Designation	Histologic Criteria
II	Diffuse astrocytoma	1 criterion: usually nuclear atypia
III	Anaplastic astrocytoma	2 criteria: usually nuclear atypia and mitoses
IV	Glioblastoma	3 criteria: usually nuclear atypia, mitoses, and endothelial proliferation and/or necrosis

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,*[8] and the College of American Pathologists bone and soft tissue cancer protocol.[9]

J. Molecular Genetic Studies

Recent studies have shown that combined 1p and 19q deletions in oligodendrogliomas are associated with enhanced chemoresponsiveness and improved survival.[10-12] 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.

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