

# **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.**

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## **No AJCC/UICC TNM Staging System**

Protocol web posting date: June 2008

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## **Procedures**

- Biopsy/Resection

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## **Summary of Changes to Checklist(s)**

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This is a significant update to the brain/spinal cord protocol.

Substantial changes have been made to the data elements of the Checklist and the Background Documentation.

### **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): \_\_\_\_\_

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## Explanatory Notes

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### 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.<sup>1-4</sup>

#### 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.<sup>5</sup> 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<sup>6,7</sup> whenever possible.

**G. Histologic Grade**

The WHO grading<sup>6,7</sup> 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-glia 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 <sup>8,9</sup>	<i>(Named as soft tissue counterpart)</i>	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<sup>6,7</sup> (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*,<sup>8</sup> and the College of American Pathologists bone and soft tissue cancer protocol.<sup>9</sup>

## J. Molecular Genetic Studies

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