COLLEGE of AMERICAN PATHOLOGISTS

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. The CAP bone protocol should be used for primary tumors of bone.

No AJCC/UICC TNM Staging System
Protocol web posting date: December 2014

Procedures
• Biopsy/Resection

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CAP Brain/Spinal Cord Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Brain/Spinal Cord 3.1.0.1

Summary of Changes
The following changes have been made since the January 2013 release.

Biopsy/Resection

Ancillary Studies
The following note was added:

Note: For biomarker reporting for gliomas and embryonal tumors, the CAP CNS Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

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

Protocol web posting date: December 2014

BRAIN/SPINAL CORD/NERVE: Biopsy/Resection

Select a single response unless otherwise indicated.

Tumor Site (select all that apply) (Note A)
___ Skull
+ Specify precise location, if known: _____
___ Dura
+ Specify precise location, if known: _____
___ Leptomeninges
+ Specify precise location, if known: _____
___ Brain
___ Cerebral lobes (specify precise location, if known: _____)
___ Basal ganglia
___ Thalamus
___ Hypothalamus
___ Pineal
___ Cerebellum
___ Cerebellopontine angle
___ Other (specify, if known: _____)
___ Sellar/suprasellar/pituitary
___ Cranial nerve
+ Specify I-XII, if known: _____
___ Ventricle
+ Specify precise location, if known: _____
___ Brain stem
+ Specify precise location, if known: _____
___ Spine (vertebral column)
+ Specify precise location, if known: _____
___ Spinal Cord
+ Specify precise location, if known: _____
___ Spinal nerve root(s)
+ Specify precise location, if known: _____
___ Peripheral nerve
+ Specify site, if known: _____
___ Ganglion
+ Specify site, if known: _____
___ Other (specify): _____
___ Not specified

Laterality (Note A)
___ Right
___ Left
___ Midline
___ Bilateral
___ Not specified
___ Not applicable

+ Data elements preceded by this symbol are not required. These elements may be clinically important but are not yet validated or regularly used in patient management.

Procedure (Note B)
___ Open biopsy
___ Resection
___ Stereotactic biopsy
___ Other (specify): _____
___ Not specified

Histologic Type (WHO classification of tumors of the central nervous system) (Note C)
Specify: _____
___ Cannot be determined

Histologic Grade (WHO histologic grade) (Note D)
Specify: _____
___ Not Applicable
___ Cannot be determined

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

+ Specimen Handling (select all that apply) (Note F)
+ ___ Squash/smear/touch preparation
+ ___ Frozen section
+ ___ Tissue for electron microscopy
+ ___ Frozen tissue
+ ___ Unfrozen, formalin-fixed for permanent paraffin sections
+ ___ Other (specify): _____
+ ___ Not specified

+ Margins (malignant peripheral nerve sheath tumor only) (Note G)
+ ___ Not Applicable
+ ___ Cannot be assessed
+ ___ Margins not involved by tumor
    + Distance of tumor from closest margin: ___ cm
    + Specify, if possible: _____
+ ___ Margins involved by tumor
    + Specify, if possible: _____

+ Ancillary Studies, if applicable (select all that apply) (Note H)

Note: For biomarker reporting for gliomas and embryonal tumors, the CAP CNS Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

+ Designate block for future studies: _____

+ Special Stains
+ Specify: _____
+ ___ None performed

+ Immunohistochemistry
+ Specify: _____
+ ___ None performed

+ Electron Microscopy
+ Specify: _____
+ ___ None performed

+ Molecular Genetic Studies
+ Specify: _____
+ ___ None performed

+ ___ Other (specify): _____

+ Additional Pathologic Findings
+ Specify: _____

+ History of Previous Tumor/Familial Syndrome (Note I)
+ ___ None known
+ ___ Known (specify: _____)
+ ___ Not specified

+ Neuroimaging Findings (Note J)
+ Specify: _____
+ ___Not available

+ Focality (Note A, J)
+ ___ Multifocal
+ ___ Unifocal
+ ___ Cannot be determined

+ Preresection Treatment (select all that apply) (Note K)
+ ___ No therapy
+ ___ Chemotherapy
+ ___ Radiation therapy
+ ___ Corticosteroids
+ ___ Embolization
+ ___ Therapy performed, type not specified
+ ___ Unknown

+ Treatment Effect (Note K)
+ ___ Not identified
+ ___ Present
    + Specify percent of tumor that is necrotic: ____%
+ ___ Cannot be determined

+ Comment(s)

Explanatory Notes

A. Primary Tumor Site, Laterality, and Focality
Since the anatomic site of a neoplasm may correlate with tumor type and prognosis, it should be recorded, if known.

- For skull location, specify bone involved, such as frontal, parietal, temporal, occipital, etc, if known. The College of American Pathologists (CAP) cancer protocol for bone[1] should be used for primary tumors of bone (Note L).
- For dural location, indicate cerebral convexity/lobe, falx, tentorium, posterior fossa, sphenoid wing, skull base, spinal, or other, if known.
- For leptomeningeal location, indicate cerebral convexity/lobe, posterior fossa, spinal, or other, if known.
- For cerebral lobe location, indicate frontal, temporal, parietal, or occipital lobe, if known. For a deep gray matter location, indicate basal ganglia, thalamus, or hypothalamus.
- For an intraventricular location, indicate lateral, third, fourth, or aqueduct, if known.
- For a brain stem location, indicate midbrain, pons, or medulla, if known.
- For spine (verterbral bone), spinal cord, spinal root or spinal ganglion, indicate level (eg, C5, T2, L3), if known. The CAP cancer protocol for bone[1] should be used for primary tumors of bone.

The laterality of a neoplasm should be indicated as involving the left or right side of the central nervous system (CNS) structure. In some instances, such as tumors arising in the pineal, pituitary, third ventricular, and other locations, the tumor will be situated in the midline. A tumor would be considered bilateral if it involved both sides of the brain, such as glioblastoma extending through the corpus callosum to involve the left and right hemispheres. The focality of a lesion should be indicated, if possible. Multifocality implies that multiple, noncontiguous lesions are noted on neuroimaging, such as might be seen in primary CNS lymphoma. A solitary lesion would be considered unifocal.

B. 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. Histologic Type
Classification should be made according to the WHO classification of tumors of the nervous system[2,3] whenever possible. The list below contains WHO 2007 diagnostic entities:

<u>Astrocytic Tumors</u>
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)

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)

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)

Malignant perineurioma (WHO grade III)
Ganglioneuroma (WHO grade I)
Malignant peripheral nerve sheath tumor (MPNST) (WHO grade II-IV)
- 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)

Mesenchymal (Nonmeningothelial) Tumors
Note: The CAP cancer protocols for bone[1] and soft tissue[4] should be used for those tumors that are primary to bone and soft tissue, respectively (Note L).
Lipoma
Angiolipoma
Hibernoma
Liposarcoma (intracranial)
Solitary fibrous tumor
Fibrosarcoma
Malignant fibrous histiocytoma
Leiomyoma
Leiomyosarcoma
Rhabdomyoma
Rhabdomyosarcoma
Chondroma
Chondrosarcoma
Osteoma
Osteosarcoma
Osteochondroma
Hemangioma
Epithelioid hemangioendothelioma
Hemangiopericytoma
Anaplastic 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)

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 (WHO grade I)
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/Nonclassifiable
Other(s) (specify)
Malignant neoplasm, type cannot be determined
Pediatric low grade glioma (pLGG) not otherwise specified (NOS) (Grade I/II)

D. Histologic Grade
Below is a list of possible WHO grades for central nervous system tumors. The WHO grading[2,3] 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.

WHO Grades for Tumors of the Nervous System
WHO grade I
WHO grade II
WHO grade III
WHO grade IV
WHO grade not assigned

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			

Tumor histology and grade are strong predictors of clinical behavior for astrocytomas and meningiomas. Tables 2 and 3 list the grading criteria for these common CNS tumor types.[2,3]

Table 2. WHO Grading System for Diffuse Infiltrating Astrocytomas

WHO Grade	WHO Designation	Histologic Criteria
II	Diffuse astrocytoma	Nuclear atypia
III	Anaplastic astrocytoma	Nuclear atypia and mitotic figures
IV	Glioblastoma	Nuclear atypia, mitotic figures, and endothelial proliferation and/or necrosis

Table 3. WHO Grading of Meningiomas

WHO grade I Benign meningioma
WHO grade II Atypical meningioma Mitotic figures ≥4/10 high-power fields (HPF) *or* At least 3 of 5 parameters: Sheeting architecture (loss of whorling and/or fascicles) Small cell formation Macronucleoli Hypercellularity Spontaneous necrosis *or* Brain invasion *or* Clear cell meningioma *or* Chordoid meningioma
WHO grade III Anaplastic (malignant) meningioma Mitotic figures ≥ 20/10 HPF *or* Frank anaplasia (sarcoma, carcinoma, or melanoma-like histology) *or* Papillary meningioma *or* Rhabdoid meningioma

E. Specimen Size

For most CNS tumors, specimen size is not used for staging or grading. However, in heterogeneous lesions, tissue sampling may become important, and the size of the biopsy relative to the overall size of the lesion provides useful information concerning whether the sample is representative of the overall lesion. The total specimen size may not correspond to the tumor size within the specimen, and this discrepancy should be noted.

F. 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 of freezing tissue)
- 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 cytologic details are essential for interpreting CNS neoplasms, previously frozen tissue with its inherent artifacts is suboptimal, especially for subclassifying and grading gliomas. Recommendations for optimal freezing and frozen sections from CNS tissue 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. It is more appropriate to wrap small biopsies in lens paper or into tissue sacs prior to submitting in cassettes. If frozen and permanent sections are nondiagnostic, tissue that was retained in glutaraldehyde may be submitted for additional paraffin sections.

In touch, smear, and squash preparations, the presence of cells with long delicate processes is suggestive of a primary CNS cell type. 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.

G. 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.

H. Ancillary Studies
Immunohistochemical and molecular genetic studies are often performed to assist with diagnosis, prognosis, or to predict therapeutic response. For information regarding biomarker testing for gliomas and embryonal tumors, the CAP CNS Biomarker Template should be referenced.[6]

I. Relevant History
Patient Age
Patient age may be important for predicting tumor behavior and is predictive of survival in many malignant CNS neoplasms. For diffusely infiltrating astrocytomas, age and histologic grade are the two strong predictors of patient outcome, with age greater than 50 years and high-grade histology serving as negative indicators.[7-10]

Duration of Symptoms
A long clinical history of neurological symptoms prior to the diagnosis of a CNS tumor is suggestive of a slowly growing neoplasm. Alternatively, a sudden onset of clinical symptoms or a rapidly progressive neurological deficit may indicate a high-grade tumor, hemorrhage, infarct, or active demyelinating disease.

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.

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

J. Neuroimaging Findings
Knowledge of neuroimaging features is extremely helpful in specimen interpretation.[11] 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.

K. Preoperative Treatment and Treatment Effect
Knowledge of preoperative treatment, including radiation therapy, chemotherapy, corticosteroid therapy, embolization, and other therapy, is helpful for specimen interpretation.[7-9] 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). The addition of chemotherapy to radiation, either concurrently or in the adjuvant setting, may exacerbate the side effects of radiation. For patients with malignant gliomas, the presence and degree of radiation necrosis appear to be of prognostic significance. Tumors that show evidence of radiation necrosis are associated with a longer survival, and the degree of necrosis appears to be prognostically significant.[12] Corticosteroid treatment can alter the pathologic features of some CNS diseases. In particular, the treatment of primary CNS lymphoma with corticosteroids can be associated with widespread tumor necrosis or infiltration by macrophages, which may limit or misguide interpretation. Embolization of certain tumor types, especially meningiomas, may introduce histologic changes in the neoplasm.

L. 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 are performed corresponding to the WHO monograph, *Tumours of Soft Tissue and Bone*.[13] The CAP cancer protocols for bone[1] and soft tissue[4] should be used for those tumors that are primary to bone and soft tissue, respectively.

References
1. Rubin BP, Antonescu CR, Cooper K, et al. Protocol for the examination of specimens from patients with tumors of bone. In: Washington K, ed. *Reporting on Cancer Specimens: Case Summaries and Background Documentation.* Northfield, IL: College of American Pathologists; 2013.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. *WHO Classification of Tumours of the Central Nervous System.* Lyon, France: IARC Press; 2007.
3. Brat DJ, Parisi JE, Kleinschmidt-DeMasters BK, et al. Surgical neuropathology update: a review of changes introduced by the World Health Organization (WHO) Classification of Tumors of the Central Nervous System, 4th Edition. *Arch Pathol Lab Med.* 2008;132:993-1007.
4. Rubin BP, Cooper K, Fletcher CDM, et al. Protocol for the examination of specimens from patients with tumors of soft tissue. In: Washington K, ed. *Reporting on Cancer Specimens: Case Summaries and Background Documentation.* Northfield, IL: College of American Pathologists; 2013.

5. Burger PC, Nelson JS. Stereotactic brain biopsies: specimen preparation and evaluation. *Arch Pathol Lab Med.* 1997;121:477-480.
6. Brat DJ, Cagle P, Dillon D, et al. Template for reporting results of biomarker testing of specimens from patients with tumors of the central nervous system. cap.org/cancerprotocols. In press.
7. Burger PC, Scheithauer BW, Vogel FS. *Surgical Pathology of the Nervous System and Its Coverings.* 4th ed. New York: Churchill Livingstone; 2002.
8. Perry A, Brat DJ. Practical Surgical Pathology: A Diagnostic Approach. Philadelphia: Elsevier; 2010.
9. McLendon RE, Rosenblum MK, Bigner DD, eds. *Russell and Rubinstein's Pathology of Tumors of the Nervous System*. 7th ed. New York: Hodder Arnold; 2006.
10. Burger PC, Scheithauer BW. *Atlas of Tumor Pathology, Third Series. Tumors of the Central Nervous System.* Washington, DC: Armed Forces Institute of Pathology; 2003.
11. Vincentelli C, Hwang SN, Holder CA, Brat DJ. The use of neuroimaging to guide the histologic diagnosis of central nervous system lesions. *Adv Anat Pathol.* 2012;19:97-107.
12. Forsyth PA, Kelly PJ, Cascino TL, et al. Radiation necrosis or glioma recurrence: is computer-assisted stereotactic biopsy useful? *J Neurosurg.* 1995;82:436-444.
13. Fletcher CDM, Unni KK, Mertens F, eds. *World Health Organization Classification of Tumours. Pathology and Genetics. Tumours of Soft Tissue and Bone.* Lyon, France: IARC Press; 2002:12-18.