**Protocol for the Examination of Specimens from Patients with Tumors of the Central Nervous System\***

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| --- | --- |
| **Version:** CNS 4.0.0.0 | **Protocol Posting Date:** August 2018 |
| **This protocol is NOT required for accreditation purposes** |

\*This protocol applies to primary neoplasms of the brain and spinal cord

**The following tumor types should NOT be reported using this protocol:**

|  |
| --- |
| **Tumor type** |
| Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols) |
| Primary bone tumors (consider the Primary Bone Tumor protocol) |
| Metastatic tumors |
| Malignant peripheral nerve sheath tumor (consider the Soft Tissue Tumor protocol) |
| Mesenchymal tumors (consider the Soft Tissue Tumor protocol) |

**Authors**

Eyas M Hattab, MD, MBA\*; Sarah E Bach, MD; Arieli Karime Cuevas-Ocampo, MD; Brent T Harris, MD, PhD; William F Hickey, MD; Karra A Jones, MD, PhD; Lindsey O Lowder, DO; Muchou Joe Ma, MD; Maria Martinez-Lage, MD; Roger E McLendon, MD; Brian Edward Moore, MD; Arie Perry, MD; Amyn M Rojiani, MD, PhD; Matthew J. Schniederjan MD; Andrea Wiens, DO, MS

With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

*\* Denotes primary author. All other contributing authors are listed alphabetically.*

**Accreditation Requirements**

The use of this protocol is recommended for clinical care purposes, but is not required for accreditation purposes.

**Important Note**

There is no American Joint Committee on Cancer (AJCC) pTNM classification system for primary central nervous system (CNS) neoplasms. The World Health Organization (WHO) grading system is recommended.

**CAP CNS Protocol Summary of Changes**

Version 4.0.0.0

**The following data elements were modified:**

Histological Classification World Health Organization (WHO) 2016

Histologic Grade World Health Organization (WHO) 2016

Ancillary Studies

**The following data elements were added:**

Integrated Diagnosis

Biomarker Information

**Surgical Pathology Cancer Case Summary**

Protocol posting date: August 2018

**CNS: Integrated Diagnosis**

***Note: This case summary is recommended for reporting the integrated diagnosis for CNS neoplasms, but is not required for accreditation purposes. If CNS Integrated Diagnosis section is not applicable, proceed to histological assessment summary.***

***Select a single response unless otherwise indicated.***

**Integrated Diagnosis (WHO 2016) (Note A)**

\_\_\_ (Specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Pending

\_\_\_ Not applicable (proceed to Histological Assessment Case Summary)

**Histologic Type (WHO 2016) (Note B)**

\_\_\_ (Specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined

**Histologic Grade (WHO 2016) (Note C)**

\_\_\_ WHO grade I

\_\_\_ WHO grade II

\_\_\_ WHO grade III

\_\_\_ WHO grade IV

\_\_\_ Other (Specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not applicable

\_\_\_ Cannot be assessed

**Biomarker Studies (Note D)**

*Note: For biomarker reporting the CAP CNS Biomarker Template should be used.*

\_\_\_ Testing performed (complete relevant findings in CNS Biomarker Template): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not performed

\_\_\_ Not applicable

Testing Performed on Block Number(s): \_\_\_\_\_\_\_\_\_\_\_\_\_

**Comment(s)**

**Surgical Pathology Cancer Case Summary**

Protocol posting date: August 2018

**CNS: Histological Assessment**

***Note: This case summary is recommended for reporting the histologic assessment of CNS neoplasms, but is not required for accreditation purposes.***

***Select a single response unless otherwise indicated.***

**History of Prior Therapy for this Neoplasm (Note E)**

\_\_\_ Not administered

\_\_\_ Not known

\_\_\_ Administered (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**History of Previous Tumor and/or Familial Syndrome (not the current neoplasm) (Note E)**

\_\_\_ Not known

\_\_\_ Known (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**Neuroimaging Findings (Note F)**

\_\_\_ (specify):\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not available

**Procedure (Note G)**

\_\_\_ Open biopsy

\_\_\_ Resection

\_\_\_ Stereotactic biopsy

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**Specimen Size, gross description (Note H)#**

Greatest dimension (centimeters): \_\_\_ cm

\_\_\_ Additional dimensions (centimeters): \_\_\_ x \_\_\_ cm

\_\_\_ Cannot be determined (explain)

*# For fragmented tissue, an aggregate size may be given*

**Tumor Site (select all that apply) (Note I)**

\_\_\_ 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): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Deep grey matter (specify precise location, if known): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Ventricle (specify precise location, if known): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cerebellum (specify precise location, if known): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Brain stem (specify precise location, if known): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify, if known): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cerebellopontine angle

\_\_\_ Sellar/Suprasellar/Pituitary

\_\_\_ Pineal

\_\_\_ Cranial nerve (specify I–XII, 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): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**Tumor Laterality (Note I)**

\_\_\_ Right

\_\_\_ Left

\_\_\_ Midline

\_\_\_ Bilateral

\_\_\_ Not specified

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Tumor Focality (Note I)**

\_\_\_ Unifocal

\_\_\_ Multifocal (specify number of lesions): \_\_\_\_\_\_

\_\_\_ Cannot be determined

**Histologic Type (WHO 2016) (Note B)**

\_\_\_ (Specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined

**Histologic Grade (WHO 2016) (Note C)**

\_\_\_ WHO grade I

\_\_\_ WHO grade II

\_\_\_ WHO grade III

\_\_\_ WHO grade IV

\_\_\_ Other (Specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not applicable

\_\_\_ Cannot be assessed

**Treatment Effect (Histological Evidence of Prior Therapy) (Note J)**

\_\_\_ Not identified

\_\_\_ Present (specify type of response): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined

**Additional Pathologic Findings**

Specify: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Biomarker Studies (Note D)**

*Note: For biomarker reporting the CAP CNS Biomarker Template should be used.*

\_\_\_ Testing performed (complete relevant findings in CNS Biomarker Template)

\_\_\_ Pending#

\_\_\_ Not performed

\_\_\_ Not applicable

*# Pending biomarker studies may be listed in the Comments section.*

Designate block for future studies: \_\_\_\_\_

**Comment(s)**

**CNS Biomarker Reporting Template**

Protocol posting date: August 2018

**CNS Biomarker Reporting Template**

***Note: This case summary is recommended for reporting biomarkers for CNS neoplasms at the completion of testing, but is not required for accreditation purposes.***

***Select a single response unless otherwise indicated.***

**Testing Performed on Block Number(s): \_\_\_\_\_\_\_\_\_\_\_\_\_**

**Biomarker Studies (Note D)**

*Note: Pending biomarker studies may be listed in the Comments section of this report.*

***ATRX***

##### *ATRX* mutation

\_\_\_ Absent

\_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### ATRXexpression (immunohistochemistry)

\_\_\_ Intact nuclear expression

\_\_\_ Loss of nuclear expression

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***BRAF* alterations**

##### *BRAF* mutation

\_\_\_ Absent

*\_\_\_ BRAF* V600E *(c.1799T>A)* mutation present

\_\_\_ Other *BRAF* mutation present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *KIAA:BRAF* rearrangement/duplication

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### BRAF V600Eexpression (immunohistochemistry)

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Beta-Catenin expression / *CTNNB1* mutation**

##### Beta-catenin expression (immunohistochemistry)

\_\_\_ Absence of nuclear expression

\_\_\_ Positive nuclear expression

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *CTNNB1* mutation

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *C19MC* alteration

\_\_\_ Absent

\_\_\_ Absent with low level gain

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Chromosomal arm1p/19q codeletion

\_\_\_ No deletion

\_\_\_ 1p/19q codeletion

\_\_\_ 1p only deleted

\_\_\_ 19q only deleted

\_\_\_ Polysomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Monosomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Relative deletion (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Chromosomal 7 gain#

#typically identified by *EGFR* locus, often combined with chromosome 10 loss

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Chromosome 10q23 (*PTEN* locus) deletion and *PTEN* mutation**

##### Chromosome 10q23 (*PTEN* locus) deletion

\_\_\_ No deletion

\_\_\_ Deletion identified

\_\_\_ Polysomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Monosomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *PTEN* mutation

\_\_\_ Absent

\_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***EGFR* amplification and *EGFRvIII* mutation**

##### *EGFR* amplification

\_\_\_ Absent

\_\_\_ Absent with low level gain

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *EGFRvIII* mutation

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *FGFR1* mutation

\_\_\_ Absent

\_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### GAB1 expression (immunohistochemistry)

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Histone H3 mutation and K27me3**

##### H3 gene family mutation

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Histone H3 K27M expression (immunohistochemistry)

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### H3 K27me3 expression (immunohistochemistry)

\_\_\_ Intact nuclear expression

\_\_\_ Loss of nuclear expression

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***IDH1/IDH2* mutation**

##### *IDH1/IDH2* mutation

\_\_\_ Absent

\_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *IDH1 R132H* expression (immunohistochemistry)

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Isochromosome 17q (i17q)

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Ki-67 expression (immunohistochemistry)

Hotspot percentage of positive tumor cell nuclei: \_\_\_\_ %

##### L1CAM expression (immunohistochemistry)

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### LIN28A expression (immunohistochemistry)

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *MGMT* promoter methylation

\_\_\_ Absent

\_\_\_ Present

If laboratory reports by level:

\_\_\_ Low level

 \_\_\_ High level

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Monosomy 6

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***MYC* gene family amplification**

##### *MYC* amplification

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *MYCN* amplification

\_\_\_ Absent

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***NAB2-STAT6* fusion**

##### *NAB2-STAT6* fusion

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### STAT6 expression (immunohistochemistry)

\_\_\_ Absence of nuclear expression

\_\_\_ Positive nuclear expression

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Pituitary hormones and transcription factors immunohistochemistry**

##### Tumor Cell(s) Reactivity (select all that apply)

\_\_\_ Alpha subunit

\_\_\_ Adrenocorticotrophic hormone (ACTH)

\_\_\_ Follicular stimulating hormone (beta FSH)

\_\_\_ Human growth hormone

\_\_\_ Luteinizing hormone (beta LH)

\_\_\_ Prolactin

\_\_\_ PIT1

\_\_\_ SF1

\_\_\_ Thyroid stimulating hormone (beta TSH)

\_\_\_ TPIT

\_\_\_ Other (specify)

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *RELA* fusion

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***SMARCA4/BRG1* alteration**

##### *SMARCA4/BRG1* mutation

\_\_\_ Absent

\_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### BRG1 expression (immunohistochemistry)

\_\_\_ Intact nuclear expression

\_\_\_ Loss of nuclear expression

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***SMARCB1/INI1/HSNF5* alteration**

##### *SMARCB1/INI1/HSNF5* mutation

\_\_\_ Absent

\_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### INI1 (BAF47) expression (immunohistochemistry)

\_\_\_ Intact nuclear expression

\_\_\_ Loss of nuclear expression

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### *TERT* promoter mutation

\_\_\_ Absent

\_\_\_ Hotspot mutation (C228T or C250T)

\_\_\_ Other *TERT* mutation (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***TP53* mutation**

##### *TP53* mutation

\_\_\_ Absent

\_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### p53 expression (immunohistochemistry)

\_\_\_ Negative or rare

\_\_\_ Intermediate

\_\_\_ Positive (diffuse and strong nuclear positivity)

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***YAP1***

##### *YAP1* fusion

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### YAP1 expression (immunohistochemistry)

\_\_\_ Negative

\_\_\_ Positive

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Other biomarker(s)**

##### Point Mutations (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Copy Number Alterations (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Insertions (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

##### Deletions (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Comment(s)**

**Explanatory Notes**

**A. Integrated Diagnosis**

Historically, the diagnosis and classification of CNS tumors has been based exclusively on the histologic appearance of the tumor. In recent decades, however, our knowledge of the molecular basis of many of these tumors has increased significantly. In the updated 2016 WHO Classification of Tumours of the Central Nervous System1, molecular information is now integrated into some of the tumor diagnostic entities. In such cases, including the diffuse gliomas and embryonal tumors, the final diagnosis should reflect the integration of both histologic and molecular information.

When applicable, it is suggested that all histologic and molecular information be presented in a “layered” report format as follows2:

Layer 1: Integrated diagnosis (incorporating all tissue-based information)

Layer 2: Histological classification

Layer 3: Histologic (WHO) grade

Layer 4: Biomarker studies

At centers where molecular testing is not available, an NOS (not otherwise specified) designation is available for some tumor entities. The NOS designation implies that insufficient information is available to provide a more specific integrated diagnosis, and may occasionally be used for tumors that do not precisely fit into one of the defined tumor categories.

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. *World Health Organization Classification of Tumours of the Central Nervous System*. Lyon, France: IARC Press; 2016.
2. Louis DN, Perry A, Burger P, et al. International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading. *Brain Pathol.* 2014;24:429-435.

**B. Histologic Type**

Classification should be made according to the WHO classification of tumors of the nervous system and the WHO classification of tumors of the endocrine organswhenever possible.1,2 The list below contains WHO 2016 diagnostic entities for which the Central Nervous System (CNS) Cancer Protocol is recommended:

Diffuse astrocytic and oligodendroglial tumors

Diffuse astrocytoma, NOS

Diffuse astrocytoma, IDH-mutant

Diffuse astrocytoma, IDH-wildtype

Gemistocytic astrocytoma, IDH-mutant

Anaplastic astrocytoma, NOS

Anaplastic astrocytoma, IDH-mutant

Anaplastic astrocytoma, IDH-wildtype

Glioblastoma, NOS

Glioblastoma, IDH-mutant

Glioblastoma, IDH-wildtype

Epithelioid glioblastoma

Giant cell glioblastoma

Gliosarcoma

Diffuse midline glioma, H3 K27M-mutant

Oligodendroglioma, NOS

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Anaplastic oligodendroglioma, NOS

Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Oligoastrocytoma, NOS

Anaplastic oligoastrocytoma, NOS

Other astrocytic tumors

Pilocytic astrocytoma

Pilomyxoid astrocytoma

Subependymal giant cell astrocytoma

Pleomorphic xanthoastrocytoma

Anaplastic pleomorphic xanthoastrocytoma

Ependymal tumors

Subependymoma

Myxopapillary ependymoma

Ependymoma

Clear cell ependymoma

Papillary ependymoma

Tanycytic ependymoma

Ependymoma, RELA fusion-positive

Anaplastic ependymoma

Other gliomas

Chordoid glioma of the third ventricle

Angiocentric glioma

Astroblastoma

Choroid plexus tumors

Choroid plexus papilloma

Atypical choroid plexus papilloma

Choroid plexus carcinoma

Neuronal and mixed neuronal–glial tumors

Dysembryoplastic neuroepithelial tumor

Gangliocytoma

Ganglioglioma

Anaplastic ganglioglioma

Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)

Desmoplastic infantile astrocytoma and ganglioglioma

Papillary glioneuronal tumor

Rosette-forming glioneuronal tumor

Diffuse leptomeningeal glioneuronal tumor

Central neurocytoma

Extraventricular neurocytoma

Cerebellar liponeurocytoma

Paraganglioma

Tumors of the pineal region

Pineocytoma

Pineal parenchymal tumor of intermediate differentiation

Pineoblastoma

Papillary tumor of the pineal region

Embryonal tumors

Medulloblastomas, histologically defined

Medulloblastoma, NOS

Medulloblastoma, classic

Medulloblastoma, desmoplastic/nodular

Medulloblastoma with extensive nodularity

Medulloblastoma, large cell/anaplastic

Medulloblastomas, genetically defined

Medulloblastoma, NOS

Medulloblastoma, WNT-activated

Medulloblastoma, SHH activated

Medulloblastoma, SHH activated and TP53-mutant

Medulloblastoma, SHH activated and TP53-wildtype

Medulloblastoma, non-WNT/non-SHH

Medulloblastoma, non-WNT/non-SHH: Medulloblastoma, group 3

Medulloblastoma, non-WNT/non-SHH: Medulloblastoma, group 4

Atypical teratoid/rhabdoid tumor

Embryonal tumor with multilayered rosettes, NOS

Embryonal tumor with multilayered rosettes, C19MC-altered

Medulloepithelioma

CNS neuroblastoma

CNS ganglioneuroblastoma

CNS embryonal tumor, NOS

CNS embryonal tumor with rhabdoid features

Meningiomas

Meningioma

Angiomatous meningioma

Fibrous meningioma

Lymphoplasmacyte-rich meningioma

Meningothelial meningioma

Metaplastic meningioma

Microcystic meningioma

Psammomatous meningioma

Secretory meningioma

Transitional meningioma

Chordoid meningioma

Clear cell meningioma

Atypical meningioma

Papillary meningioma

Rhabdoid meningioma

Anaplastic (malignant) meningioma

Mesenchymal, non-meningothelial tumors

Solitary fibrous tumor/hemangiopericytoma, NOS

Solitary fibrous tumor/hemangiopericytoma, grade 1

Solitary fibrous tumor/hemangiopericytoma, grade 2

Solitary fibrous tumor/hemangiopericytoma, grade 3

Hemangioblastoma

Melanocytic tumors

Meningeal melanocytosis

Meningeal melanocytoma

Meningeal melanoma

Meningeal melanomatosis

Germ cell tumors

Germinoma

Embryonal carcinoma

Yolk sac tumor

Choriocarcinoma

Teratoma

Mature teratoma

Immature teratoma

Teratoma with malignant transformation

Mixed germ cell tumor

Tumors of the sellar region

Craniopharyngioma

Adamantinomatous craniopharyngioma

Papillary craniopharyngioma

Granular cell tumor of the sellar region

Pituicytoma

Spindle cell oncocytoma

Pituitary tumors

Pituitary adenomas

Pituitary adenoma

Corticotroph adenoma

Gonadotroph adenoma

Lactotroph adenoma

Somatotroph adenoma

Thyrotroph adenoma

Null cell adenoma

Plurihormonal and double adenomas

Pituitary carcinoma

Pituitary carcinoma

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. *World Health Organization Classification of Tumours of the Central Nervous System*. Lyon, France: IARC Press; 2016.
2. Lloyd RV, Osamura RY, Klöppel G, et al. *WHO Classification of Tumours: Pathology & Genetics of Tumours of Endocrine Organs.* Lyon, France: IARC Press; 2017.

**C. Histologic Grade**

Below is a list of possible WHO grades for CNS tumors.1 The WHO grading 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 CNS Tumors

WHO grade I

WHO grade II

WHO grade III

WHO grade IV

WHO grade not assigned

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. *World Health Organization Classification of Tumours of the Central Nervous System*. Lyon, France: IARC Press; 2016.

**D. Biomarker Studies**

Immunohistochemical and molecular genetic studies are often performed to assist with diagnosis, prognosis, or to predict therapeutic response.1 The most recent update of the World Health Organization’s Classification of Tumours of the Central Nervous System has incorporated many of these biomarkers into this formal diagnostic classification system, thereby formally encouraging their use in the evaluation of these neoplasms. Currently, the 2016 WHO Classification of Tumours of the Central Nervous System and the 2017 (WHO) Pathology & Genetics of Tumours of Endocrine Organs incorporates molecular genetic studies into several entities while the diagnosis of the majority of CNS tumors remain largely morphologic.1,2 It is expected that, as our understanding of the biology of CNS tumors improves, the list of entities requiring molecular genetic studies will continue to grow. For those defined entities, the use of the biomarker template is encouraged.

Additional common ancillary molecular testing in neurooncology includes *MGMT* promoter methylation studies; *ATRX* expression/mutations; *TP53* expression/mutations; copy number alterations in *EGFR* and *PTEN*; and *BRAF* alterations and mutations.3-5 For medulloblastoma, assessment of *MYC* or *MYCN* amplification and beta-catenin nuclear localization has prognostic significance.

In the absence of access to these biomarkers, the WHO has provided the “NOS” nomenclature appended to the end of the histologic diagnosis to indicate the absence of molecular testing on the individual case.

Embryonal neoplasms may benefit from ancillary studies for proper diagnostic categorization. Assigning medulloblastomas to appropriate genetic groups may be done by immunohistochemistry in most cases: WNT-activated (group 1) cases show nuclear beta-catenin and YAP1 expression; SHH-activated (group 2) cases express markers GAB1 and YAP1; groups 3 and 4 do not express neither GAB1 nor YAP1 and exhibit only nonnuclear beta-catenin immunostaining, if any.6,7 Some copy number changes are useful for molecular grouping of medulloblastomas, but are not necessary to assess in most cases: monosomy 6 is present in the vast majority of WNT-activated cases; deletion of 9q (*PTCH* gene) is common in SHH-activated cases; loss of 17p and duplication of 17 (resulting in an “isochromosome 17q”) is limited to groups 3 and 4.8 SHH-activated medulloblastomas can be diagnostically segregated by *TP53* mutation status; those medulloblastomas with a *TP53* mutation have a much worse prognosis.9 Aberrant p53 immunostaining is an effective surrogate for the presence of a mutation, either as diffuse, strong nuclear reactivity or, less commonly, complete lack of nuclear expression in all tumor cells. Additional assessment for *MYC* or *MYCN* amplification for prognosis is indicated regardless of molecular group.

Any embryonal neoplasm with lumen-forming, multilayered rosettes can be tested for amplification of the C19MC region on chromosome 19.10 The immunostain LIN28A, when strongly and diffusely positive, correlates highly with C19MC amplification, which confers a grim prognosis.11 Medulloepitheliomas have multilayered rosettes, yet may not always exhibit C19MC amplification or LIN28 expression. Such cases should be specified as non-C19MC altered.

Embryonal tumors can be assessed for *SMARCB1/INI1* status to identify atypical teratoid/rhabdoid tumors (AT/RT), which have a significantly different treatment regimen from other CNS embryonal malignancies. This may be effectively done by demonstrating absence of SMARCB1/INI1 nuclear immunostaining in tumor cells (for example using the BAF47 antibody).11 Morphologically rhabdoid embryonal malignancies with retained SMARCB1/INI1 nuclear expression can be assessed for loss of SMARCA4/BRG1, which is also diagnostic for AT/RT. The diagnosis "CNS embryonal tumor with rhabdoid features, NOS (WHO grade IV)" should be used when SMARCB1/INI1 or SMARCA4/BRG1 expression is retained or cannot be assessed in a malignant embryonal neoplasm with rhabdoid morphology.

Pediatric embryonal tumors in the supratentorial compartment can be tested for the H3F3A K27 or G34 mutations typically found in pediatric glioblastomas, which can display embryonal, neuroblastic morphology and immunophenotype.13 Antibodies are available for immunohistochemical detection of both the H3K27M and the mutant proteins.14 H3 G34-mutant glioblastomas have high rates of ATRX loss and TP53 mutations, immunostaining for which can help distinguish them from the embryonal tumors.

Supratentorial ependymomas can be tested for fusion rearrangements of the *RELA* gene, which are associated with a poor prognosis and constitute a separate diagnostic category in the WHO 2016 classification.15 Immunostaining for L1CAM is a surrogate marker for *RELA* fusion in ependymomas, although it may also be seen in other tumor types. Gain of 1q implies worse prognosis in posterior fossa ependymomas. In posterior fossa tumors, loss of H3 K27me3 staining reliably identifies the PF-A ependymomas, which have a much worse prognosis than PF-B.15

The advent of DNA next generation sequencing (NGS) techniques has led to the evaluation of many more biomarkers than can be performed one at a time in most FISH or immunohistochemical laboratories. NGS also allows the evaluation of biomarkers that are too large for routine sequencing methods such as *NF1*. The capture of these data may lead to the identification of less common genetic alterations that the oncologists may identify as clinically relevant, targetable pathways, particularly in the less common tumors of childhood and young adulthood.16 In such cases in which NGS analyses are obtained, we have left room at the end of the section to record the deviations found in these biomarkers. Similarly, research in brain tumor biomarkers is ongoing, making the updating of this protocol a dynamic process. Such new discoveries can be added also in the additional spaces provided.

Additional biomarker information and references developed by the International Collaboration on Cancer Reporting (ICCR) may be found at [http://www.iccr-cancer.org/datasets/published-datasets/central-nervous-system.](http://www.iccr-cancer.org/datasets/published-datasets/central-nervous-system.%2015)17

The ICCR Central Nervous System Molecular Notes includes an overview of selected molecular diagnostic markers for CNS tumors:

**Overview of selected molecular diagnostic markers for CNS tumours**

The table below summarizes selected molecular diagnostic markers for CNS tumours; the list of tests is not exhaustive and other assays may be helpful in some diagnostic circumstances. In addition, the tests listed are those related to ruling in the corresponding diagnoses; however, it should be realized that the assays may also be used in particular diagnostic situations to rule out other diagnoses. An example of this would be ATRX immunohistochemistry, which is commonly used to support a diagnosis of IDH-mutant diffuse astrocytoma, but which is also used to evaluate a possible diagnosis of oligodendroglioma, IDH-mutant and 1p/19q-codeleted. Some specific tests recommended in the commentaries below represent one of several validated and equivalent approaches to the evaluation of the described molecular variable; for those tests that have multiple testing modalities (e.g., sequencing and immunohistochemistry for BRAF V600E), it is assumed that only one of these testing modalities would be used per case unless one test yields equivocal results (e.g., a result of weak immunohistochemical positivity versus nonspecific background staining should be followed by gene sequencing). For some tests, relevance may be related to the age of the patient (e.g., *EGFR* gene amplification in adult high-grade gliomas rather than paediatric ones).

**Summary of tests by tumour type**

Note: this is a summary and the reader is referred to the specific notes for details on use of each test.17

|  |  |  |  |
| --- | --- | --- | --- |
| **Test** | **Gliomas** | **Embryonal tumours**  | **Other** |
|  | **DA, AA** | **O, AO** | **Diffuse midline glioma** | **Glioblastoma** | **Pilocytic astrocytoma** | **PXA, GG** | **Ependymoma - supratentorial** | **Ependymoma – posterior fossa** | **Medulloblastoma** | **AT/RT** | **ETMR** | **Extraventricular neurocytoma** | **Meningioma** | **SFT/HPC** | **Craniopharyngioma** | **MPNST** | **Pituitary adenomas** |
| ***ATRX* mutation** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *ATRX* mutation  | **D** |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ATRX loss of expression (immunohistochemistry) | **D** |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***BRAF* alterations**  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *BRAF* mutation | **(D)** |  |  | **(D)** | **D** | **D** |  |  |  |  |  |  |  |  | **D** |  |  |
| BRAF V600E expression (immunohistochemistry) | **(D)** |  |  | **(D)** | **D** | **D** |  |  |  |  |  |  |  |  | **D** |  |  |
| *BRAF* rearrangement/duplication |  |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |
| C19MC alteration |  |  |  |  |  |  |  |  |  |  | **W** |  |  |  |  |  |  |
| Chromosomal arm 1p/19q codeletion |  | **W** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chromosome 7 gain combined with chromosome 10 loss  |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chromosome 10q23 (PTEN locus) deletion and *PTEN* mutation  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chromosome 10q23 *(PTEN* locus)deletion or monosomy 10 |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *PTEN* mutation |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***EGFR* amplification and EGFRvIII mutation** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *EGFR* amplification |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EGFRvIII mutation |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Histone H3 mutation and H3 K27 trimethylation (me3)** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histone H3 K27M mutation (sequencing) and expression (immunohistochemistry) | **(D)** |  | **W** | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histone H3 G34 mutation (sequencing) and expression (immunohistochemistry) | **(D)** |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histone H3 K27me3 expression (immunohistochemistry) |  |  | **D** |  |  |  |  | **D** |  |  |  |  |  |  |  | **D** |  |
| ***IDH1/IDH2* mutation**  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *IDH1/IDH2* mutation | **W** | **W** |  | **W** |  |  |  |  |  |  |  | **D\*** |  |  |  |  |  |
| IDH1 R132Hexpression (immunohistochemistry) | **W** | **W** |  | **W** |  |  |  |  |  |  |  | **D\*** |  |  |  |  |  |
| Ki-67 immunohistochemistry |  | **D** |  |  |  |  |  |  |  |  |  |  | **D** |  |  |  | **D** |
| L1CAM expression (immunohistochemistry) |  |  |  |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |
| LIN28A expression (immunohistochemistry) |  |  |  |  |  |  |  |  |  |  | **D** |  |  |  |  |  |  |
| **Medulloblastoma immunohistochemistry**  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| β-catenin nuclear expression (immunohistochemistry) |  |  |  |  |  |  |  |  | **D** |  |  |  |  |  | **D** |  |  |
| GAB1 expression (immunohistochemistry) |  |  |  |  |  |  |  |  | **D** |  |  |  |  |  |  |  |  |
| YAP1 expression (immunohistochemistry) |  |  |  |  |  |  |  |  | **D** |  |  |  |  |  |  |  |  |
| *MGMT* promoter methylation |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Monosomy 6 |  |  |  |  |  |  |  |  | **D** |  |  |  |  |  |  |  |  |
| **MYC gene family amplification**  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *MYC* amplification |  |  |  |  |  |  |  |  | **D** |  |  |  |  |  |  |  |  |
| *MYCN* amplification |  |  |  |  |  |  |  |  | **D** |  |  |  |  |  |  |  |  |
| ***NAB2-STAT6* fusion** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *NAB2-STAT6* fusion |  |  |  |  |  |  |  |  |  |  |  |  |  | **D** |  |  |  |
| STAT6 nuclear expression (immunohistochemistry) |  |  |  |  |  |  |  |  |  |  |  |  |  | **D** |  |  |  |
| Pituitary hormones and transcription factors immunohistochemistry |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **W** |
| *RELA* fusion |  |  |  |  |  |  | **W** |  |  |  |  |  |  |  |  |  |  |
| ***SMARCA4/BRG1* alteration** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *SMARCA4/BRG1* mutation |  |  |  |  |  |  |  |  | **D** | **W** |  |  |  |  |  |  |  |
| BRG1 loss of expression (immunohistochemistry) |  |  |  |  |  |  |  |  | **D** | **W** |  |  |  |  |  |  |  |
| ***SMARCB1/INI1/HNSF5* alteration** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *SMARCB1/INI1/HNSF5* mutation |  |  |  |  |  |  |  |  | **D** | **W** |  |  |  |  |  |  |  |
| INI1 (BAF47) loss of expression (immunohistochemistry) |  |  |  |  |  |  |  |  | **D\*** | **W** |  |  |  |  |  |  |  |
| *TERT* promoter mutation |  | **D** |  | **D** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***TP53* mutation**  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *TP53* mutation  | **D** |  |  |  |  |  |  |  | **W** |  |  |  |  |  |  |  |  |
| p53 expression (immunohistochemistry) | **D** |  |  |  |  |  |  |  | **W** |  |  |  |  |  |  |  |  |
| *YAP1* fusion |  |  |  |  |  |  | **D** |  |  |  |  |  |  |  |  |  |  |

**W** = component of the 2016 CNS WHO diagnostic criteria and 2017 WHO diagnostic criteria for pituitary adenomas

**D** = commonly used to support or refine the diagnosis, or provide important ancillary information in the corresponding tumour type

**D**\* = commonly used to rule out the diagnosis; see commentary for details

**(D)** = can be used to support or refine the diagnosis, or provide important ancillary information in specific tumour subtype(s); see commentary for details

**DA** = diffuse astrocytoma; AA = anaplastic astrocytoma; O = oligodendroglioma; AO = anaplastic oligodendroglioma; PXA = pleomorphic xanthoastrocytoma; GG = ganglioglioma; AT/RT = atypical teratoid / rhabdoid tumour; ETMR = embryonal tumour with multilayered rosettes; SFT/HPC = solitary fibrous tumour / haemangiopericytoma; MPNST = malignant peripheral nerve sheath tumour

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**E. Relevant History**

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.1,2

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).3,4

References

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**F. Neuroimaging Findings**

Knowledge of neuroimaging features is extremely helpful in specimen interpretation.1 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 (e.g., contrast enhancement with hypocellularity). A close collaboration with the neuroradiologist and neurosurgeon is essential.

References

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**G. 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.

Specimen Handling, Triage, and Special Procedures

(While the reporting of specimen handling is not required in this protocol, the following information may be helpful.) 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.1 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.

References

1. Burger PC, Nelson JS. Stereotactic brain biopsies: specimen preparation and evaluation. *Arch Pathol Lab Med.* 1997;121:477-480.

**H. 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. The protocol may not be applicable to biopsy specimen if the tissue sample is limited.

**Table 1**. WHO Grading System for Some of the More Common Tumors of the CNS1,2

|  |  |  |
| --- | --- | --- |
| **Tumor Group** | **Tumor Type** | **Grade** |
| **I** | **II** | **III** | **IV** |
| **Diffuse astrocytic and oligodendroglial tumors** | Diffuse astrocytoma, IDH-mutant |  | X |  |  |
| Anaplastic astrocytoma, IDH-mutant |  |  | X |  |
| Glioblastoma, IDH-wildtype |  |  |  | X |
| Glioblastoma, IDH-mutant |  |  |  | X |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeleted |  | X |  |  |
| Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted |  |  | X |  |
| **Other astrocytic tumors** | Pilocytic astrocytoma | X |  |  |  |
| Subependymal giant cell astrocytoma | X |  |  |  |
| Pleomorphic xanthoastrocytoma |  | X |  |  |
| Anaplastic pleomorphic xanthoastrocytoma |  |  | X |  |
| **Ependymal tumors** | Subependymoma | X |  |  |  |
| Myxopapillary ependymoma | X |  |  |  |
| Ependymoma |  | X |  |  |
| Ependymoma, RELA fusion-positive |  | X | X |  |
| Anaplastic ependymoma |  |  | X |  |
| **Other gliomas** | Angiocentric glioma | X |  |  |  |
| Chordoid glioma of the third ventricle |  | X |  |  |
| **Choroid plexus tumors** | Choroid plexus papilloma | X |  |  |  |
| Atypical choroid plexus papilloma |  | X |  |  |
| Choroid plexus carcinoma |  |  | X |  |
| **Neuronal and mixed neuronal–glial tumors** | Dysembryoplastic neuroepithelial tumor | X |  |  |  |
| Gangliocytoma | X |  |  |  |
| Ganglioglioma | X |  |  |  |
| Anaplastic ganglioglioma |  |  | X |  |
| Central neurocytoma |  | X |  |  |
| Extraventricular neurocytoma |  | X |  |  |
| Cerebellar liponeurocytoma |  | X |  |  |
| **Tumors of the pineal region** | Pineocytoma | X |  |  |  |
| Pineal parenchymal tumor of intermediate |  | X | X |  |
| Pinealoblastoma |  |  |  | X |
| Papillary tumor of the pineal region |  | X | X |  |
| **Embryonal tumors** | Medulloblastoma (all subtypes) |  |  |  | X |
| Embryonal tumor with multilayered rosettes |  |  |  | X |
| Medulloepithelioma |  |  |  | X |
| CNS embryonal tumor, NOS |  |  |  | X |
| Atypical teratoid/rhabdoid tumor |  |  |  | X |
| CNS embryonal tumor with rhabdoid features |  |  |  | X |
| **Meningiomas** | Meningioma | X |  |  |  |
| Atypical meningioma |  | X |  |  |
| Anaplastic (malignant) meningioma |  |  | X |  |
| **Mesenchymal, non-meningothelial tumors** | Solitary fibrous tumor/hemangiopericytoma | X | X | X |  |
| Hemangioblastoma | X |  |  |  |
| **Tumors of the sellar region** | Craniopharyngioma | X |  |  |  |
| Granular cell tumor of the sellar region | X |  |  |  |
| Pituicytoma | X |  |  |  |
| Spindle cell oncocytoma | 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.1

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

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. *World Health Organization Classification of Tumours of the Central Nervous System*. Lyon, France: IARC Press; 2016.
2. Lloyd RV, Osamura RY, Klöppel G, et al. *WHO Classification of Tumours: Pathology & Genetics of Tumours of Endocrine Organs.* Lyon, France: IARC Press; 2017.

**I. 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 should be used for primary tumors of bone.1
* 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 cerebral aqueduct, if known.
* For a brain stem location, indicate midbrain, pons, or medulla, if known.
* For spine (vertebral bone), spinal cord, spinal root or spinal ganglion, indicate level (eg, C5, T2, L3), if known. The CAP cancer protocol for bone should be used for primary tumors of bone.1

The laterality of a neoplasm should be indicated as involving the left or right side of the 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.

Margins

Resection margins provide no prognostic information and generally are not required for most CNS neoplasms.

References

1. Laurini JA, Antonescu CR, Cooper K, et al. Protocol for the examination of specimens from patients with tumors of bone. 2017. Available at www.cap.org/cancerprotocols.

**J. Preoperative Treatment and Treatment Effect**

Knowledge of preoperative treatment, including radiation therapy, chemotherapy, corticosteroid therapy, embolization, and other therapy, is helpful for specimen interpretation.1-3 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 (e.g., coagulative [nonpalisading] necrosis, vascular hyalinization, and gliosis). The addition of chemotherapy to radiation may further alter histomorphological appearance. 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.4 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.

References

1. Burger PC, Scheithauer BW, Vogel FS. *Surgical Pathology of the Nervous System and Its Coverings.* 4th ed. New York: Churchill Livingstone; 2002.
2. Perry A, Brat DJ. Practical Surgical Pathology: A Diagnostic Approach. Philadelphia: Elsevier; 2010.
3. 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.
4. 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.