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Tumours of the Central Nervous System (CNS) Histological Assessment Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

SCOPE OF THIS DATASET

CLINICAL INFORMATION

PRIOR THERAPY (Note 1)

- ◯ Not administered
- ◯ Prior treatment not known
- ◯ Administered, *specify*

RELEVANT PATIENT/FAMILY HISTORY (Note 2)

(Select all that apply)

◯ Not provided

- ☐ Previous history of cancer, *specify*
- ☐ History of neurological tumour syndrome, *specify*
- ☐ Relevant familial history, *specify*
- ☐ Other, *specify*

OPERATIVE PROCEDURE (Note 3)

◯ Not provided

- ◯ Biopsy, *specify*
- ◯ Resection, *specify*
- ◯ Other, *specify*

RADIOLOGICAL INFORMATION

TUMOUR SITE(S) (Note 4)

◯ No macroscopically visible tumour ◯ Indeterminate

OR select all that apply:

- ☐ **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*
  - ☐ Ventricle, *specify precise location, if known*
- ☐ **Pineal,** *specify*
- ☐ **Sellar/suprasellar/pituitary**
- ☐ **Brain stem**, *specify precise location, if known*
- ☐ **Cerebellum**, *specify site, 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*
- ☐ **Other,** *specify*

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TUMOUR LATERALITY (Note 5)

- ◯ Right
- ◯ Left
- ◯ Midline
- ◯ Bilateral
- ◯ Other, *specify*
- ◯ Not specified

TUMOUR FOCALITY (Note 6)

- ◯ Unifocal
- ◯ Multifocal
- ◯ Indeterminate

Specify number of lesions

TUMOUR DIMENSIONS (largest/dominant lesion) (Note 7)

mm x mm x mm

RELATIONSHIP OF TUMOUR TO ADJACENT TISSUE (Note 8)

- ◯ Well demarcated
- ◯ Diffuse/infiltrative
- ◯ Mixed (both well-demarcated and diffuse in different areas)
- ◯ Indeterminate

Peritumoral edema

- ◯ Absent
- ◯ Present

CONTRAST ENHANCEMENT (Note 9)

- ◯ Non-enhancing
- ◯ Enhancing
  - ◯ Diffuse/solid
  - ◯ Patchy/heterogeneous
  - ◯ Ring or rim
- ◯ Information not available

SPECIMEN DETAILS

SPECIMEN DIMENSION (Record for each specimen submitted) (Note 10)

mm x mm x mm

- ◯ Cannot be assessed, *specify*

SPECIMEN DESCRIPTION (Note 11)

ADEQUACY OF SPECIMEN FOR HISTOLOGICAL ASSESSMENT (Note 12)

- ◯ Specimen is adequate for analysis
- ◯ Specimen is adequate but limited by, *specify*
- ◯ Specimen is inadequate for analysis, *specify* (select all that apply)
  - ☐ Crush
  - ☐ Autolysis
  - ☐ Cautery
  - ☐ Necrosis
  - ☐ Other, *specify*

ADEQUACY OF SPECIMEN FOR DIAGNOSTIC PURPOSES (Note 13)

- ◯ Specimen is adequate for diagnostic purposes
- ◯ Specimen is adequate but limited by, *specify*
- ◯ Specimen is inadequate for diagnostic purposes (e.g. not representative of likely clinic-radiological diagnosis), *specify*

HISTOLOGICAL APPEARANCE (Note 14)

Describe the appearance from the WHO 2016 entities and variants based on histological appearance only

- ☐ Other, *specify*
- ◯ Cannot be determined

HISTOLOGICAL GRADE (Note 15)

- ◯ WHO grade I
- ◯ WHO grade II
- ◯ WHO grade III
- ◯ WHO grade IV
- ◯ Not applicable
- ◯ Cannot be determined, *specify*

INVASION (Note 16)

- ◯ Not identified (i.e. tumour is well-demarcated from surrounding brain or other tissues)
- ◯ Cannot be assessed (e.g. only tumour is present), *specify*
- ◯ Present, *specify type*

HISTOLOGICAL EVIDENCE OF PRIOR THERAPY (Note 17)

- ◯ No evidence of prior therapy
- ◯ Positive response, *specify type of response* (select all that apply)
  - ☐ Vascular changes
  - ☐ Radiation type necrosis
  - ☐ Granulation and/or scar tissue
  - ☐ Ischemic type of necrosis
  - ☐ Foreign material (e.g. embolisation/procoagulant material)
  - ☐ Reactive glial changes
  - ☐ Inflammatory changes
  - ☐ Other, *specify*

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Scope

The dataset has been developed for the histological assessment of benign and malignant tumours of the central nervous system (CNS) and its coverings, as well as tumours from those aspects of the peripheral nervous system immediately adjacent to the CNS. This dataset applies to both biopsy and resection specimens. Haematological lesions that may originate in the brain are included. Tumours of the anterior pituitary gland are included as the majority of these tumours are reported by neuropathologists worldwide (a separate dataset specifically for pituitary tumours may be considered when the 5th series of the World Health Organisation (WHO) Classification of Tumours is being developed).

It is intended that this dataset should be used in conjunction with the 'Molecular information for CNS specimens' and the 'Final integrated report/diagnosis for CNS specimens' datasets. A full diagnosis of CNS tumours should ideally conform to the final integrated diagnoses in the 2016 World Health Organisation (WHO) Classification of Tumours of the CNS (2016 CNS WHO), which requires integration of elements from histological and ancillary analyses. Nonetheless, it is realized that some diagnoses may not fit precisely within existing diagnostic categories.[1]

Note 1 - Prior therapy (Non-core)

Reason/Evidentiary Support

Detail on prior treatment may not be available at the time of tumour diagnosis. Nonetheless, it can be helpful to know whether the patient has had specific therapies such as radiation therapy, chemotherapy, corticosteroid therapy, embolization, or radiosurgery. In particular, knowledge of such prior therapy may help to interpret changes such as necrosis, vasculature changes, cellular atypia and inflammatory cells.

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Note 2 - Relevant patient/family history (Non-core)

Reason/Evidentiary Support

Several genetic conditions (such as neurofibromatosis 1 and 2, and Turcot/Lynch, tuberous sclerosis, von-Hippel-Lindau, Cowden, Li-Fraumeni and Gorlin syndromes) are known to predispose individuals to specific primary CNS tumours. Knowledge of this information may therefore help in differential diagnoses. In addition, the behaviour of tumours in such syndromes may differ from those of their sporadic counterparts, and thus knowledge of a genetic condition may inform prognostic estimation.

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Note 3 - Operative procedure[2] (Non-core)

Reason/Evidentiary Support

The physical size of tissue specimens submitted for pathological assessment varies greatly depending on the operative procedure. Specimens obtained by stereotactic or, less commonly, endoscopic biopsy are typically the smallest and may be crushed during handling. Those from open biopsy are more ample and typically less damaged than those of stereotactic biopsy. Resection specimens are largest, and require careful macroscopic inspection in order to sample properly. Importantly, the size of the submitted sample does not always reflect the procedure; use of ultrasonic surgical aspirators, for example, may decrease the size of the submitted material relative to the total amount of resected material. Because the reliability of pathological diagnosis depends heavily on the representative nature and adequacy of material assessed, it is important to pay attention to any discrepancy

between submitted material and clinical information, including operative procedures and imaging findings. Doing so can help to minimise the influence of sampling and/or regional heterogeneity on the rendered diagnosis.

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Note 4 - Tumour site(s) (Non-core)

Reason/Evidentiary Support

Imaging studies are crucial in guiding neurosurgical and radiotherapeutic management of brain tumours.[3] Knowledge of the specific anatomic area in which the tumour resides can aid in the differential diagnosis and may correlate with tumour type and outcome. If known, it should be recorded whether a tumour is intra-axial (cerebrum, deep white matter, cerebellum, brain stem, spinal cord), extra-axial (dural/leptomeningeal, cerebellopontine angle, intraventricular, intra- or extradurally in the spinal canal), or located in the skull, skull base, sellar/suprasellar region, pineal gland, spine, etc. When available, the pathologist should indicate the exact location (e.g. cerebral convexity/lobe, lateral versus third or fourth ventricle, etc.).

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Note 5 - Tumour laterality (Non-core)

Reason/Evidentiary Support

Tumour laterality, as determined by imaging studies and as indicated by the surgeon, should be indicated as occurring on the right or left side of the CNS (e.g., right frontal lobe, left occipital convexity, right lateral ventricle, etc.). Midline tumours arising in the sellar, pineal, third or fourth ventricular, and spinal locations, among others, should be recorded as such. Occasionally, tumours may involve both sides of the brain and should be referred to as bilateral; a “butterfly” glioblastoma crossing the corpus callosum and involving both sides of the cerebrum is an example.

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Note 6 - Tumour focality (Non-core)

Reason/Evidentiary Support

While most CNS tumours are solitary (unifocal), multifocal examples exist, often representing malignant brain tumours (e.g., glioblastoma and CNS lymphoma). For tumours to be considered multifocal, they should be noncontiguous, as determined by neuroimaging studies—although it is recognised that histological autopsy studies of such radiologically multifocal tumours may reveal contiguity between lesions. Gliomatosis cerebri, previously recognised as a distinct diffuse glioma entity involving multiple cerebral lobes, is now recognised as a growth pattern in the 2016 WHO Classification of CNS Tumours.[4]

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Note 7 - Tumour dimensions (Non-core)

Reason/Evidentiary Support

Radiologic tumour dimensions serve as approximate guidance as to whether tumours have been sampled adequately, particularly when dealing with small biopsies. Post-surgery, they also give information regarding how

much of the tumour has been resected. For example, radiologic-pathologic correlations can guard against making a diagnosis of low-grade glioma on a stereotactic biopsy sample obtained from the edge of a large, heterogeneously enhancing cerebral lesion.

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Note 8 - Relationship of tumour to adjacent tissue (Non-core)

Reason/Evidentiary Support

The interface between tumour and adjacent brain as depicted by neuroimaging (MRI, CT) provides information on the growth pattern and on the dynamics of tumour growth. Hyperintensity on fluid-attenuated inversion recovery (FLAIR) images may indicate an infiltrative tumour growth and reflect invasiveness of the tumour. This may also be reflected by diffuse or patchy contrast enhancement at the interface between tumour and normal brain (see below). Absence of peritumoural alterations on T2 and FLAIR sequences suggests a more benign nature of a lesion. The MRI patterns may also vary within one tumour with partly well-demarcated areas and partly infiltrative growth. Oedemais visualised as a hypointense signal alteration on T1-weighted sequences without contrast and, similar to infiltrative growth, as hyperintense signal on FLAIR sequences. Differentiation between infiltrative growth and oedema is often impossible, notably in gliomas. Slowly growing, more benign tumours induce relatively less oedema than fast growing, malignant tumours. Information provided by the surgeon on where the tissue specimens were collected relative to the MRI changes also aids the pathologist in interpreting the histological findings.

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Note 9 - Contrast enhancement (Non-core)

Reason/Evidentiary Support

Contrast enhancement is commonly interpreted as reflecting blood-brain barrier disturbance. Extra-axial tumours growing outside the brain parenchyma (e.g., meningiomas) commonly take up contrast vividly. For intrinsic brain tumours such as gliomas, contrast enhancement is commonly interpreted as a sign of increasing malignancy, but this correlation is far from complete. For example, it is not uncommon for non-enhancing diffuse gliomas to be deemed anaplastic on histological examination. Moreover, pilocytic astrocytomas, gangliogliomas, and others are exceptions since they take up contrast, but are assigned to WHO grade I and carry a favourable prognosis. Ring enhancement is commonly associated with extensive central necrosis and reflects a high grade of histological malignancy, but is occasionally seen in benign tumours as well. Contrast enhancement is subject to pharmacological modification (e.g., by corticosteroids) or antiangiogenic agents, (e.g., bevacizumab). Thus, pharmacotherapy may be a challenge for MRI interpretation. Changes in contrast enhancement have traditionally played a central role in response assessment in neuro-oncology, (e.g., in the Macdonald criteria), but the additional consideration of T2 and FLAIR sequences has increasingly been implemented into response assessment in recent years.

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Note 10 - Specimen dimension (Core)

Reason/Evidentiary Support

Intrinsic tumours grow diffusely within the brain and in many instances cannot be completely removed. Clinical factors (e.g., performance status) and tumour location often determine the extent of resection, ranging from a stereotactic biopsy to a resection of a lobe. Surgical technique may result in a discrepancy of the amount of tissue

resected and received in the pathology department, in particular when a surgical ultrasonic aspirator is used and the collected tissue is partly discarded.

It is important to record the volume of tissue arriving in the pathology department and thus the amount of tissue available for diagnosis (and where possible for frozen tissue banking for subsequent studies). If a tumour, for example a schwannoma or meningioma, arrives in one piece, it can be measured relatively accurately. Brain tumour surgery, however, often results in tissue fragments, making an accurate assessment difficult. Where possible, the size of large resection specimens should be recorded in three dimensions and piecemeal resections should be estimated by their aggregate size in three dimensions. Alternatively, an accurate and reproducible determination of the tissue volume may be achieved by weighing tissue fragments, compared to visual estimates in three dimensions, but this is not a common practice.

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Note 11 - Specimen description (Non-core)

Reason/Evidentiary Support

The description of resection margins is generally not applicable for intra-axial CNS tumours as surgical technique results in fragmented specimens in most instances, except when complete resection of a lobe can be achieved. Therefore, staging and assessment of resection margins is generally not possible and thus not included in published protocols. Additionally, diffusely infiltrative tumours have often invaded well beyond designated surgical margins, even when tumour cells are not evident at that margin. Extra-axial tumours, such as meningiomas, schwannomas, and other well-demarcated tumours can often be resected and submitted intact. This allows a description of the lesion itself, and adherent structures, such as meninges, nerve roots, and CNS tissue. However, when arriving in fragmented state, the report may necessarily be limited to a description of individual components, and the degree of fragmentation.

When applicable, description should also include the presence of other components, such as CNS tissue, dura mater, skin, bone, blood clot and extrinsic components such as haemostatic material, metal clips, synthetic bone, mesh, shunt ducts etc.

Specimens may arrive fresh or in fixative. This should be indicated when describing the colour of the specimen as it changes with fixation.

Specimens may also arrive in already processed forms, such as blocks or slides. In such situations, description should be given for blocks and slides, indicating the number of blocks and/or slides. Slides may be described in greater detail, e.g. total number of glass slides, comprising number of H&E and other slides (e.g., immunohistochemistry, smears, controls), as well as other materials (e.g., EM prints, neuroimaging files).

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Note 12 - Adequacy of specimen for histological assessment (Non-core)

Reason/Evidentiary Support

The adequacy of a specimen for histological assessment can be affected by various intraoperative procedures, tissue fixation issues (duration in/volume of fixative), and technical processing issues in the histology laboratory. These include, but are not limited to, electrocautery/heat/laser treatment intraoperatively, distortion of tissue due to surgical instrumentation, delay in placing wet tissue into fixative by the surgeon/operating room technician, less than 10:1 fixative-to-tissue volume ratio, and excessive fracturing/knife chatter in tissue during cutting of the frozen tissue/paraffin block. Tiny size of a biopsy can lead to tissue exhaustion during processing. Highly necrotic, mucinous, fibrous, calcified, or ossified specimens may cause suboptimal processing/sectioning. Any of these conditions can obscure nuclear/nucleolar features, distort degree of cellularity, blur tumour margins, and or make mitotic activity impossible to assess. Prior freezing of the tissue for frozen section intraoperative diagnosis may

negatively impact cytological assessment in the fixed, embedded tissues and immunohistochemistry for some antibodies. In each case, the pathologist should state which of these conditions make the tissue inadequate/suboptimal for histological assessment.

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Note 13 - Adequacy of specimen for diagnostic purposes (Non-core)

Reason/Evidentiary Support

Many intraparenchymal brain lesions are surgically assessed by either small open excisional biopsy or stereotactic biopsy. While navigational equipment is usually employed to optimise targeting, the known ability of brain tissue to swell during an operative procedure can cause shifting of brain tissue during the procedure, which can result in biopsies that are suboptimally centred on the area(s) of interest. Examples of suboptimally centred tissues include: biopsies from diffuse infiltrating gliomas taken from the edge, not centre, of the tumour; biopsies from infections in which the necrotic/purulent centre may be submitted by the surgeon for culture(s), leaving the pathologist with reactive, but not organism-containing, edges of the process. Occasionally, tissue lost to intraoperative suctioning or lesional tissues given in overly generous amounts to brain banks can render the tissue sent to the pathologist suboptimal for diagnosis.

Any of these situations can leave the pathologist with tissue that can be misleading in terms of type of tumour, grade of tumour, or inability to detect organisms, if present. The diagnosis possible on the submitted tissues may be under-representative or misrepresentative of the lesion based on the neuroimaging studies. In a few instances, more sophisticated testing (e.g., molecular) may be required for full/correct diagnosis, but the small tissue size, tissue processing issues, or suboptimal targeting of biopsy materials may make this testing impossible. The pathologist should specify any, and all, limitations of the tissue in achieving optimal diagnosis.

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Note 14 - Histological appearance (Non-core)

Reason/Evidentiary Support

In nearly all pathology reports of CNS neoplasms, the diagnosis should ideally include one of the >150 entities and variants listed in the 2016 CNS WHO[4,5] (see Table 1 below) and when additionally possible, the histological appearance should further be combined with signature molecular alterations to establish a more specific "integrated diagnosis" (e.g., diffuse astrocytoma, IDH-mutant; see section on **Integrated Diagnosis**). When using such an approach, histological impressions such as "oligoastrocytoma" and "anaplastic oligoastrocytoma" will virtually always be altered to either astrocytoma or oligodendroglioma categories based on specific molecular patterns identified. Similar modifications also apply to the RELA-fusion positive supratentorial ependymomas, diffuse midline gliomas, the solitary fibrous tumours/haemangiopericytomas, and the overarching group of embryonal neoplasms, such as medulloblastoma variants, atypical teratoid/rhabdoid tumour, and embryonal tumour with multilayered rosettes, each of which require additional molecular (or surrogate immunohistochemical biomarker) testing before a definitive diagnosis can be made. However, in the majority of entities still lacking disease-defining molecular signatures, the final diagnosis will be based on classical histopathology alone. In either approach (histological or integrated), obtaining as precise a final diagnosis as possible is critically important, as this forms the basis for all subsequent patient management decisions, accruing patients to the appropriate clinical trials, epidemiologically assessing disease trends over time, and establishing valid research conclusions.[6-9] As such, the strict application of WHO 2016 diagnostic guidelines is required to enhance both accuracy and interobserver reproducibility across the globe and it is noteworthy that for many entities, criteria have changed dramatically from the earlier 2007 WHO classification. In the remaining cases that do not neatly conform to a well-recognised entity or variant (see last category listed as "Other (specify)"), a descriptive diagnosis should be rendered instead, providing as much information as possible including relevant molecular information (e.g., small round cell sarcoma

of indeterminate type; low-grade neuroepithelial tumour with oligodendroglial-like histological features suggestive of dysembryoplastic neuroepithelial tumour or paediatric oligodendroglioma; high-grade glioneuronal neoplasm; poorly differentiated malignancy; etc.). Such cases can be considered Not Elsewhere Classified (NEC).[1]

It should be noted that in some cases the results are not clear cut and the addition of a secondary diagnosis may be of benefit to record in the report.

This element should be considered CORE if it constitutes the final diagnosis.

Table 1 Histologically Defined Diagnostic Category (based on histological appearance <u>only, i.e., not full 2016 CNS WHO diagnoses)</u>

Diffuse glioma
Diffuse astrocytoma
Gemistocytic astrocytoma
Anaplastic astrocytoma
Glioblastoma
Giant cell glioblastoma
Gliosarcoma
Epithelioid glioblastoma
Oligodendroglioma
Anaplastic oligodendroglioma
Oligoastrocytoma
Anaplastic oligoastrocytoma
Pilocytic astrocytoma
Pilomyxoid astrocytoma
Subependymal giant cell astrocytoma
Pleomorphic xanthoastrocytoma
Anaplastic pleomorphic xanthoastrocytoma
Chordoid glioma of third ventricle
Angiocentric glioma
Astroblastoma
Subependymoma
Myxopapillary ependymoma
Ependymoma
Papillary ependymoma
Clear cell ependymoma
Tanycytic ependymoma
Anaplastic ependymoma

Choroid plexus papilloma
Atypical choroid plexus papilloma
Choroid plexus carcinoma
Dysembryoplastic neuroepithelial tumour
Gangliocytoma
Ganglioglioma
Anaplastic ganglioglioma
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos disease)
Desmoplastic infantile astrocytoma or ganglioglioma (DIA or DIG)
Papillary glioneuronal tumour
Rosette-forming glioneuronal tumour
Diffuse leptomeningeal glioneuronal tumour
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Paraganglioma
Pineocytoma
Pineal parenchymal tumour of intermediate differentiation
Pineoblastoma
Papillary tumour of the pineal region
CNS Embryonal tumour
CNS Embryonal tumour with rhabdoid features
Medulloblastoma
Medulloblastoma, classic
Medulloblastoma, desmoplastic/nodular
Medulloblastoma with extensive nodularity
Medulloblastoma, large cell/anaplastic
Embryonal tumour with multilayered rosettes
Medulloepithelioma
CNS Neuroblastoma
CNS Ganglioneuroblastoma
Schwannoma
Cellular schwannoma
Plexiform schwannoma
Melanotic schwannoma
Neurofibroma

Plexiform neurofibroma
Perineurioma
Hybrid nerve sheath tumour
Malignant peripheral nerve sheath tumour (MPNST)
Epithelioid MPNST
Melanotic MPNST
MPNST with mesenchymal differentiation
MPNST with glandular differentiation
MPNST with perineurial differentiation
Meningioma
Meningothelial meningioma
Fibrous meningioma
Transitional meningioma
Psammomatous meningioma
Angiomatous meningioma
Microcystic meningioma
Secretory meningioma
Lymphoplasmacyte-rich meningioma
Metaplastic meningioma
Chordoid meningioma
Clear cell meningioma
Atypical meningioma
Papillary meningioma
Rhabdoid meningioma
Anaplastic (malignant) meningioma
Solitary fibrous tumour/haemangiopericytoma
Haemangioblastoma
Haemangioma
Epithelioid hemangioendothelioma
Angiosarcoma
Kaposi sarcoma
Ewing sarcoma-peripheral primitive neuroectodermal tumour
Lipoma
Angiolipoma
Liposarcoma
Desmoid-type fibromatosis
Myofibroblastoma
Inflammatory myofibroblastic tumour
Benign fibrous histiocytoma

Fibrosarcoma
Undifferentiated pleomorphic sarcoma (UPS)/malignant fibrous histiocytoma (MFH)
Leiomyoma
Leiomyosarcoma
Rhabdomyoma
Rhabdomyosarcoma
Chondroma
Chondrosarcoma
Osteoma
Osteochondroma
Osteosarcoma
Diffuse melanocytosis
Meningeal melanocytoma
Melanoma
Meningeal melanomatosis
Diffuse large B cell lymphoma (DLBCL) of the CNS
Immunodeficiency-associated lymphoproliferative disorders of the CNS
Low grade B cell lymphomas of the CNS
T-cell and NK/T-cell lymphomas of the CNS
Anaplastic large cell lymphoma
Lymphomatoid granulomatosis
Intravascular large B-cell lymphoma
MALT lymphoma of the dura
Langerhans cell histiocytosis
Erdheim-Chester disease
Rosai-Dorfman disease
Juvenile xanthogranuloma
Histiocytic sarcoma
Germinoma
Embryonal carcinoma
Yolk sac tumour
Choriocarcinoma
Teratoma
Mature teratoma
Immature teratoma
Teratoma with malignant transformation
Mixed germ cell tumour

Craniopharyngioma
Adamantinomatous craniopharyngioma
Papillary craniopharyngioma
Granular cell tumour
Pituicytoma
Spindle cell oncocytoma
Pituitary adenoma
Somatotroph adenoma
Lactotroph adenoma
Thyrotroph adenoma
Corticotroph adenoma
Gonadotroph adenoma
Null cell adenoma
Plurihormonal and double adenomas
Pituitary carcinoma
Pituitary blastoma
Gangliocytoma and mixed gangliocytoma-adenoma
Granular cell tumour
Pituicytoma
Spindle cell oncocytoma
Metastatic carcinoma
Metastatic melanoma
Metastatic sarcoma
Metastatic lymphoma/leukemia

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Note 15 - Histological grade (Core)

Reason/Evidentiary Support

In as many pathology reports of CNS neoplasms as possible, the diagnosis should include a grade based on the WHO 2016 classification (see Table 2 below).[4,5] This scheme differs from the approaches in many other organ systems in that in most circumstances, the diagnosis dictates a given WHO grade rather than a range of grades within a diagnostic category. The scale of WHO grades from I to IV reflects the natural histories of various tumour types, rather than their shifting prognoses with changes in therapeutic practice over time.[6] Roughly speaking, a WHO grade I tumour is considered benign and potentially curable by surgery, although in unfavourable locations, such tumours may still create significant morbidity. WHO grade II tumours typically are slowly growing malignancies that often recur and are associated with significant mortality, albeit with survival times of many years

in most cases. WHO grade III tumours are rapidly growing malignancies with typical survivals of only a few years if treated with surgery alone. Nearly all such tumours are designated as "anaplastic". WHO grade IV neoplasms are highly aggressive malignancies with rapid mortality (typically in less than 2 years after diagnosis) in the absence of adjuvant therapies (e.g., glioblastomas and embryonal neoplasms). Progression from lower-grade malignancy to higher-grade forms occurs in some CNS neoplasms, most commonly the diffuse gliomas (Table 3) and to a lesser extent in the meningiomas (Table 4). There are exceptions to the automatic assignment of a single WHO grade based on diagnosis, mostly in entities for which definite parameters for histological grading have not been established yet. Other bone and soft tissue neoplasms occurring within the neural axis are classified and graded using the same criteria as in other parts of the body. Lastly, it should be noted that in some cases, assigning a WHO grade is not possible or could cause more confusion than clarification for clinical colleagues (e.g., when the exact tumour subtype remains unclear). In such cases, it is preferable to omit the WHO grade from the final diagnosis.

Table 2 WHO Grades Based on Histologically Defined Diagnostic Category (based on histological appearance only, i.e., not full 2016 CNS WHO diagnoses)[#]

Tumour Group	Tumour Type	Grade I	Grade II	Grade III	Grade IV
Astrocytic tumours	Diffuse astrocytoma		X		
	Anaplastic astrocytoma			X	
	Glioblastoma (and variants)				X
	Pilocytic astrocytoma	X			
	Pilomyxoid astrocytoma (grade not assigned)				
	Subependymal giant cell astrocytoma	X			
	Pleomorphic xanthoastrocytoma		X		
	Anaplastic pleomorphic xanthoastrocytoma			X	
Oligodendrogliomas	Oligodendroglioma		X		
	Anaplastic oligodendroglioma			X	
Oligoastrocytomas	Oligoastrocytoma		X		
	Anaplastic oligoastrocytoma			X	
Ependymal tumours	Ependymoma		X		
	Anaplastic ependymoma			X	
	Subependymoma	X			
	Myxopapillary ependymoma	X			
Choroid plexus tumours	Choroid plexus papilloma	X			
	Atypical choroid plexus papilloma		X		
	Choroid plexus carcinoma			X	
Other neuroepithelial tumours	Chordoid glioma of the third ventricle		X		
	Angiocentric glioma	X			
Neuronal-glial tumours	Gangliocytoma	X			
	Desmoplastic infantile ganglioglioma/ astrocytoma (DIG/DIA)	X			

Tumour Group	Tumour Type	Grade I	Grade II	Grade III	Grade IV
	Dysembryoplastic neuroepithelial tumour	X			
	Ganglioglioma	X			
	Anaplastic ganglioglioma			X	
	Central neurocytoma		X		
	Extraventricular neurocytoma		X		
	Cerebellar liponeurocytoma		X		
	Papillary glioneuronal tumour	X			
	Rosette-forming glioneuronal tumour of the fourth ventricle	X			
	Paraganglioma of the spinal cord	X			
Pineal parenchymal tumours	Pineocytoma	X			
	Pineal parenchymal tumour of intermediate differentiation		X	X	
	Pineoblastoma				X
	Papillary tumour of the pineal region		X	X	
Embryonal tumours	Medulloblastoma				X
	CNS embryonal tumour, NOS				X
	Medulloepithelioma				X
	CNS Neuroblastoma				X
	CNS Ganglioneuroblastoma				X
	Ependymoblastoma				X
	Atypical teratoid/rhabdoid tumour				X
Cranial and peripheral nerve tumours	Schwannoma (and variants)	X			
	Neurofibroma (and variants)	X			
	Perineurioma	X			
	Malignant peripheral nerve sheath tumours (MPNST)		X	X	X
Meningeal tumours	Meningioma (and variants)	X			
	Atypical meningioma		X		
	Clear cell meningioma		X		
	Chordoid meningioma		X		
	Anaplastic meningioma			X	
	Papillary meningioma			X	
	Rhabdoid meningioma			X	
Mesenchymal tumours[10,11]	(Named as soft tissue counterpart)	X	X	X	X
	Solitary fibrous tumour / Haemangiopericytoma	X	X	X	
Tumours of uncertain histogenesis	Haemangioblastoma	X			

Tumour histology and grade are strong predictors of clinical behaviour for different CNS tumours, including diffusely infiltrating astrocytomas and meningiomas. Tables 3 and 4 list the grading criteria for these common CNS tumour types.

Table 3 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 microvascular proliferation and/or necrosis

Table 4 WHO Grading of Meningiomas[#]

WHO grade I	**Benign meningioma** (and variants) None of the criteria below for WHO grades II or III
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**

[#]Modified from the original versions in Brat DJ, Parisi JE, DeMasters BK et al. Protocol for the Examination of Specimens From Patients with Tumors of the Central Nervous System. 2014. Available at www.cap.org/cancerprotocols.

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Note 16 - Invasion (Non-core)

Reason/Evidentiary Support

Most neuroepithelial tumours, particularly infiltrating gliomas, demonstrate diffuse infiltration of tumour cells beyond grossly discernable margins. Isolated tumour cells are often present in grossly normal-appearing parenchyma surrounding the lesions. Involvement of leptomeninges and Virchow-Robin spaces are also common in gliomas, even in benign examples such as pilocytic astrocytoma and ganglioglioma. These “invasions” provide no prognostic significance beyond the given biological malignancy of each tumour. Furthermore, direct invasion into adjacent structures, such as dura and skull, is quite exceptional in gliomas. Assessment of such features therefore, has not been included as an element for the dataset for intra-axial CNS tumours.

On the other hand, invasion of adjacent structures may be relevant in some non-neuroepithelial tumours, meningioma in particular, and can be assessed if the interface between the tumour and the adjacent tissue is appropriately submitted for assessment. Brain invasion is a criterion for atypical meningioma in the 2016 CNS WHO Classification[12] and is characterised by irregular, tongue-like protrusions of tumour tissue into underlying parenchyma without an intervening layer of leptomeninges; however, extension along Virchow-Robin spaces does not constitute brain invasion. Bone involvement has been associated with increased recurrence rates in the setting of atypical meningioma.[13]

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Note 17 - Histological evidence of prior therapy[14] (Non-core)

Reason/Evidentiary Support

Prior therapy,including prior surgery, intravascular embolization, chemotherapy and radiotherapy—may significantly alter the histological appearance of tissues and result in difficulties in tumour typing and grading. Information on prior therapy (see **Note 1 Prior Therapy**) is, however, not always available to the pathologist and the absence of histological evidence does not necessarily imply absence of prior therapy.

Therapy-associated histological findings are often non-specific, except for iatrogenically introduced foreign materials such as embolic agents, and are not always adequately distinguished form tumour-associated findings. In this regard, WHO grades may not be readily assigned to the specimens after adjuvant therapies. Histological changes of radiation damage are particularly common in specimens from recurrent diffuse gliomas. These include large foci of coagulative necrosis with hypocellular edges and microcalcifications; hyalinised or necrotic vessels with enlarged, atypical endothelial cells; and pale, rarefied parenchyma with fibrin deposits. The presence of such changes is highly suggestive of prior radiation therapy, even if a clear clinical history of prior radiation has not been provided.

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