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Tumours of the Central Nervous System 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.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET SECTION

CLINICAL INFORMATION (Note 1)

◯ Information not provided

◯ Information provided (select all that apply)

- ☐ Previous therapy, *specify*
- ☐ Previous history of tumour, *specify*
- ☐ History of known cancer predisposition syndrome, *specify*
- ☐ Relevant familial history, *specify*
- ☐ Other clinical informtion, *specify*

OPERATIVE PROCEDURE (Note 2)

◯ Not specified

◯ Biopsy, *specify*

◯ Resection, *specify*

◯ Other, *specify*

RADIOLOGICAL INFORMATION

TUMOUR SITE[a] (select all that apply) (Note 3)

◯ Not specified

◯ Indeterminate

◯ No macroscopically visible tumour

- ☐ Skull, *specify site(s) if known*
- ☐ Dura, *specify site(s) if known*
- ☐ Leptomeninges, *specify site(s) if known*
- ☐ Cerebrum
  - ☐ Cerebral lobes, *specify site(s) if known*
  - ☐ Midline, *specify site(s) if known*
  - ☐ Ventricle, *specify site(s) if known*
- ☐ Pineal, *specify site(s) if known*
- ☐ Sellar/suprasellar/pituitary, *specify site(s) if known*
- ☐ Brain stem, *specify site(s) if known*
- ☐ Cerebellum, *specify site(s) if known*
- ☐ Spine/vertebral column, *specify site(s) if known*
- ☐ Spinal cord, *specify site(s) if known*
- ☐ Spinal nerve root(s), *specify site(s) if known*
- ☐ Peripheral nerve, *specify site(s) if known*
- ☐ Other, *specify site(s) if known*

[a] *Core for medulloblastomas, ependymal tumours, diffuse midline gliomas and pineal region tumours and others (refer to Note); in all other tumours it is non-core.*

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TUMOUR LATERALITY (select all that apply) (Note 4)

- ◯ Not specified
- ☐ Left
- ☐ Right
- ☐ Midline
- ☐ Bilateral

TUMOUR FOCALITY (Note 5)

- ◯ Unifocal
- ◯ Multifocal
  - Specify number of lesions

TUMOUR DIMENSIONS (Note 6)

Largest/dominant lesion

mm x mm x mm

RELATIONSHIP OF TUMOUR TO ADJACENT TISSUE (Note 7)

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

Peritumoral edema

- ◯ Absent
- ◯ Present

CONTRAST ENHANCEMENT (Note 8)

- ◯ Non-enhancing
- ◯ Enhancing
  - ◯ Diffuse/solid
  - ◯ Patchy/heterogeneous
  - ◯ Ring or rim

SPECIMEN DETAILS

SPECIMEN DIMENSIONS (Note 9)

(Record for each specimen submitted)

mm x mm x mm

- ◯ Cannot be assessed, *specify*

SPECIMEN DESCRIPTION (Note 10)

ADEQUACY OF SPECIMEN FOR HISTOLOGICAL ASSESSMENT (Note 11)

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

ADEQUACY OF SPECIMEN FOR DIAGNOSTIC PURPOSES (Note 12)

- ◯ 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 clinicoradiological diagnosis), *specify*

HISTOLOGICAL APPEARANCE[b] (Note 13)

- ◯ Cannot be determined

Describe the histological appearance according to the World Health Organization (WHO) Classification of Central Nervous System Tumours (2021)

[b] *Core if histological appearance is an essential component of the final (integrated) diagnosis (refer to Note).*

INVASION INTO SURROUNDING TISSUE/STRUCTURES (Note 14)

- ◯ Not identified (i.e., tumour is well-demarcated from surrounding brain or other tissues)
- ◯ Present, *specify type*
- ◯ Cannot be assessed (e.g., no surrounding tissue present), *specify*

HISTOLOGICAL EVIDENCE OF PREVIOUS THERAPY (Note 15)

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

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC).

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

⬆ Back

Scope

This dataset section has been developed for the histological assessment of benign and malignant primary tumours of the central nervous system (CNS) and its coverings, as well as tumours from those structures of the peripheral nervous system immediately adjacent to the CNS. This dataset applies to both biopsy and resection specimens of adult and paediatric CNS tumours. Haematological lesions involving the CNS and germ cell tumours are not covered in detail as these are not the primary focus of the CNS dataset. Most sarcomas are not included and are covered by separate ICCR datasets.[2,3] Secondary tumours of the CNS (for example, metastatic tumours from carcinomas, sarcomas or melanomas in other organs) are not covered in this dataset. Tumours of the pituitary gland are included as the majority of these tumours are reported by neuropathologists worldwide.

This dataset section on histological assessment should be used in conjunction with the ICCR dataset sections on Molecular information and the Integrated final diagnosis, where appropriate.

The 2nd edition of this dataset incorporates the World Health Organisation (WHO) Classification of Tumours of the CNS, 5th edition (CNS5), 2021.[4] The ICCR dataset includes 5th edition Corrigenda, July 2024.[5] A complete diagnosis of CNS tumours should ideally conform to the final integrated diagnoses in the 2021 WHO CNS5 Tumour Classification, which for most tumour types now requires integration of elements from histological and ancillary analyses. Nonetheless, it is realised that some diagnoses may not fit precisely within existing diagnostic categories.[6]

A list of changes in this dataset edition can be accessed here.

The authors of this dataset can be accessed here.

Back

Note 1 – Clinical information (Core and non-core)

For optimal tissue diagnosis and patient treatment, it is important that pathologists receive key clinical information with the specimen. Therefore, the clinical information received with the specimen is a core element for reporting. However, in acknowledging that the pathologist is only capable of documenting the clinical information that they receive, the clinical information sub-values (e.g., previous therapy) are classified as non-core.

Details on previous treatment may not be available at the time of tumour diagnosis. Nonetheless, in some situations it is crucial to know whether the patient has had specific therapies such as radiation therapy, chemotherapy, corticosteroid therapy, embolisation, or radiosurgery. In particular, knowledge of such previous therapy may help to interpret changes such as necrosis, vasculature changes, cellular atypia and inflammatory cells.

Several genetic conditions (such as neurofibromatosis type 1 and 2, congenital mismatch repair deficiency syndrome Lynch syndrome, tuberous sclerosis, von-Hippel-Lindau, Cowden, Li-Fraumeni and naevoid basal cell carcinoma/Gorlin syndromes) are known to predispose individuals to specific primary CNS tumours. Knowledge of this information may therefore be relevant in differential diagnoses. In addition, the behaviour of tumours in such syndromes may differ from those of their sporadic counterparts. Therefore, knowledge of a genetic condition may inform prognostic estimation, guide clinical management and trigger genetic counselling.

Back

Note 2 – Operative procedure (Non-core)

The physical size of tissue specimens submitted for pathological assessment varies greatly depending on the operative procedure. Specimens obtained by stereotactic or endoscopic biopsy are typically the smallest and may be crushed during handling. Those from open biopsy are more ample and typically less damaged. Resection specimens are largest and require careful macroscopic inspection in order to sample properly.[7] 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.

As the reliability of neuropathological 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 errors and/or regional heterogeneity on the rendered diagnosis.[7]

Back

Note 3 – Tumour site (Core)

Tumour site is a core element for tumour entities where the information is essential for making the correct diagnosis. Examples include medulloblastomas, ependymal tumours, diffuse midline gliomas, and pineal region tumours. For other tumour entities, tumour site should ideally be recorded as well, as this can aid in the differential diagnosis and may correlate with outcome.

Imaging studies are crucial in guiding neurosurgical and radiotherapeutic management of CNS tumours.[8] Imaging and intra-operative findings can be used to designate a CNS tumour as being:

- intra-axial (intraparenchymal tumour in cerebrum, 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.

Back

Note 4 – Tumour laterality (Non-core)

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.). The term 'midline' in diffuse midline glioma, H3 K27-altered, refers to tumours that originate in the brainstem, thalamic region, spinal cord or cerebellum. Tumours arising in other midline structures such as third or fourth ventricle, (supra)sellar region or pineal region, should also 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.

Back

Note 5 – Tumour focality (Non-core)

While most CNS tumours are solitary (unifocal), multifocal examples exist, often representing malignant brain tumours (e.g., glioblastoma, IDH-wildtype and primary CNS lymphoma). For tumours to be considered multifocal, they should be noncontiguous, as determined by neuroimaging studies. However, it is recognised that autopsy studies of such radiologically multifocal tumours may histologically reveal contiguity between lesions. Gliomatosis cerebri, previously recognised as a distinct diffuse glioma entity involving multiple cerebral lobes, is in the WHO CNS5 Tumour Classification recognised as a growth pattern and not a distinct tumour type.[4]

Back

Note 6 – Tumour dimensions (Non-core)

Preoperative radiological 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.

Back

Note 7 – Relationship of tumour to adjacent tissue (Non-core)

The interface between tumour and adjacent brain as depicted by neuroimaging (magnetic resonance imaging (MRI), computed tomography (CT)) provides information on the growth pattern and on the dynamics of tumour growth. Hyperintensity on fluid-attenuated inversion recovery (FLAIR) images may indicate 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 **Note 8 – CONTRAST ENHANCEMENT**). Absence of peritumoural alterations on T2 and FLAIR sequences suggests a more benign lesion.

The MRI patterns may also vary within the tumour with partly well-demarcated areas and partly infiltrative growth. Oedema is 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 diffuse 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.

Back

Note 8 – Contrast enhancement (Non-core)

Contrast enhancement of intra-axial tumours 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 diffuse gliomas, contrast enhancement is commonly interpreted as a sign of increasing malignancy, but this correlation is far from complete. For example, pilocytic astrocytomas, gangliogliomas, and other tumours take up contrast, but are assigned to CNS WHO grade 1 and carry a favourable prognosis. Vice versa, lack of contrast-enhancement may occur in high-grade IDH-wildtype diffuse glioma/glioblastoma. Ring enhancement is commonly associated with extensive central necrosis and reflects a high grade of histological malignancy but is rarely 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[8]), but the additional consideration of T2 and FLAIR sequences has increasingly been implemented into response assessment.[9]

Back

Note 9 – Specimen dimensions (Core)

Intrinsic tumours grow diffusely within the brain and in many instances cannot be completely removed. Clinical factors (e.g., performance status), tumour location, and where relevant, intraoperative diagnosis, 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.

⬆ **Back**

Note 10 – Specimen description (Non-core)

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, for example, total number of glass slides, comprising number of haematoxylin and eosin and other slides (e.g., immunohistochemistry, smears, controls), as well as other materials (e.g., neuroimaging files).

⬆ **Back**

Note 11 – Adequacy of specimen for histological assessment (Non-core)

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, lipidised, 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.

Back

Note 12 – Adequacy of specimen for diagnostic purposes (Non-core)

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 adjacent to a tumour (gliosis with Rosenthal fibres next to a craniopharyngioma); and 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 some instances, small tissue size, tissue processing issues, or suboptimal targeting of biopsy materials may make molecular testing impossible. The pathologist should specify the limitations of the tissue in achieving optimal diagnosis.

Back

Note 13 – Histological appearance (Core)

This element is core if it is an essential component of the final (integrated) diagnosis. Histological features that are essential for diagnosing the tumour according to the WHO CNS5 Tumour Classification should be reported.

In nearly all pathology reports of CNS neoplasms, the diagnosis should ideally include one of the >100 tumour types listed in the WHO CNS5 Tumour Classification (see Table 1). [4,10] The information on haematolymphoid tumours in Table 2 is based on the WHO 5th edition classification of those tumours.[11] For many CNS tumours, the histological assessment should be combined with molecular (or surrogate immunohistochemical biomarker) testing for signature molecular alterations to reach an 'integrated diagnosis' (e.g., diffuse astrocytoma, IDH-mutant, CNS WHO grade 2; see ICCR dataset section on Integrated final diagnosis). For other tumour types, the final diagnosis can still be based on classical histopathology alone. In either approach (purely histological or integrated histological-molecular), 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.[12-14] As such, the strict application of WHO CNS5 diagnostic guidelines is required to enhance both accuracy and interobserver reproducibility across the globe.

For cases that, after adequate ancillary testing, do not neatly conform to a well-recognised tumour type (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., low grade neuroepithelial tumour with oligodendroglial-like histological features suggestive of dysembryoplastic neuroepithelial tumour; high grade glioneuronal neoplasm; poorly differentiated malignancy; etc.). Such cases should be designated 'not elsewhere classified' (NEC). And in a situation where the necessary ancillary testing could not be performed or was performed but was technically inconclusive, 'not otherwise specified' (NOS) can be added to the histological diagnosis.[6]

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.

A tentative or provisional grade may be assigned after histological evaluation alone, but in an increasing number of tumour types, molecular findings need to be integrated for a definitive, 'integrated' grade (see ICCR dataset section on Integrated final diagnosis - **Note 2 – TUMOUR GRADE**).

Table 1. World Health Organization classification and grade of central nervous system tumours.[4]

Descriptor	ICD-O codes[a]	CNS WHO Grade
Gliomas, glioneuronal tumours and neuronal tumours		
Adult-type diffuse gliomas		
Astrocytoma, IDH-mutant	9400/3, 9401/3, 9445/3	2, 3, or 4
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3, 9451/3	2 or 3
Glioblastoma, IDH-wildtype	9440/3	4
Paediatric-type diffuse low grade gliomas		
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	9421/1	1
Angiocentric glioma	9431/1	1
Polymorphous low grade neuroepithelial tumour of the young	9413/0	1
Diffuse low grade glioma, MAPK pathway-altered	9421/1	n/a
Paediatric-type diffuse high grade gliomas		
Diffuse midline glioma, H3 K27-altered	9385/3	4
Diffuse hemispheric glioma, H3 G34-mutant	9385/3	4
Diffuse paediatric-type high grade glioma, H3-wildtype and IDH-wildtype	9385/3	4
Infant-type hemispheric glioma	9385/3	n/a
Circumscribed astrocytic gliomas		
Pilocytic astrocytoma	9421/1	1
High grade astrocytoma with piloid features	9421/3	n/a
Pleomorphic xanthoastrocytoma	9424/3	2 or 3
Subependymal giant cell astrocytoma	9384/1	1
Chordoid glioma	9444/1	2
Astroblastoma, *MN1*-altered	9430/3	n/a
Glioneuronal and neuronal tumours		
Ganglioglioma	9505/1	1
Gangliocytoma	9492/0	1
Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma	9412/1	1
Dysembryoplastic neuroepithelial tumour	9413/0	1
Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters*		n/a
Papillary glioneuronal tumour	9509/1	1
Rosette-forming glioneuronal tumour	9509/1	1
Myxoid glioneuronal tumour	9509/1	1
Diffuse leptomeningeal glioneuronal tumour	9509/3	n/a
Multinodular and vacuolating neuronal tumour	9509/0	1
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0	1

Descriptor	ICD-O codes[a]	CNS WHO Grade
Central neurocytoma	9506/1	2
Extraventricular neurocytoma	9506/1	2
Cerebellar liponeurocytoma	9506/1	2
Ependymal tumours		
Supratentorial ependymoma	9391/3	2 or 3
Supratentorial ependymoma, *ZFTA* fusion-positive	9396/3	2 or 3†
Supratentorial ependymoma, *YAP1* fusion-positive	9396/3	n/a
Posterior fossa ependymoma	9391/3	2 or 3
Posterior fossa group A (PFA) ependymoma	9396/3	2 or 3†
Posterior fossa group B (PFB) ependymoma	9396/3	2 or 3†
Spinal ependymoma	9391/3	2 or 3†
Spinal ependymoma, *MYCN*-amplified	9396/3	n/a
Myxopapillary ependymoma	9394/1	2
Subependymoma	9383/1	1
Choroid plexus tumours		
Choroid plexus papilloma	9390/0	1
Atypical choroid plexus papilloma	9390/1	2
Choroid plexus carcinoma	9390/3	3
Embryonal tumours		
Medulloblastomas, molecularly defined		
Medulloblastoma, WNT-activated	9475/3	4†
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3	4
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3	4
Medulloblastoma, non-WNT/non-SHH	9477/3	n/a
Medulloblastomas, histologically defined		
Medulloblastomas, histologically defined	9470/3	n/a
Other CNS embryonal tumours		
Atypical teratoid/rhabdoid tumour	9508/3	4
Cribriform neuroepithelial tumour*		n/a
Embryonal tumour with multilayered rosettes	9478/3	4
CNS Neuroblastoma, *FOXR2*-activated	9500/3	4
CNS tumour with *BCOR* internal tandem duplication	9500/3	n/a
CNS Embryonal tumour NEC/NOS	9473/3	n/a
Pineal tumours		
Pineocytoma	9361/1	1
Pineal parenchymal tumour of intermediate differentiation	9362/3	2 or 3
Pineoblastoma	9362/3	4

Descriptor	ICD-O codes[a]	CNS WHO Grade
Papillary tumour of the pineal region	9395/3	2 or 3
Desmoplastic myxoid tumour of the pineal region, *SMARCB1*-mutant*		n/a
Cranial and paraspinal nerve tumours		
Schwannoma	9560/0	1
Neurofibroma	9540/0	1
Perineurioma	9571/0	1
Hybrid nerve sheath tumour	9563/0	n/a
Malignant melanotic nerve sheath tumour	9540/3	n/a
Malignant peripheral nerve sheath tumour	9540/3	n/a
Cauda equina neuroendocrine tumour (previously paraganglioma)	8693/3	1†
Meningioma		
Meningioma	9530/0	1, 2 or 3
Mesenchymal, non-meningothelial tumours involving the CNS		
Fibroblastic and myofibroblastic tumours		
Solitary fibrous tumour	8815/1	1, 2 or 3†
Vascular tumours		
Hemangiomas and vascular malformations	9121/0, 9131/0, 9123/0	n/a
Haemangioblastoma	9161/1	1
Skeletal muscle tumours		
Rhabdomyosarcoma	8910/3	n/a
Tumours of uncertain differentiation		
Intracranial mesenchymal tumour, FET::CREB fusion-positive		n/a
CIC-rearranged sarcoma	9367/3	4†
Primary intracranial sarcoma, *DICER1*-mutant	9480/3	n/a
Ewing sarcoma	9364/3	4†
Chondrogenic tumours		
Mesenchymal chondrosarcoma	9240/3	n/a
Chondrosarcoma	9220/3	1, 2 or 3†
Notochordal tumours		
Chordoma	9370/3	n/a
Melanocytic tumours		
Diffuse meningeal melanocytic neoplasms		
Meningeal melanocytosis	8728/0	n/a
Meningeal melanomatosis	8728/3	n/a
Circumscribed meningeal melanocytic neoplasms		
Meningeal melanocytoma	8728/1	n/a

Descriptor	ICD-O codes[a]	CNS WHO Grade
Meningeal melanoma	8720/3	n/a
Tumours of the sellar region		
Adamantinomatous craniopharyngioma	9351/1	1†
Papillary craniopharyngioma	9352/1	1†
Pituicytoma, granular cell tumour of the sellar region, and spindle cell oncocytoma	9432/1, 9582/0, 8290/0	n/a
Pituitary adenoma/pituitary neuroendocrine tumour	8272/3	n/a
Pituitary blastoma	8273/3	n/a

[a] These morphology codes are from the International Classification of Diseases for Oncology, Third Edition, second revision (ICD-O-3.2).[6] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, July 2024.[5]
CNS WHO grades marked 'n/a' do not have grade included in the tumour definition.
*Provisional entity.
† These CNS WHO grades are described in the chapter but not in the definition.

Table 2. World Health Organization classification of haematological tumours involving the central nervous system.[11]

Descriptor	ICD-O codes[a]
Lymphomas	
Lymphomas with predominant primary CNS presentation	
Primary large B-cell lymphoma of the CNS	9680/3
Lymphomas arising in immune deficiency/dysregulation	
Lymphomatoid granulomatosis	9766/1, 9766/3
Intravascular large B-cell lymphoma	9712/3
Extranodal NK/T-cell lymphoma	9712/3
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (EMZL) of the dura	9699/3
Lymphoplasmacytic lymphoma (Bing-Neel syndrome)	9671/3
Other rare lymphomas with predominant primary CNS presentation	
Other indolent B-cell lymphomas of the CNS	9690/3, 9823/3
Other aggressive B-cell lymphomas	9687/3
Peripheral T-cell lymphoma, NOS	9702/3
ALK-negative and ALK-positive anaplastic large cell lymphoma	9715/3, 9714/3
Histiocytic tumours	
Erdheim-Chester disease	9749/3
Rosai-Dorfman disease	9749/3
Juvenile xanthogranuloma	9749/1

Descriptor	ICD-O codes[a]
Langerhans cell histiocytosis	9751/1
Histiocytic sarcoma	9755/3
ALK-positive histiocytosis	9750/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, Third Edition, second revision (ICD-O-3.2).[15] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented.

⬆ Back

Note 14 – Invasion into surrounding tissue/structures (Non-core)

Most neuroepithelial tumours, particularly diffuse gliomas, demonstrate diffuse infiltration of tumour cells beyond grossly discernible 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, but may be observed also in some benign tumours such as pilocytic astrocytoma and ganglioglioma. These 'invasions' provide no prognostic significance beyond the given biological malignancy of each tumour. Direct invasion into adjacent structures such as dura and skull, is quite exceptional in gliomas.

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 still a criterion for atypical (CNS WHO grade 2) meningioma in the WHO CNS5 Tumour Classification,[16] 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.[16]

⬆ Back

Note 15 – Histological evidence of previous therapy (Non-core)

Previous therapy, including previous surgery, embolisation, chemotherapy, corticosteroid therapy and radiotherapy, may significantly alter the histological appearance of tissues and result in difficulties in tumour typing and grading.[17] Information on previous therapy is, however, not always available to the pathologist and the absence of histological evidence does not necessarily imply absence of previous therapy (see **Note 1 – CLINICAL INFORMATION**).

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, CNS WHO grades may not be readily assigned to the specimens after some previous 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 previous radiation

therapy, even if a clear clinical history of previous radiation has not been provided. A notoriously difficult situation is created by the pre-surgical application of high-dose corticosteroids in patients with intracerebral aggressive B-cell lymphoma as this treatment may result in complete vanishment of the neoplastic B-cells leaving only inflammatory and other reactive changes upon histology (corticoid-mitigated primary CNS lymphoma).

Back

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