The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for tumours of the central nervous system, including the pituitary gland (4th edition)

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Comments	This edition replaces the 3rd edition of the *Dataset for tumours of the central nervous system*, published in April 2011. In accordance with the College's pre-publication policy, this document was on The Royal College of Pathologists' website for consultation from 30 September to 30 October 2015. Eighteen items of feedback were received. Please email publishing@rcpath.org to see the responses and comments. **Dr Lorna Williamson** **Director of Publishing and Engagement**

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Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Each dataset contains **core data items** that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items. Other, **non-core, data items** are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The views of the following stakeholder organisations have been sought:

- British Neuropathological Society (www.bns.org.uk)
- Society of British Neurosurgeons (www.sbns.org.uk)
- British Neuro-Oncology Society (www.bnos.org.uk)
- Children's Cancer and Leukaemia Group (www.cclg.org.uk).

Recommendations in this dataset are based on: factors used in clinical management as reported in the literature; the WHO classification of *Tumours of the nervous system,*[9] and the NICE guidelines, *Improving outcomes for people with brain and other CNS tumours.*[5]

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Working Group on Cancer Services and was on the College website for consultation with the membership from 30 September to 30 October 2015. All comments received from the Working Group and membership were addressed by the author, to the satisfaction of the Chair of the Working Group and the Director of Publishing and Engagement.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness Department and are available on request.

1 Introduction

1.1 Importance and clinical application of the dataset

1.1.1 Scope

Central nervous system (CNS) tumours have an estimated one-year prevalence of around 2,500 in the UK,[1] although there is evidence to indicate significant under-registration of CNS tumours, particularly for low-grade ('benign') entities in females and children.[1–4] CNS tumours have a high morbidity and mortality, and are the second most common form of cancer in children.[1,2] The intra-axial tumours of the CNS include those arising in the brain and spinal cord. However, extra-axial tumours, arising from the coverings of the brain and spinal cord, present with similar clinical symptoms to intra-axial tumours due to their impingement on the CNS. Pituitary tumours also arise in close proximity to the brain and may impinge upon diencephalic structures and cranial nerves. CNS intra-axial, extra-axial and pituitary tumours are dealt with by neurosurgeons within specialist neuroscience centres; their pathology is generally dealt with by neuropathologists and they are included in the National Institute of Health and Clinical Excellence (NICE) guidance, *Improving outcomes for people with brain and other CNS tumours.*[5] They therefore fall within the scope of CNS tumours for the purposes of this document.

Although the terms 'benign' and 'malignant' are sometimes used with reference to CNS tumours, this distinction is less clear than it is for tumours arising outside the CNS. Many CNS tumours, even the most malignant, while they may metastasise along CSF pathways, rarely metastasise outside the CNS. However, invasion occurs in most intra-axial tumours, regardless of tumour grade. This may preclude complete surgical resection so that, even for tumours at the 'benign' end of the biological spectrum, there may be local tumour recurrence, requiring further surgery and/or neuro-oncological treatment. Furthermore, slowly growing entities may undergo transformation into more aggressive tumours. The terms 'low grade' and 'high grade', representing WHO histological grades I–II and III–IV respectively (see below), are sometimes used as general descriptive terms and are more appropriate than 'benign' and 'malignant'. It is important to remember that there are marked biological and prognostic differences between the individual grades within these two groups. It should be noted that some highgrade lesions may, with adequate treatment, have a good prognosis. In contrast, even the most indolent lesions may cause severe impairment or death from their local effects within the confined bony surrounds of the skull. Low-grade tumours are included in the NICE guidance[5], and are therefore included within the scope of this dataset.

1.1.2 Purpose of the guidelines

These guidelines are intended to assist pathologists in the provision of the core data that should be included in the histopathological diagnostic reports of CNS tumours, and to suggest additional data items that may be usefully included for certain categories of tumours.

Accurate and standardised histopathological data in diagnostic reports of CNS tumours are important for the following reasons:

- standardised classification and grading of tumours, according to a recognised system, are necessary for the planning of appropriate treatment for the patient
- provision of appropriate histopathological data allows an assessment of prognosis
- consistency of histopathology reporting is important in communication between cancer centres
- monitoring of treatment and outcomes and in clinical audit
- provision of data for epidemiological studies, for monitoring of disease patterns and trends, and for determination of changing outcomes and survival

- allowing appropriate stratification of patients for entry into clinical trials and enabling meaningful comparison between biological research studies
- provision of accurate data for the NHS cancer data collection initiatives (being developed though the National Cancer Intelligence Network)[6] and for cancer registries.

1.1.3 Who reports CNS tumours?

CNS tumours are most commonly reported in specialist centres by neuropathologists. For the purposes of reporting CNS tumours, the NICE *Improving Outcomes* guidance defines a neuropathologist as "an accredited pathologist who is registered as a neuropathologist or histopathologist, has specialist expertise in neuro-oncology, and takes part in the national External Quality Assurance (EQA) scheme for neuropathology organised by the British Neuropathological Society".[5] NICE guidelines also emphasise the central role of the MDT meeting in the management of CNS tumours. Pathologists reporting CNS tumours should attend these meetings and participate in the relevant EQA scheme.

1.2 Site-specific issues in relation to CNS tumours

1.2.1 Intra-axial tumours

The staging of tumours and assessment of resection margins, essential information for many tumour types, are in general not applicable to CNS tumours and have therefore not been included in other published protocols. Generally, CNS tumour specimens are received in a fragmented state, precluding any systematic assessment of the margins. CNS tumours generally grow through local expansion with varying degrees of infiltration or invasion. Metastasis within the CNS may occur but extracranial metastases are very rare and spread to lymph nodes is extremely uncommon. Staging of specimens of CNS tumours is therefore not possible using the types of histopathological approaches employed for non-CNS tumours, and the current TNM classification does not include a staging scheme for CNS tumours.[7] CNS tumours can, however, be staged by other criteria. For example, evidence of cerebrospinal fluid dissemination, identified by neuroradiology or CSF cytology, is important in the staging of medulloblastoma.[8]

For lobectomy specimens, assessment of apparent involvement of margins by tumour may be possible. However, most intra-axial tumours, particularly gliomas, demonstrate a diffuse pattern of infiltration that effectively precludes total surgical resection.[9, 10] Infiltrating tumour cells are present in apparently normal brain tissue surrounding these lesions, from which recurrences may arise. This applies to both low- and high-grade diffuse gliomas and therefore a statement that resection margins are free of tumour is inappropriate for these types of tumour. Assessment of resection margins, therefore, has not been included as a field for the core dataset for intra-axial CNS tumours.

The extent of tumour resection is of predictive value for many CNS tumours.[11–14] It is of value to record an approximate aggregate size of tumour removed as an indicator of the sample on which the diagnosis has been based. It should be noted, though, that not all of the resected tumour may reach the pathology department, especially with the use of neurosurgical techniques such as ultrasonic aspiration. The pathological estimate of resected tumour volume may therefore underestimate the true extent of resection in many cases, and neurosurgical/neuroradiological data give a more accurate assessment of tumour volume. Routine collection of aspirate has been recommended to improve diagnostic accuracy.[15]

The histopathological report on a CNS intra-axial tumour may document patterns of spread, particularly across tissue boundaries, if the specimen allows such assessment (e.g. across the pia mater and into the subarachnoid space). Assessment of multifocality is generally not possible in most CNS tumour specimens. Thus, whilst inclusion of these items in the report may be useful, they have not been included as core items in the histopathological dataset.

1.2.2 Extra-axial tumours

For many extra-axial tumours, histological assessment of resection margins is also impossible in fragmented specimens, although it may be commented on for specimens submitted intact. Meningiomas have the capacity to invade the underlying brain, and to infiltrate into the skull and scalp. These latter patterns of growth may make a complete surgical resection impossible. Brain invasion is of prognostic significance and is associated with a higher risk of tumour recurrence (similar to that for atypical meningiomas).[16] For this reason, histological assessment of the brain/tumour interface for brain invasion is required for meningiomas whenever possible; it cannot be performed in all cases since the interface may not be present in the submitted specimen (see below).

For pituitary tumours, invasion of surrounding structures (particularly the dura mater) is associated with a higher risk of tumour recurrence and should be commented upon whenever possible, although it is recognised that the dura mater and other surrounding structures are not always submitted for histological examination.[17, 18]

For these reasons, it is desirable to comment upon brain invasion in meningiomas and local invasion in pituitary tumours whenever possible in histopathological reports. Because brain invasion affects meningioma grading, independently of atypical features, this is included as a core data item for extra-axial tumours (although it is acknowledged that this cannot always be assessed) and there are fields for documenting anatomical spread as non-core items.

It should be emphasised that there is a need for an adequate amount of tissue to be submitted to neuropathology if a reliable diagnosis, based on representative material, is to be made. Adequate samples are also essential if tissue is to be available for molecular investigations. This may be a particular problem with increasingly small biopsies obtained stereotactically or endoscopically. If a specimen is felt to be inadequate for reliable evaluation, this should be clearly stated in the body of the neuropathology report. Discussion of cases at the MDT meeting provides a further opportunity for evaluation of specimen adequacy (see section 5.3).

1.3 Methods used for developing a dataset

Recommendations in this dataset are based on: factors used in clinical management as reported in the literature; the WHO classification of *Tumours of the Nervous System* [9] and the NICE guidelines, *Improving Outcomes for People with Brain and Other CNS Tumours.*[5]

1.4 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and the National Cancer Intelligence Network. Standardised cancer reporting and MDT working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers, epidemiologists, and facilitates international benchmarking and research.

2 Clinical information required on the specimen request form

Clinical details, as provided by the submitting clinician on the request form, should be recorded on the pathology report.[19, 20] Clinical history is very valuable, and adequate history is essential to ensure proper interpretation of the histological findings. Some of these have been included as non-core items in the dataset to aid data recording.

Relevant clinical information may include:

- type of specimen/procedure – biopsy (stereotactic or open) or resection
- if multiple specimens are submitted representing different areas, this should be recorded.
- previous relevant diagnoses, biopsies or therapies should be noted. Radiotherapy, radiosurgical interventions and systemic or locally placed chemotherapy may considerably modify appearances, and for gliomas present difficulties in the interpretation of the histology findings and assignment of grade. Pre-operative embolisation of meningiomas may produce necrosis and increased proliferation[21] that may inappropriately affect tumour grading if this information is not known.
- site of the tumour and neuroradiological findings. Because of the nature of most neurosurgical specimens, the neuropathologist does not often have the benefit of a good appreciation of the macroscopic appearances of a lesion. Neuroradiological findings thus provide information helpful in diagnosis and provide an alert to discrepant diagnoses; for example, the presence of radiological contrast enhancement in a low-grade diffuse glioma. Access to local electronic (PACS) systems can provide useful additional information, including an impression of the location of the lesion.
- duration and nature of symptoms

3 Preparation of specimens before dissection

- In many centres, specimens are received in fixative (usually 10% neutral buffered formalin) and should be in an adequately sized specimen pot. Depending on the size of the specimen up to 24 hours fixation may be required before dissection. However, there are advantages to specimens being received in a fresh state (see points below), which requires good communication between theatre and laboratory to ensure that the specimen can be dealt with promptly.
- Submission of a fresh specimen is necessary in cases for which intra-operative diagnosis is requested (see section 8). Residual tissue should be fixed for conventional paraffin sections.
- In cases where it is likely that molecular genetic analysis may be useful, the specimen should be received freshly so that a frozen sample of tumour, and sometimes non-tumour tissue, can be frozen for nucleic acid extraction.
- Frozen tissue may be required for molecular genetic or other analyses for some clinical trials. To ensure stability, this should be at a temperature of –70°C or colder.
- In appropriate cases where it is suspected that ultrastructural examination of the specimen is likely to be required, a small sample of the tumour should be placed in glutaraldehyde.
- Some very large or encapsulated specimens may benefit from incision or slicing prior to dissection to allow adequate penetration of fixative.
- Bony and heavily calcified specimens may need to be placed in a decalcifying solution following fixation prior to dissection. An attempt should be made to remove some softer tissue pieces for histology and special studies (as described below) prior to decalcification.

Where possible, frozen material should be archived and the availability of frozen tissue recorded, as it may allow future molecular genetic studies for diagnostic or research/clinical trials purposes, subject to appropriate ethical constraints, consents and governance mechanisms. In addition to local research initiatives, this will become more important with time as national initiatives for adult and paediatric brain tumours continue to develop (e.g., Children's Cancer and Leukaemia Group, National Cancer Research Institute).[22, 23]

Systemic banking can be an important contributor to national resources.

For an increasing range of tumours (see below), conventional histology may be supplemented by molecular genetic or cytogenetic analyses. Fresh frozen tissue (–70°C or colder) may be of value for molecular and cytogenetic studies. In some centres, smear or imprint preparations, fixed in, for example, ethanol, may be prepared for interphase cytogenetic analysis using fluorescence *in situ* hybridisation (FISH). Increasingly, however, many molecular genetic and FISH techniques can be applied to paraffin embedded tissue.

4 Specimen handling and block dissection

4.1 General comments

There is a limited evidence base for the handling of specimens from CNS tumours, although there are some published guidelines.[19, 20]

- The specimen should be measured in 3 dimensions, or weighed. In many cases, specimens will be in the form of multiple fragments, and an aggregate measurement should be taken.
- The specimen should be described fully, including the following features: recognisable anatomical structures; colour, consistency and dimensions of the tumour; distance of tumour from resection margins; the presence of calcification, necrosis, haemorrhage or cystic change.

4.2 Biopsies

- These should usually be embedded in their entirety for processing.
- Levels (step sections) should be considered to increase the sampling (with retention of intervening sections for immunohistochemistry and/or molecular-genetic techniques).
- Surgical ultrasonic aspirates (e.g. CUSA) may provide information in some cases, and may be particularly useful if the biopsy is otherwise small. Even where cytology and architecture are poorly preserved, the material may be suitable for immunohistochemistry. If available, the aspirate should be embedded for histology, or processed to a clot or cytology preparation, depending on its consistency.

4.3 Intra-axial tumour resections, including lobectomy specimens

Resection specimens may be received as intact lobectomy specimens or as fragmented specimens removed piecemeal. For diffuse gliomas, complete resection is, with only rare exceptions, precluded because of the infiltrative nature of the lesion, and a resection is therefore subtotal.

- Where possible the specimen should be orientated and any anatomical structures identified.
- Lobectomy specimens may be sliced at approximately 5 mm intervals, generally perpendicular to the long axis of the specimen and through the pial surface.
- The tumour should be described with particular attention to foci of necrosis, which may be of prognostic significance. Gross extension of tumour into leptomeninges or to resection margins should be noted.
- In a number of studies, the extent of resection has been shown to be a prognostic factor.[11, 24, 25] Neuroradiological assessment from post-operative imaging/computer-assisted volumetric studies is a better measure of this than pathological measures. Nevertheless, pathological assessment of tumour volume removed provides some

indication of the extent of excision and so an approximate measurement of tumour size in three dimensions should be given.

- Photography may occasionally be helpful in selected cases to confirm the orientation of the specimen with the neurosurgeon and to demonstrate the tumour extent at MDT meetings.
- Whilst it may be good practice to describe tumour extent and distance from the edge of the specimen where possible, assessment of margins by pathology is not of prognostic/diagnostic relevance, and assessment of extent of resection is generally by post-operative neuroimaging. For resections received as fragments of tumour, the assessment of margins is precluded. In lobectomy specimens, assessment of margins may be possible. However, for diffuse gliomas (both low- and high-grade), because of their infiltrative behaviour,[10] histological evaluation of resection margins is not meaningful. Furthermore, the margin of the lobectomy may not be a true margin, because of ultrasonic aspiration (CUSA) of the tumour bed. Resection margins therefore do not require formal assessment.[19]
- Although evidence-based guidelines are not available, it would seem reasonable to conclude that the presence of heterogeneity within tumours requires that multiple blocks should be taken to allow for adequate sampling. The entire specimen should be blocked out on serial faces, unless the tissue is very large in which case enough blocks must be taken to avoid a sampling error**,** although evidence-based guidelines for the number of blocks to be taken are not available.
- Similar principles of thorough sampling apply to piecemeal resections. Embedding of surgical aspirates help to reduce sampling bias and can change grading[15] but due to the nature of this material, contains a variety of tissues, including normal or infiltrated CNS, and thus can generate valuable tissue for future studies, including control sections for antibody tests.
- In some cases, gliomas may involve multiple lobes or may be multifocal, and this information from neuroimaging and the request form should be recorded. The resection specimen or biopsy may, however, include only one lesion. If both are submitted in a specimen, histology blocks should be made from both, to allow a separate histological assessment of these areas and to ensure that the area of highest histological grade is represented.

4.4 Extra-axial tumours

The most common tumour at this site is the meningioma, but a range of tumour types may occur. As for intra-axial tumours, specimens are often resected piecemeal, making assessment of anatomical extent and margins difficult, and the approach below will need to be modified according to the limits imposed by the specimen type. This discussion focuses on meningioma, but similar issues related to infiltration of local structures, apply to other extra-axial tumour types.

- The tumour should be orientated and measured together with the distance to the nearest radial dural resection margin.
- The tumour should be sampled generously; although there is no strict evidence base for sampling, many neuropathologists use one block per centimetre diameter of tumour and this seems a reasonable, pragmatic approach to ensure that any higher grade areas are not missed.
- Blocks for histology should include not only tumour, but also samples from the brain interface (generally the smooth surface), dura and radial margin. In the case of meningiomas, the cortical interface should be sampled as brain invasion, defined as a breach of the pial barrier, is a prognostic factor.[16]

- If bone and other samples from adjacent anatomical structures accompany the specimen, these should be separately described and sampled (decalcification may be required). In the case of meningiomas, infiltration through the dura, into skull and into extra-cranial tissues occurs with tumour of all histological grades. Thus, even a grade I tumour may show this biological behaviour and this form of invasion is not considered to be indicative of malignancy. It is also not considered to be a prognostic factor in the WHO scheme. However, particularly in the skull base, it may make surgical resection more difficult and affect recurrence. Therefore invasion of extra-dural structures should be included in the report where this can be assessed.
- Sampling for electron microscopy and frozen tissue for molecular genetics should be considered whenever the presentation is unusual and the clinical differential diagnosis wide. It may aid classification in difficult cases.
- This is particularly so in children, as the differential diagnosis may include soft tissue tumours, where sampling for genetics may be necessary.
- Resection margins are often difficult to assess in specimens of extra-axial tumours and it is usually not possible to comment on the completeness of surgical resection using histological methods. Rather, this is assessed using radiological methods. This is therefore not included as a core data item, but under some circumstances it may be possible to comment on margins, or a comment on a specific margin may be requested by the surgeon. Sampling of margins should therefore be carried out where this is possible.

4.5 Pituitary tumours

In most cases, these lesions are small and the entire lesion should be blocked for histology. A small portion may be fixed in glutaraldehyde if electron microscopy is thought likely to be required. Pituitary adenomas may show local invasion and carcinomas, by definition, may show discontinuous spread. If specimens are submitted from areas suspected of being infiltrated, these should be blocked separately to allow comment on infiltration.

4.6 Section staining and use of levels

Haematoxylin and eosin stained sections are adequate for a first assessment of tumour. Levels (step sections) should be obtained as required. Immunohistochemical investigations are increasingly used for tumour classification and prognostic information and special (tinctorial) stains may be required in certain circumstances. For small biopsies in particular, all spare unstained sections between levels should be kept. This is particularly important when diagnostic features are present only on one or two levels and where additional tests, either immunohistochemical or molecular, may be indicated. In cases where diagnostic material does not remain in the block, it is best practice to retain all spare unstained sections in the file for future additional diagnostic requests if required.

5 Core data items

5.1 Summary of core data items

The dataset for brain tumours is summarised in the proforma, but these data may also be provided in the form of a conventional free-text report. Proforma reporting will assist in future data collection strategies, but it is also important to retain free-text comment. The collection of itemised data is mandated as part of the Cancer Outcomes and Services Dataset (COSD) from January 2016.

Separate proformas are provided for:

- intra-axial CNS tumours
- extra-axial CNS tumours
- pituitary tumours.

5.1.1 Clinical

- Anatomical location of the lesion.
- Type of operative procedure.

5.1.2 Pathological

Macroscopic items

- Estimate tumour size in three dimensions or the volume of tumour tissue if submitted piecemeal, or provide the tumour weight.

Microscopic items

- Tumour type.
- Tumour sub-type when relevant.
- Tumour grade (WHO 2007).

  [Evidence level A–D – Tumour type, sub-type and WHO grade are important prognostic indicators. The evidence level varies from A to D depending on the tumour type. The WHO grading of astrocytomas has been reproduced in multiple large studies, whilst for other entities, definitions are based on case reports or small series].

- For extra-axial tumours (particularly meningiomas) – presence of brain invasion.

  [Evidence level B – The presence of brain invasion is an adverse prognostic indicator for extra-axial tumours. The stated evidence level relates to meningiomas, for other tumour types there is less evidence available due to smaller cohorts].

Molecular genetic results (where performed) and testing method used

5.2 Notes on core dataset items

5.2.1 Histological classification (tumour type, tumour sub-type and tumour grade)

Primary tumours of the nervous system are classified and graded according to the WHO grading scheme.[9] The scheme is used in all neuropathology centres in the UK and its classification and grading schemes for tumours are endorsed by the British Neuropathology Society and by its National EQA scheme. The WHO scheme is also widely used internationally, allowing comparison of data from European and North American centres. This provides a uniform system of nomenclature, essential for comparative studies and multicentre trials.[26] The latest, 2007, edition of the WHO scheme should be the basis of classification and grading.[9] Since this edition, a number of new entities have been described and accepted in current authoritative textbooks. A new edition of the scheme is currently in preparation by an international panel of experts and is likely to be published in 2016. In addition to new entities, this will reflect progress in the inclusion of molecular genetic information.

Haematoxylin and eosin stained sections have been the cornerstone of pathological evaluation of tumours, supplemented as required by special stains and by an increasingly powerful range of immunohistochemical stains for diagnostic and/or prognostic biomarkers. Various molecular analyses are likely to be required for some definitive diagnoses in the near future. Thus, the use of immunohistochemistry and molecular-genetic techniques should always be subject to appropriate internal and external quality controls. This should involve the use of appropriate

controls for all techniques and the laboratory should be a participant in the appropriate UKNEQAS schemes.[27]

The WHO classification also includes a widely accepted, but more recently challenged, scheme for tumour grading (Table 1), which has largely replaced older schemes such as Ringertz, Kernohan and St Anne Mayo.[9] The scheme is somewhat unlike other histology-based grading schemes for other organ systems, in that it was originally devised as a malignancy scale covering a wide variety of intracranial neoplasms in the context of no, or limited, effective therapy. The scheme is widely accepted by neuropathologists, neuro-oncologists and neurosurgeons, and WHO grading is required as part of the BNS EQA scheme. WHO grading therefore forms a core dataset item for primary CNS tumours. WHO grading is a four-point scheme for which the astrocytomas are the prototypic group. The scheme is applied to other CNS tumours, intra and extra-axial, in comparison to this group.

Table 1: Simplified table illustrating the structure of the current WHO scheme applied to the common astrocytomas.

Illustrative histological features are included, but it should be noted that appearances can be varied and complex. For example, it should also be noted that necrosis and vascular proliferation can be seen within the entity of grade 1 pilocytic astrocytoma, and that, rarely, pilocytic astrocytoma can be malignant. Diagnostic textbooks should be consulted for the range of histologically features that can be present.

WHO grade	Histological designation	Histological features
I	Pilocytic astrocytoma	Circumscribed tumour entity with bipolar astrocytic cells in a biphasic solid/cystic pattern
II	Diffuse astrocytoma	Diffusely infiltrating astrocytic cells with pleomorphism allowed
III	Anaplastic astrocytoma	As diffuse astrocytoma + mitotic activity
IV	Glioblastoma	As anaplastic astrocytoma + vascular proliferation +/or necrosis

In the WHO scheme grade I is applied to distinct tumour entities such as pilocytic astrocytoma. The diffuse astrocytomas form a distinct clinical and biological group. For these, there is spectrum of malignancy so that the scheme represents a true grading scheme, with grades II to IV representing increasing biological aggression with associated poorer prognosis. Within the astrocytomas, distinction of grade IV (glioblastoma) from grade III (anaplastic astrocytoma) is usually straightforward, if representative samples have been taken, because it is based on the assessment of qualitative criteria, namely vascular proliferation and necrosis. Distinction of grade III from grade II astrocytomas is based on mitotic activity and may be problematic in some cases. In the St Anne/Mayo system, the presence of a single mitosis was sufficient, but there may be a difference between a small biopsy and a larger resection, where a diligent search of many fields may raise the probability of finding a mitosis. In the latter context, the presence of an isolated mitosis does not predict worse behaviour.[28]

Therefore in the WHO scheme, a single mitosis is no longer an absolute criterion for the distinction of grade II from grade III astrocytoma.[29] There can be difficulty in inter-pathologist recognition of histological features used as grading criteria.[30] The assessment of borderline tumours for prognostic and therapeutic purposes may also be aided by discussion in an MDT meeting, where additional clinical and radiological factors such as patient age, tumour size, the presence of contrast enhancement and rate of growth and serial scans provide additional

information. In grade II astrocytomas, for example, factors such as patient age, pre-operative neurological deficits, tumour diameter and tumour crossing the midline can help to identify lower and higher risk groups.[31] Combining neuroradiological findings with pathological and genetic findings may further refine the diagnosis for treatment purposes.[32] WHO grade may therefore form one, albeit important, component of an integrated prognostic assessment.

Whilst forming a true grading scheme for the astrocytomas and some other groups, for some tumour types it is in essence a statement of degree of malignancy,[29] as these tumour types have only one histological grade (e.g. medulloblastomas are all WHO grade IV). Nevertheless, it is recommended that the WHO grade be given as well as the diagnosis for all primary CNS tumours where the WHO scheme has assigned a grade, to avoid confusion among neurosurgeons and oncologists. This reflects practice in the BNS EQA scheme, and is also one of the requirements of the Quality Performance Indicators for CNS tumours in Scotland.[33] The current scheme provides better grading criteria for meningiomas, based on careful histological study in a large patient series,[16, 34] which clarified the prognostic significance of brain invasion. Brain invasive meningiomas that have either histologically benign or atypical features have similar recurrence and mortality rates to atypical meningiomas and so meningiomas with brain invasion are designated grade II in the WHO scheme. Although retrospective, this has resulted in more clearly defined criteria for grading, including the introduction of mitotic rate cut-offs for the diagnosis of atypical and malignant meningiomas. Inclusion of mitotic counts has increased objectivity, although some of the criteria remain subjective. In comparison to the older grading method, application of the new scheme appears in practice to result in the diagnosis of a higher proportion of meningiomas as atypical.[35]

Lymphomas may occur as primary tumours, localised to the CNS at presentation, or manifest in the CNS as part of a systemic lymphoma. Guidance on lymphoma reporting is available in The Royal College of Pathologist's *Dataset for the pathological reporting of lymphoma* (https://www.rcpath.org/profession/publications/cancer-datasets.html).

Pituitary tumours are usually localised to the pituitary fossa, but may show suprasellar extension of invasion of adjacent structures. Tumour extent may be available from clinical information, and should be recorded if known to the pathologist, but assessment of tumour extent and invasion are generally not possible from the surgical specimen. Pituitary tumours are classified according to cell type, based on hormone production within the tumour cells, rather than tinctorial properties although reticulin is recommended to aid distinction between normal pituitary, hyperplasia and adenoma. Hormonal type is generally determined by immunohistochemistry to the conventional adenohypophysial hormones (ACTH, LH, FSH, alpha-subunit, TSH, prolactin, growth hormone), though in some cases ultrastructural examination may aid classification; for example the differential diagnosis of adenomas showing growth hormone and prolactin positivity, where it may aid in the recognition of the more aggressive acidophil stem cell variant. Histological prognostic factors are poorly defined for pituitary tumours. Retrospective studies have shown that the Ki-67 proliferation labelling index increases progressively in invasive adenomas and pituitary carcinomas, but cut-off levels and methodology for assessment are not defined. Although not clearly defined, atypical adenomas can show invasive growth, high mitotic index, Ki-67 >3% and extensive nuclear p53 reactivity.[17, 36]

5.2.2 Role of the multidisciplinary team meeting

Cases of CNS neoplasia should be discussed in the context of the MDT meeting, which is regarded in the NICE guidelines as central to patient management.[5] In the context of the pathology dataset, discussion in this forum allows review of the biopsy with clinical and neuroradiological information. This may be of particular value in the assessment of small biopsies to ensure that the tissue is likely to be representative of the lesion. Thus the clinical, surgical, pathological and radiological findings can be compared and integrated for clinical management purposes. The MDT also allows clear communication of the pathological diagnosis, including diagnostic subtleties and uncertainties, to the treating clinicians. In some cases, a final neuropathological report may need to be revised to reinterpret the histological

findings in the light of additional information. However, in general, the data in the pathology dataset should be derived from the pathological findings in the tissue sample.

5.2.3 Date and coding

The final report should include a date of report and SNOMED codes for statistical purposes.

5.2.4 Additional prognostic and predictive factors

Proliferation markers

In general, evaluation of prognostic and predictive factors by immunohistochemistry is poorly validated for CNS tumours and does not form a core dataset item. The use of proliferation markers, such as Ki-67, is widespread in diagnostic practice and gives a useful impression of proliferative potential, particularly in a small biopsy. Ki-67 labelling indices (mostly using the MIB-1 antibody) have been demonstrated to have prognostic value in a number of tumour types, including gliomas and meningiomas.[28, 37–39] The relative rate of proliferation, as assessed by visual inspection, may be of particular use in the assessment of borderline tumours, and in identifying areas in which mitotic figures, which are validated prognostic factors, should be sought. However, in most cases there is little evidence that assessment of Ki-67 adds independent value to the standard pathological assessment. There are also issues related to tumour heterogeneity, sampling and variation in methodology, which may affect standardisation of the determination of tumour labelling index between centres.[40] Reproducible cut-off values for diagnostic categories have also not been established. Therefore, although a valuable technique at the discretion of the pathologist, the inclusion of a Ki-67 labelling index count in the core dataset is not warranted.

Molecular and cytogenetic biomarkers

Cytogenetic and molecular genetic analyses of tumours have made considerable inroads into an improved understanding of the pathogenesis of brain tumours, contributing towards better classification of brain tumours. A wide range of putative molecular markers has been, and continues to be, published. It is not the purpose of these guidelines to review these comprehensively, but mention is made here of markers for which there is good evidence of diagnostic, prognostic or predictive utility, and which are now being widely used in diagnostic practice. It should be noted that, in the current classification, the primary histological classification should be based on the histological findings, but molecular findings may provide important additional information for an increasing range of tumour types. New consensus guidelines also suggest a move towards more integrated reporting of histopathological and molecular genetic findings, where the molecular findings are integral to the final diagnostic formulation.[41] It remains to be seen how this will be incorporated into the forthcoming WHO classification, but it seems likely that molecular markers will become central to diagnostic workup and therefore become part of standard good practice. Molecular analysis of key markers may also be prerequisite for entry of patients into some trials. Consequently a field for molecular or cytogenetic findings is included in the core data items where such investigation has been conducted, so that a final integrated histological and molecular diagnosis is given where appropriate.

Application of molecular markers in adult diffuse gliomas

Evidence is emerging for the utility of several molecular biomarkers from clinical trials in the field of gliomas. Critical reviews suggest variable levels of robustness for analytical and clinical performance as biomarkers,[42] but they are now increasingly available and likely to become more widely integrated into diagnostic practice.[41]

i. It has been previously reported that approximately two thirds of classical oligo-dendrogliomas show loss of 1p and 19q chromosomal arms. This may be demonstrated by a number of techniques, including FISH, polymerase chain reaction (PCR)-based methods, conventional and array comparative genomic hybridisation, and Illumina 450k

methylation arrays.[43–45] Large trials have confirmed that 1p,19q co-deletion identifies a subgroup of oligodendrogliomas with better prognosis that appear to be less biologically aggressive.[46, 47] Thus, demonstration of 1p, 19q co-deletion provides additional information to classical histopathological analyses and these combined features are useful diagnostically and in predicting outcomes.[48, 49] Indeed some authors now suggest that oligodendroglioma is best defined by the combination of 1p, 19q co-deletion together with an *IDH1* or *IDH2* mutation (see below).[50]

ii. Mutations of the isocitrate dehydrogenase 1 gene, *IDH1*, and the related *IDH2* are found in a clinically and genetically distinct subset of gliomas, in particular astrocytomas and oligodendrogliomas (both WHO grades II and III) and the 'secondary' glioblastomas that evolve from lower grade astrocytomas. Patients with mutations in these genes have a better outcome than those without mutations. The mutations are confined to the codons for single amino acids in the respective genes, simplifying detection. The commonest *IDH1* mutation (*IDH1-R132H)* is also detectable by immunohistochemistry of the mutant protein. The antibody is of particular diagnostic value as it confirms the presence of this common *IDH1* mutation that is specific to tumour cells,[51–54] and recent evidence-based evaluation of analytical performance, clinical performance and utility, indicates that IDH1 immunohistochemistry can be recommended for routine clinical practice.[42] *IDH* sequencing may be of use in immuno-negative cases,[55] in particular in astrocytic or oligodendroglial tumours. IDH1 immunocytochemistry may also be of value in confirming the unequivocal presence of tumour cells in biopsies of diffuse astrocytic or oligodendroglial tumours, where solid tumour is not present.

iii. Mutations of the *ATRX* gene are present at high frequency in diffuse astrocytomas (and in Histone H3 mutant gliomas of young adults), but are very rare in primary glioblastoma and oligodendroglial tumours. Mutation results in a truncated product with loss of expression, detection of which immunohistochemically may be valuable in distinguishing oligodendrogliomas from astrocytomas.[50, 56]

iv. Combined analysis of 1p/19q, *IDH*-mutation and ATRX loss is of value in the assessment of diffuse gliomas and in their differential diagnosis (in adults; this is not relevant to children's tumours). Current consensus guidelines are suggesting that these markers can be incorporated into an integrated histological/molecular diagnosis,[41] and may be particularly of help in the final histotype classification of gliomas with ambiguous histology, and in determining whether oligoastrocytomas are best regarded as oligodendroglial or astrocytic in terms of behaviour.[50, 57] It remains to be seen how this shift from primarily morphological definitions of oligodendroglial and astrocytic tumours is to be reflected in the recommendations of the upcoming WHO classification. However, testing for 1p,19q, IDH1 and ATRX status is becoming widely available in the UK, and is becoming a standard of care in the histopathological analysis and differential diagnosis of oligodendrogliomas and astrocytomas.

v. O6 methylguanine-DNA methyl transferase (MGMT) is a DNA repair enzyme that can repair the damage induced by chemotherapeutic alkylating agents, leading to chemoresistance. Epigenetic silencing of the MGMT gene by promoter methylation plays an important role in regulating MGMT expression in gliomas. MGMT promoter methylation has shown value as a predictive marker for temozolamide sensitivity in recent trials. Promoter methylation correlates with better progression free and overall survival in glioblastoma. In anaplastic tumours, MGMT status is a prognostic factor but is not predictive for outcome to combination chemotherapy.[58] Current methods of immunohistochemical evaluation of MGMT protein expression are not reliable, so methylation analysis is required. However, the optimal method to carry out this analysis and interpret the results has yet to be agreed.[59–62]

Application of markers in paediatric tumours

i. The *KIAA1549-BRAF* fusion gene occurs in over 70% of pilocytic astrocytomas and is emerging as a diagnostic marker and a therapeutic target. This can be identified by interphase FISH or by RT-PCR from frozen or FFPE tumour tissue.[63, 64] The identification

of this genetic aberration may help differentiate other tumour forms from pilocytic tumours in difficult cases. In negative cases, other *BRAF* fusion genes, a V600E *BRAF* mutation or other mutations of MAPK pathway genes may be present.[65]

ii. *Medulloblastomas*. Subclassification of medulloblastoma is of increasing importance for stratification into low, standard and high-risk groups for tailored treatment. Morphological identification of desmoplastic and large cell/anaplastic subtyping is now important. In particular, diagnosis of large cell or anaplastic subtyping leads to more aggressive treatment regimes. Similarly, identification of *MYC* or *MYCN* amplification (usually by FISH) is associated with a worse prognosis and patients are offered more aggressive treatment. In addition, several studies have identified molecular subtypes of medulloblastoma. The current consensus is to recognise 4 subtypes: WNT, SHH, Group 3 and Group 4.[66] Importantly children (but possibly not adults) with WNT subgroup have a very good prognosis and can be identified by nuclear reactivity β-catenin and/or mutations in the β-catenin gene (*CTNNB1*). In some laboratories WNT tumours are confirmed by monosomy for chromosome 6.[67–69]

iii. *Atypical rhabdoid/teratoid tumour (ATRT).* These are malignant tumours, usually arising in young children and almost always caused by mutations affecting the *SMARCB1* (*INI1*) gene, which can be demonstrated by the loss of INI1 immunoreactivity.[70] The presence of retained staining in non-tumour cells (endothelial cells and inflammatory cells) provides an important internal control. Rare cases are caused by mutations in the related *SMARCA4* (*BRG1*) gene. Identification of ATRT is important because treatment responses are poor and because a significant proportion of patients carry germline mutations (Rhabdoid Tumour Predisposition Syndrome) and therefore genetic counselling may be appropriate. While some ATRTs show typical rhabdoid features, the histology features may be very variable. Therefore, routine use of INI1 immunohistochemistry is recommended in high-grade tumours in young children.

iv. *Embryonal tumour with abundant neuropil and true rosettes (ETANTR)/Embryonal tumour with multilayered rosettes (ETMR).* This is an embryonal tumour of young children that is recognised in the WHO as a subtype of CNS-primitive neuroectodermal tumour (CNS-PNET). Recent data indicates that the tumour is associated with immunoreactivity for LIN28a and amplification of the *C19MC* microRNA cluster (which is detectable by FISH) both of which can be applied in diagnostic practice.[71, 72] Identification of these tumours is important, as the prognosis in these cases is very poor when compared to other embryonal CNS tumours. It has been proposed that the tumour previously regarded as ependymoblastoma or medulloeptihelioma are in fact better regarded as ETANTR/ETMR.[73, 74] Definitive diagnostic criteria have not been determined but use of immunohistochemistry and/or FISH should be considered in embryonal tumours in young children.

v. *High-grade gliomas in children.* High-grade gliomas in children are genetically and probably clinically distinct from those in adults. For example, they are frequently associated with recurrent mutations in histone genes (H3.3 (*H3F3A*) or H3.1 (*HIST1H3B*)) but are rarely associated with *IDH1* mutations or 1p19q deletion.[75–79]

vi. *CNS/supratentorial-primitive neuroectodermal tumours (CNS-PNET).* Several studies have indicated that many tumours previously designated as CNS-PNETs are molecularly more similar to other tumour types.[80] The nosology of CNS-PNETs has therefore become controversial. From a diagnostic point of view, it is important to consider investigations that differentiate other tumours that may mimic a CNS-PNET but have different treatment or prognosis. Most significantly, it is important to excluded ATRT, ETANTR/ETMR and high-grade glioma.

Pituitary tumours

i. Low molecular weight cytokeratin expression is of value in identifying the paranuclear fibrous bodies of sparsely granulated somatotroph adenomas, as well as the extensive ring-like cytokeratin deposition of Crooke cell adenomas. Both the subtypes may be more aggressive and sparsely granulated somatotroph adenomas may develop

resistance to somatostatin analogues. Widespread nuclear p53 reactively along with elevated Ki-67 (>3%), increased mitotic activity and invasion may identify atypical adenomas, although there is lack of standardisation of how to assess the findings for both Ki-67 and p53. Molecular markers of cytodifferentiation, such as Pit-1 immunohistochemistry, may also be useful, but there remains a need for better biomarkers of aggressiveness for pituitary tumours.[81, 82]

Given that different methods may be used to demonstrate particular molecular or cytogenetic changes in different laboratories, a field has been included to specify the method used. Molecular analyses should be carried out in a laboratory participating in an appropriate EQA scheme.

6 Non-core data items

Although not core items for dataset purposes, documentation of additional information in the report is of value, is good clinical practice and should be included in the report. As appropriate, such items may include the following.

6.1 Clinical

- Clinical presentation (symptoms).
- Duration of history.
- Neuroradiological findings.
- Pre-operative treatment to the lesion.
- Previous procedures related to the CNS lesion.
- Patient's consents and preferences.
- Known hereditary tumour syndrome.

6.2 Pathological

- Frozen tissue archived.
- Tissue banked in research tissue archives.

6.3 Hereditary tumour syndromes

Whilst most CNS tumours are sporadic, they may arise in the context of a number of hereditary cancer syndromes. These include disorders such as neurofibromatosis types 1 and 2, Von Hippel Lindau disease, tuberous sclerosis, Li-Fraumeni syndrome, Cowden disease, Turcot syndrome, Gorlin syndrome, rhabdoid tumour predisposition syndrome, etc.[83] These raise particular clinical issues related to the pathobiology of the disease and the association with multiple tumours of the CNS or other organs. There is also a need to assess the epidemiology of such cancer syndromes. A field has therefore been provided to indicate a hereditary tumour syndrome if this is known.

7 Diagnostic coding and staging

TNM staging is not applicable. The use of SNOMED T and M codes or equivalent codes in SNOMED CT is recommended (see Appendix B).

8 Reporting of small biopsy specimens

Diagnostic biopsies may be obtained using conventional open biopsy, stereotactic or endoscopic techniques. These are often necessarily small, and in such cases all of the tissue should normally be processed for diagnostic purposes. Small portions may be archived frozen if this is felt by the neuropathologist not to prejudice the diagnosis. Correctly targeted stereotactic diagnostic biopsies, their location determined on the basis of radiological findings, are generally sufficient to establish the core dataset items and there may be sufficient material for molecular investigations in appropriate cases. However, if the biopsy does not contain solid tumour, it may not be possible to derive a definitive tumour classification and WHO grade, as the sample may not be representative. Particularly for intra-axial tumours, neurosurgical sampling may be limited to the diagnostic biopsy, without further definitive resection.

9 Reporting of frozen sections and smear preparations

Either smear preparations and/or frozen sections may be used intra-operatively.[84] Intra-operative diagnosis shows good prediction of final histology, but may use up precious tissue. Although the evidence base for the benefit of the technique is limited in the current imaging era and its use varies according to local protocols and preferences, it is a well-established procedure that is valued by neurosurgeons. It can be an important addition and complementation to preoperative imaging, in particular for ring enhancing lesions, where the differential diagnosis may include high-grade glioma, metastasis, lymphoma or abscess. In addition to guiding ongoing surgical treatment intraoperatively, it has also been used to determine whether intra-operative adjuvant therapy is appropriate, with the placement of chemotherapy wafers. NICE therefore recommends its availability in neurosurgical centres.[5] It should be noted, however, that final diagnosis, treatment planning and patient counselling should be based on the final report of the paraffin histology. Any diagnostic information present in the intra-operative preparations should be included in the final analysis. The fact that intra-operative diagnosis has been carried out should be recorded for audit purposes but, as the findings from any intraoperative preparations are included in the total evaluation of the specimen, it is not recorded as a separate dataset item.

10 Specific aspects of individual tumours not covered elsewhere

Specific information on issues related to diagnosis, subtyping and grading of individual tumours is provided in the WHO classification (see Appendix A).

11 Criteria for audit

The following are recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013, https://www.rcpath.org/resource-library-homepage/clinical-effectiveness/key-performance-indicators-kpi.html:

- Cancer resections must be reported using a template or proforma, including items listed in the English COSD, which are by definition core data items in RCPath cancer datasets. English Trusts are required to implement the structured recording of core pathology data in the COSD by January 2016.

  Standard: 95% of reports must contain structured data.

- Histopathology cases that are reported, confirmed and authorised within 7–10 calendar days of the procedure.

Standard: 80% of cases must be reported within seven calendar days and 90% within 10 calendar days.

Potential audits include the completeness of provision of core dataset items, including:

i. 100% of reports should containg the basic demographic patient identification data
ii. provision of tumour type using WHO categories and subtype if relevant in 100% of cases
iii. 100% of tumours should be reported with their WHO grade (where a grading is applicable)
iv. 100% of cases – availability of core clinical information.

The dataset may also be audited for provision of molecular data for specific tumour types. In Scotland it is recommended that results of molecular tests be available by 21 days post-neurosurgery.[33]

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Appendix A SNOMED codes for tumours of the central nervous system

Topography codes

Tumour	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Brain	T-A0100	12738006	Brain structure (body structure)
Cerebellum	T-A6000	113305005	Cerebellar structure (body structure)
Cerebral hemisphere	T-A2000	11628009	Structure of telencephalon (body structure)
Choroid plexus	T-A1900	80621003	Structure of choroid plexus (body structure)
Cranial nerve	T-A8000	25238003	Cranial nerve structure (body structure)
Meninges NOS	T-A1110	1231004	Meninges structure (body structure)
Pineal gland	T-B2000	45793000	Pineal structure (body structure)
Pituitary gland	T-B1000	56329008	Pituitary structure (body structure)
Skull	T-11100	89546000	Bone structure of cranium (body structure)
Spinal cord NOS	T-A7010	2748008	Spinal cord structure (body structure)
Spinal nerve root	T-A7160	69733000	Spinal nerve root structure (body structure)
Spine	T-11500	44300000	Entire vertebral column (body structure)

Morphology codes and WHO grade (according to WHO classification of CNS tumours[14])

Tumour	WHO grade	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Pilocytic astrocytoma	1	M-94211	128854008	Pilocytic astrocytoma (morphologic abnormality)
Pilomyxoid astrocytoma	2	M-94253	388600004	Pilomyxoid astrocytoma (morphologic abnormality)
Subependymal giant cell astrocytoma	1	M-93841	1586004	Subependymal giant cell astrocytoma (morphologic abnormality)
Pleomorphic xanthoastrocytoma	2	M-94243	78838008	Pleomorphic xanthoastrocytoma (morphologic abnormality)

Tumour	WHO grade	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Diffuse astrocytoma (low-grade)	2	M-94003	38713004	Astrocytoma, no International Classification of Diseases for Oncology (ICDO) subtype (morphologic abnormality)
Fibrillary astrocytoma	2	M-94203	71314006	Fibrillary astrocytoma (morphologic abnormality)
Gemistocytic astrocytoma	2	M-94113	73982001	Gemistocytic astrocytoma (morphologic abnormality)
Protoplasmic astrocytoma	2	M-94103	55094006	Protoplasmic astrocytoma (morphologic abnormality)
Anaplastic astrocytoma	3	M-94013	55353007	Astrocytoma, anaplastic (morphologic abnormality)
Glioblastoma	4	M-94403	63634009	Glioblastoma, no ICDO subtype (morphologic abnormality)
Giant cell glioblastoma	4	M-94413	44529004	Giant cell glioblastoma (morphologic abnormality)
Gliosarcoma	4	M-94423	35262004	Gliosarcoma (morphologic abnormality)
Gliomatosis cerebri		M-93813	26138003	Gliomatosis cerebri (morphologic abnormality)
Oligodendroglioma	2	M-94503	73348003	Oligodendroglioma, no ICDO subtype (morphologic abnormality)
Anaplastic oligodendroglioma	3	M-94513	3102004	Oligodendroglioma, anaplastic (morphologic abnormality)
Oligoastrocytoma	2	M-93823	22217002	Mixed glioma (morphologic abnormality)
Anaplastic oligoastrocytoma	3	M-93823	22217002	Mixed glioma (morphologic abnormality)
Subependymoma	1	M-93831	4553004	Subependymal glioma (morphologic abnormality)
Myxopapillary ependymoma	1	M-93941	1623000	Myxopapillary ependymoma (morphologic abnormality)
Ependymoma	2	M-93913	57706008	Ependymoma, no ICDO subtype (morphologic abnormality)
Cellular ependymoma	2	M-93913	57706008	Ependymoma, no ICDO subtype (morphologic abnormality)
Papillary ependymoma	2	M-93933	128839002	Papillary ependymoma (morphologic abnormality)

Tumour	WHO grade	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Clear cell ependymoma	2	M-93913	57706008	Ependymoma, no ICDO subtype (morphologic abnormality)
Tancytic ependymoma	2	M-93913	57706008	Ependymoma, no ICDO subtype (morphologic abnormality)
Anaplastic ependymoma	3	M-93923	21589007	Ependymoma, anaplastic (morphologic abnormality)
Choroid plexus papilloma	1	M-93900	18021007	Choroid plexus papilloma, no ICDO subtype (morphologic abnormality)
Atypical choroid plexus papilloma		M-93901	128904001	Atypical choroid plexus papilloma (morphologic abnormality)
Choroid plexus carcinoma	3	M-93903	88252006	Choroid plexus carcinoma (morphologic abnormality)
Astroblastoma		M-94303	48952003	Astroblastoma (morphologic abnormality)
Choroid glioma of the third ventricle	2	M-94441	128789002	Chordoid glioma (morphologic abnormality)
Angiocentric glioma	1	M-94311	450900009	Angiocentric glioma (morphologic abnormality)
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)		M-94930	128791005	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos) (morphologic abnormality)
Desmoplastic inflantile astrocytoma/ganglioglioma	1	M-94121	128787000	Desmoplastic infantile astrocytoma (morphologic abnormality)
Dysembryoplastic neuroepithelial tumour	1	M-94130	128788005	Dysembryoplastic neuroepithelial tumor (morphologic abnormality)
Gangliocytoma	1	M-94920	128919000	Gangliocytoma (morphologic abnormality)
Ganglioglioma	1	M-95051	89880005	Ganglioglioma, no ICDO subtype (morphologic abnormality)
Anaplastic ganglioglioma	3	M-95053	128912009	Ganglioglioma, anaplastic (morphologic abnormality)
Central neurocytoma	2	M-95061	128858006	Central neurocytoma (morphologic abnormality)
Extraventricular neurocytoma	2	M-95061	128858006	Central neurocytoma (morphologic abnormality)
Cerebellar liponeurocytoma	2	M-95061	128858006	Central neurocytoma (morphologic abnormality)
Papillary glioneuronal tumour	1	M-95091	450902001	Papillary glioneuronal tumor (morphologic abnormality)

Tumour	WHO grade	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Rosette-forming glioneuronal tumour of the fourth ventricle	1	M-95091	450902001	Papillary glioneuronal tumor (morphologic abnormality)
Paraganglioma	1	M-86801	803009	Paraganglioma (morphologic abnormality)
Pineocytoma	1	M-93611	89096009	Pineocytoma (morphologic abnormality)
Pineal parenchymal tumour of intermediate differentiation	2 to 3	M-93623	31671006	Pineoblastoma (morphologic abnormality)
Pineoblastoma	4	M-93623	31671006	Pineoblastoma (morphologic abnormality)
Papillary tumour of the pineal region	2 to 3	M-93953	450899004	Papillary tumor of the pineal region (morphologic abnormality)
Medulloblastoma	4	M-94703	83217000	Medulloblastoma, no ICDO subtype (morphologic abnormality)
Desmoplastic/nodular medulloblastoma	4	M-94713	32456001	Desmoplastic medulloblastoma (morphologic abnormality)
Medulloblastoma with extensive nodularity	4	M-94713	32456001	Desmoplastic medulloblastoma (morphologic abnormality)
Anaplastic medulloblastoma	4	M-94743	128790006	Large cell medulloblastoma (morphologic abnormality)
Large cell medulloblastoma	4	M-94743	128790006	Large cell medulloblastoma (morphologic abnormality)
CNS primitive neuroectodermal tumour	4	M-94733	39781001	Primitive neuroectodermal tumor (morphologic abnormality)
CNS neuroblastoma	4	M-95003	87364003	Neuroblastoma (morphologic abnormality)
CNS ganglioneuroblastoma	4	M-94903	69515008	Ganglioneuroblastoma (morphologic abnormality)
Medulloepithelioma	4	M-95013	39005004	Medulloepithelioma (morphologic abnormality)
Ependymoblastoma	4	M-93923	21589007	Ependymoma, anaplastic (morphologic abnormality)
Atypical teratoid/ Rhabdoid tumour	4	M-95083	128792003	Atypical teratoid/rhabdoid tumour (morphologic abnormality)

Tumour	WHO grade	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Schwannoma (neurilemoma, neurinoma)	1	M-95600	985004	Neurilemoma (morphologic abnormality)
Cellular schwannoma	1	M-95600	985004	Neurilemoma (morphologic abnormality)
Plexiform schwannoma	1	M-95600	985004	Neurilemoma (morphologic abnormality)
Melanotic schwannoma	1	M-95600	985004	Neurilemoma (morphologic abnormality)
Neurofibroma	1	M-95400	89084002	Neurofibroma, no ICDO subtype (morphologic abnormality)
Plexiform neurofibroma	1	M-95500	41252002	Plexiform neurofibroma (morphologic abnormality)
Perineurioma, NOS	1 to 3	M-95710	128795001	Perineurioma (morphologic abnormality)
Malignant perineurioma	2 to 4	M-95713	128796000	Perineurioma, malignant (morphologic abnormality)
Epithelioid MPNST	2 to 4	M-95403	19897006	Malignant peripheral nerve sheath tumor (morphologic abnormality)
MPNST with mesenchymal differentiation	2 to 4	M-95403	19897006	Malignant peripheral nerve sheath tumor (morphologic abnormality)
Melanocytic MPNST	2 to 4	M-95403	19897006	Malignant peripheral nerve sheath tumor (morphologic abnormality)
MPNST with glandular differentiation	2 to 4	M-95403	19897006	Malignant peripheral nerve sheath tumor (morphologic abnormality)
Meningioma	1	M-95300	19453003	Meningioma, benign, no ICDO subtype (morphologic abnormality)
Meningothelial meningioma	1	M-95310	68944005	Meningothelial meningioma (morphologic abnormality)
Fibrous (fibroblastic) meningioma	1	M-95320	511008	Fibrous meningioma (morphologic abnormality)
Transitional (mixed) meningioma	1	M-95370	64967004	Transitional meningioma (morphologic abnormality)
Psammomatous meningioma	1	M-95330	38431002	Psammomatous meningioma (morphologic abnormality)
Angiomatous meningioma	1	M-95340	73918009	Angiomatous meningioma (morphologic abnormality)
Microcystic meningioma	1	M-95300	19453003	Meningioma, benign, no ICDO subtype (morphologic abnormality)

Tumour	WHO grade	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Secretory meningioma	1	M-95300	19453003	Meningioma, benign, no ICDO subtype (morphologic abnormality)
Lymphoplasmacyte-rich meningioma	1	M-95300	19453003	Meningioma, benign, no ICDO subtype (morphologic abnormality)
Metaplastic meningioma	1	M-95300	19453003	Meningioma, benign, no ICDO subtype (morphologic abnormality)
Choroid meningioma	2	M-95381	57606003	Clear cell meningioma (morphologic abnormality)
Clear cell meningioma	2	M-95381	57606003	Clear cell meningioma (morphologic abnormality)
Atypical meningioma	2	M-95391	128914005	Atypical meningioma (morphologic abnormality)
Papillary meningioma	3	M-95383	128840000	Papillary meningioma (morphologic abnormality)
Rhabdoid meningioma	3	M-95383	128840000	Rhabdoid meningioma (morphologic abnormality)
Anaplastic (malignant) meningioma	3	M-95303	78303004	Meningioma, malignant (morphologic abnormality)
Adenocarcinoma, metastatic	N/A	M-81406	4590003	Adenocarcinoma, metastatic (morphologic abnormality)
Carcinoma, metastatic	N/A	M-80106	79282002	Carcinoma, metastatic (morphologic abnormality)
Melanoma	N/A	M-87203	2092003	Malignant melanoma, no ICDO subtype (morphologic abnormality)
Sarcoma, NOS	N/A	M-88003	2424003	Sarcoma, no ICDO subtype (morphologic abnormality)
Teratoma, NOS	N/A	M-90801	55818009	Teratoma, no ICDO subtype (morphologic abnormality)
Germinoma, NOS	N/A	M-90643	28307001	Germinoma, no ICDO subtype (morphologic abnormality)

Other SNOMED codes may be used if appropriate.

Appendix B List of abbreviations

CNS	Central nervous system
EQA	External quality assurance
FISH	Fluorescence *in situ* hybridisation
MDT	Multidisciplinary team
MGMT	06 methylguanine-DNA methyl transferase
NICE	National Institute for Health and Clinical Excellence
NCRI	National Cancer Research Institute
PCR	Polymerase chain reaction
UKCCSG	United Kingdom Children's Cancer Study Group
WHO	World Health Organization

Appendix C Reporting proforma for intra-axial tumours

Surname…… Forenames……..… Date of birth…….… Sex…..
Hospital……..…….…… Hospital no…….…..... NHS/CHI no…….....
Date of receipt……..……. Date of reporting……..... Report no…….....….
Pathologist……..……... Surgeon……..…….

CORE ITEMS

Clinical details

Site of lesion†: Cerebrum □ Cerebellum □ Brainstem □ Spinal cord □ Not known □
Laterality†: Left □ Right □ Midline □ Not known □
Multifocal†: Unifocal □ Multifocal □ Not known □

Details of location: …….

Type of procedure†: Biopsy □
Resection: Partial □ Total macroscopic □ Extent uncertain □

Macroscopic items

Specimen dimensions (mm x mm x mm): ……
Estimated tumour dimensions† (mm x mm x mm): …… **or** weight (g) ……..

Microscopic items

Tumour type†: ……
Tumour subtype (if relevant)†: ……
WHO tumour grade†: I □ II □ III □ IV □

Molecular testing

Molecular diagnostic results†:
Evidence of IDH1 or IDH2 mutation □ Evidence of methylation of MGMT gene CpG island □
Evidence of total loss of 1p and 19q □ Evidence of KIAA 1549-BRAF fusion gene □
Molecular testing not performed □ Molecular testing result not available □
Other (specify below) □

Other molecular tests and results:
……

Integrated histological-molecular diagnosis (if relevant)
……

Signature …… Date ……

SNOMED codes: T ……. M ……..……

† - Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6.

Appendix D Reporting proforma for extra-axial tumours

Surname…… Forenames…… Date of birth…… Sex…..
Hospital…… Hospital no…… NHS/CHI no…….....
Date of receipt…… Date of reporting……..... Report no…….....….
Pathologist…….. Surgeon…….

CORE ITEMS

Clinical details

Site of lesion†: Cerebral meninges □ Spinal meninges □ Skull □ Paraspinal □ Not known □

Laterality†: Left □ Right □ Midline □ Not known □

Multifocal†: Unifocal □ Multifocal □ Not known □

Details of location …….

Type of procedure†: Biopsy □
Resection: Partial □ Total macroscopic □ Extent uncertain □

Macroscopic items

Specimen dimensions (mm x mm x mm) ……

Estimated tumour dimensions† (mm x mm x mm) …… **or** weight (g) ……..

Microscopic items

Tumour type† …… Tumour subtype† (if relevant) ……

Microscopic brain invasion: Present □ Not identified □

WHO tumour grade†: I □ II □ III □ IV □ N/A □

Other grading system: …… Grade†: 1 □ 2 □ 3 □ 4 □

Molecular testing
Molecular testing details (tests/methods/results):

……

……

Signature …… Date ……

SNOMED† codes: T ……. M ……

† - Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6.

Appendix E Reporting proforma for pituitary tumours

Surname…… Forenames…… Date of birth…… Sex…..
Hospital…… Hospital no…….... NHS/CHI no…….....
Date of receipt…… Date of reporting……..... Report no…….....….
Pathologist……... Surgeon…….

CORE ITEMS

Clinical details

Site of lesion†: Intrasellar □ Suprasellar □ Both □ Not known □

Macroscopic items

Specimen dimensions (mm x mm x mm): …… ……

Estimated tumour dimensions† (mm x mm x mm): …… **or** weight (g) ……..

Microscopic items

Tumour type†: …… Tumour subtype† (if relevant): ……

WHO tumour grade†: N/A □ □ II □ III □ IV □

Hormone expression by immunohistochemistry† (for primary adenohypophyseal tumours):
ACTH □ GH □ Prl □ FSH □ LH □ Alpha sub-unit □ TSH □

Signature …… Date ……

SNOMED† codes: T …… M ……

† - Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6.

Appendix F Proforma for intra-axial tumours in list format

Element name	Values	Implementation notes
Site of lesion	Single selection value list: • cerebrum • cerebellum • brainstem • spinal cord • not known	
Laterality	Single selection value list: • left • right • midline • not known	
Multifocal	Single selection value list: • unifocal • multifocal • not known	
Details of location	Free text	
Type or procedure	Single selection value list: • Biopsy • Resection, partial • Resection, total macroscopic • Resection, extent uncertain	
Specimen dimensions	Size in mm x mm x mm	
Estimated tumour dimensions	Size in mm x mm x mm	Either estimated tumour dimensions or tumour weight should be given
Tumour weight	Weight in g	Either estimated tumour dimensions or tumour weight should be given
Tumour type	Free text	May be selected from complete list of WHO tumour types/subtypes
Tumour subtype (if relevant)	Free text	May be selected from complete list of WHO tumour types/subtypes
WHO grade	Single selection value list: • I • II • III • IV	

Element name	Values	Implementation notes
Molecular testing	Multiple select value list: • Evidence of IDH1 or IDH2 mutation • Evidence of methylation of MGMT gene CpG island • Evidence of total loss of 1p and 19q • Evidence of KIAA 1549-BRAF fusion gene • Molecular testing not performed • Molecular testing result not available • Other (specify below)	
Other molecular testing and results	Free text	To be completed if Molecular testing, Other (specify below) selected
Integrated histological-molecular diagnosis	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables	

Appendix G Proforma for extra-axial tumours in list format

Element name	Values	Implementation notes
Site of lesion	Single selection value list: • cerebral meninges • spinal meninges • skull • paraspinal • not known	
Laterality	Single selection value list: • left • right • midline • not known	
Multifocal	Single selection value list: • unifocal • multifocal • not known	
Details of location	Free text	
Type or procedure	Single selection value list: • Biopsy • Resection, partial • Resection, total macroscopic • Resection, extent uncertain	
Specimen dimensions	Size in mm x mm x mm	
Estimated tumour dimensions	Size in mm x mm x mm	Either estimated tumour dimensions or tumour weight should be given
Tumour weight	Weight in g	Either estimated tumour dimensions or tumour weight should be given
Tumour type	Free text	May be selected from complete list of WHO tumour types/subtypes
Tumour subtype (if relevant)	Free text	May be selected from complete list of WHO tumour types/subtypes
Microscopic brain invasion	Single selection value list: • Present • Not identified	

Element name	Values	Implementation notes
WHO grade	Single selection value list: • I • II • III • IV • N/A	
Other grading system	Free text	
Grade	• 1 • 2 • 3 • 4	
Molecular testing details	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables	

Appendix H Proforma for pituitary tumours in list format

Element name	Values	Implementation notes
Site of lesion	Single selection value list: • intrasellar • suprasellar • both • not known	
Specimen dimensions	Size in mm x mm x mm	
Estimated tumour dimensions	Size in mm x mm x mm	Either estimated tumour dimensions or tumour weight should be given
Tumour weight	Weight in g	Either estimated tumour dimensions or tumour weight should be given
Tumour type	Free text	May be selected from complete list of WHO tumour types/subtypes
Tumour subtype (if relevant)	Free text	May be selected from complete list of WHO tumour types/subtypes
WHO grade	Single selection value list: • I • II • III • IV • N/A	
Hormone expression by immunohistochemistry	Multiple select value list: • ACTH • GH • Prl • FSH • LH • Alpha sub-unit • TSH	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix I Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008; 337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group

Appendix J AGREE compliance monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines (www.agreetrust.org). The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	1
2 The health question(s) covered by the guideline is (are)specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	N/A
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, 1
12 There is an explicit link between the recommendations and the supporting evidence	5, 6
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	5, 6
16 The different options for management of the condition or health issue are clearly presented	All sections
17 Key recommendations are easily identifiable	5,6
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	11
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword