World Health Organization Classification of Tumors of the Central Nervous System 2016

World Health Organization Classification of Tumors of the Central Nervous System

In a review, Lucas et al. summarized the rapidly evolving spectrum of recurrent genetic alterations described in central nervous system tumor entities since the publication of the WHO 2016.

The 2016 CNS WHO represents a substantial step forward over the World Health Organization Classification of Tumors of the Central Nervous System 2007 in that, for the first time, molecular biomarkers are used to establish brain tumor diagnoses.

The most recent WHO Classification has been issued in May 2016 and includes several changes, as detailed in the “Blue Book.”

While this has introduced challenges in nomenclature, nosology and reporting structure, and while it is likely that the next CNS WHO classification will view the present one as an intermediate stage to the further incorporation of objective molecular data in classification, the 2016 CNS WHO sets the stage for such progress. It is hoped that these more objective and more precisely defined entities will allow for improved tailoring of patient therapy, better classification for clinical trials and experimental studies, and more precise categorization for epidemiological purposes. Moreover, while the classification has left some “wastebasket” categories, it allows for more focused study of these less defined groups that will eventually lead to clarification of their status. In addition, while the classification still enables diagnoses to be made in the absence of molecular data in many situations, those settings are clearly designated, allowing distinction of molecularly defined and non-molecularly defined groups. In the long run, we trust that the 2016 CNS WHO will facilitate the clinical, experimental and epidemiological studies that will lead to improvements in the lives of patients with brain tumors.

The 2016 World Health Organization Classification of Tumors of the Central Nervous System is both a conceptual and practical advance over its 2007 predecessor. For the first time, the WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era. As such, the 2016 CNS WHO presents major restructuring of the diffuse gliomas, medulloblastomas and other embryonal tumors, and incorporates new entities that are defined by both histology and molecular features, including glioblastoma, IDH-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M-mutant; RELA fusion-positive ependymoma; medulloblastoma, WNT-activated and medulloblastoma, SHH-activated; and embryonal tumour with multilayered rosettes, C19MC-altered. The 2016 edition has added newly recognized neoplasms, and has deleted some entities, variants and patterns that no longer have diagnostic and/or biological relevance. Other notable changes include the addition of brain invasion as a criterion for atypical meningioma and the introduction of a soft tissue-type grading system for the now combined entity of solitary fibrous tumor / hemangiopericytoma-a departure from the manner by which other CNS tumors are graded. Overall, it is hoped that the 2016 CNS WHO will facilitate clinical, experimental and epidemiological studies that will lead to improvements in the lives of patients with brain tumors.

The 2016 WHO Classification reflects a paradigm shift and transitional stage to a combined histological/molecular approach. While the new classification has been quickly adopted all over the world, some practical issues need to be resolved and new developments implemented by regular discussions, conferences, and updates. Genetic data and insight into molecular pathogenesis continue.
to be revealed at a rapid pace and soon will find their way into diagnosis and clinical management. This is an exciting time for neuropathological brain tumor classification and for understanding brain tumor biology. Progress will be even more successful with critical input from neurosurgeons.  

WHO classification of tumours of the central nervous system

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In the revised 4th edition of the World Health Organization Classification of Tumors of the Central Nervous System published in 2016, classification of especially diffuse gliomas has fundamentally changed: for the first time a large subset of these tumours is now defined based on presence/absence of IDH mutation and 1p19q codeletion. Following this approach, the diagnosis of anaplastic oligoastrocytoma can be expected to largely disappear.

Diffuse astrocytic tumor and oligodendroglial tumor

see Diffuse astrocytic tumor and oligodendroglial tumor.
Other astrocytic tumors

see Other astrocytic tumors.

Ependymal tumors

see Ependymal tumors classification

Other gliomas

Chordoid glioma of the third ventricle

Angiocentric glioma

Astroblastoma

Choroid plexus tumors

Choroid plexus papilloma

Atypical choroid plexus papilloma

Choroid plexus carcinoma

Neuronal and mixed neuronal glial tumors

see Neuronal and mixed neuronal glial tumors.

Dysembryoplastic neuroepithelial tumor

Gangliocytoma

Ganglioglioma

Anaplastic ganglioglioma

Dysplastic cerebellar gangliocytoma

Desmoplastic infantile astrocytoma and ganglioglioma

Papillary glioneuronal tumor

Rosette forming glioneuronal tumor

Diffuse leptomeningeal glioneuronal tumor

Central neurocytoma

Extraventricular neurocytoma

Cerebellar liponeurocytoma

Paraganglioma
**Tumours of the pineal region**

Pineocytoma

Pineal parenchymal tumor of intermediate differentiation

Pineoblastoma

Papillary tumor of the pineal region

**Embryonal tumours**

Medulloblastoma genetic defined

Medulloblastoma NOS

**Germ cell tumours**

Germinoma

Embryonal carcinoma

Yolc sac tumor

**Tumours of the sellar region**

Craniopharyngioma

-Adamantinomatous craniopharyngioma

-Papillary craniopharyngioma

Granular cell tumour of the sellar region

Pituicytoma

Spindle cell oncocytoma

**Metastatic Tumours**

see Metastases

**Introduction**

For the past century, the classification of brain tumors has been based largely on concepts of histogenesis that tumors can be classified according to their microscopic similarities with different putative cells of origin and their presumed levels of differentiation. The characterization of such histological similarities has been primarily dependent on light microscopic features in hematoxylin and eosin-stained sections, immunohistochemical expression of lineage-associated proteins and ultrastructural characterization.

The classification of Tumors of the Central Nervous System is both a conceptual and practical advance over its 2007 predecessor.
For the first time, the WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era.

As such, the 2016 CNS WHO presents major restructuring of the diffuse gliomas, medulloblastomas and other embryonal tumors, and incorporates new entities that are defined by both histology and molecular features, including glioblastoma, IDH-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M-mutant; RELA fusion-positive ependymoma; medulloblastoma, WNT-activated and medulloblastoma, SHH-activated; and embryonal tumour with multilayered rosettes, C19MC-altered. The 2016 edition has added newly recognized neoplasms, and has deleted some entities, variants and patterns that no longer have diagnostic and/or biological relevance. Other notable changes include the addition of brain invasion as a criterion for atypical meningioma.

For example, the 2007 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (2007 CNS WHO) grouped all tumors with an astrocytic phenotype separately from those with an oligodendroglial phenotype, no matter if the various astrocytic tumors were clinically similar or disparate.

Studies over the past two decades have clarified the genetic basis of tumorigenesis in the common and some rarer brain tumor entities, raising the possibility that such an understanding may contribute to classification of these tumors.

Some of these canonical genetic alterations were known as of the 2007 CNS WHO, but at that time it was not felt that such changes could yet be used to define specific entities; rather, they provided prognostic or predictive data within diagnostic categories established by conventional histology. In 2014, a meeting held in Haarlem, the Netherlands, under the auspices of the International Society of Neuropathology, established guidelines for how to incorporate molecular findings into brain tumor diagnoses, setting the stage for a major revision of the 2007 CNS WHO classification.

The current update (2016 CNS WHO) thus breaks with the century-old principle of diagnosis based entirely on microscopy by incorporating molecular parameters into the classification of CNS tumor entities. To do so required an international collaboration of 117 contributors from 20 countries and deliberations on the most controversial issues at a three-day consensus conference by a Working Group of 35 neuropathologists, neurooncological clinical advisors and scientists from 10 countries.

The present review summarizes the major changes between the 2007 and 2016 CNS WHO classifications.

**Classification**

The 2016 CNS WHO represents an update of the 2007 4th Edition rather than a formal 5th Edition. At this point, a decision to undertake the 5th Edition series of WHO Blue Books has not been made, but given the considerable progress in the fields, both the Hematopoietic/Lymphoid and CNS tumor volumes were granted permission for 4th Edition updates.

**General principles and challenges**

The use of “integrated” phenotypic and genotypic parameters for CNS tumor classification adds a level of objectivity that has been missing from some aspects of the diagnostic process in the past. It is hoped that this additional objectivity will yield more biologically homogeneous and narrowly defined diagnostic entities than in prior classifications, which in turn should lead to greater diagnostic accuracy as well as improved patient management and more accurate determinations of prognosis.
and treatment response. It will, however, also create potentially larger groups of tumors that do not fit into these more narrowly defined entities (e.g., the not otherwise specified/NOS designations)—groups that themselves will be more amenable to subsequent study and improved classification.

A compelling example of this refinement relates to the diagnosis of oligoastrocytoma—a diagnostic category that has always been difficult to define and that suffered from high interobserver discordance, with some centers diagnosing these lesions frequently and others diagnosing them only rarely. Using both genotype (i.e., IDH mutation and 1p/19q codeletion status) and phenotype to diagnose these tumors results in nearly all of them being compatible with either an astrocytoma or oligodendroglioma, with only rare reports of molecularly “true” oligoastrocytomas consisting of histologically and genetically distinct astrocytic (IDH-mutant, ATRX-mutant, 1p/19q-intact) and oligodendrogial (IDH-mutant, ATRX-wildtype and 1p/19q-codeleted) tumor populations.

As a result, both the more common astrocytoma and oligodendroglioma subtypes become more homogeneously defined. In the 2016 CNS WHO, therefore, the prior diagnoses of oligoastrocytoma and anaplastic oligoastrocytoma are now designated as NOS categories, since these diagnoses should be rendered only in the absence of diagnostic molecular testing or in the very rare instance of a dual genotype oligoastrocytoma.

The diagnostic use of both histology and molecular genetic features also raises the possibility of discordant results, e.g., a diffuse glioma that histologically appears astrocytic but proves to have IDH mutation and 1p/19q codeletion, or a tumor that resembles oligodendroglioma by light microscopy but has IDH, ATRX and TP53 mutations in the setting of intact 1p and 19q. Notably, in each of these situations, the genotype trumps the histological phenotype, necessitating a diagnosis of oligodendroglioma, IDH-mutant and 1p/19q-codeleted in the first instance and diffuse astrocytoma, IDH-mutant in the second.

The latter example of classifying astrocytomas, oligodendrogliomas and oligoastrocytomas leads to the question of whether classification can proceed on the basis of genotype alone, i.e., without histology. At this point in time, this is not possible: one must still make a diagnosis of diffuse glioma (rather than some other tumor type) to understand the nosological and clinical significance of specific genetic changes. In addition, WHO grade determinations are still made on the basis of histologic criteria. Another reason why phenotype remains essential is that, as mentioned above there are individual tumors that do not meet the more narrowly defined phenotype and genotype criteria, e.g., the rare phenotypically classical diffuse astrocytoma that lacks the signature genetic characteristics of IDH and ATRX mutations. Nevertheless, it remains possible that future WHO classifications of the diffuse gliomas, in the setting of deeper and broader genomic capabilities, will require less histological evaluation—perhaps only a diagnosis of “diffuse glioma.” For now, the 2016 CNS WHO is predicated on the basis of combined phenotypic and genotypic classification, and on the generation of “integrated” diagnoses.

Lastly, it is important to acknowledge that changing the classification to include some diagnostic categories that require genotyping may create challenges with respect to testing and reporting, which have been discussed in detail elsewhere. These challenges include: the availability and choice of genotyping or surrogate genotyping assays; the approaches that may need to be taken by centers without access to molecular techniques or surrogate immunostains; and the actual formats used to report such “integrated” diagnoses. Nonetheless, the implementation of combined phenotypic-genotypic diagnostics in some large centers and the growing availability of immunohistochemical surrogates for molecular genetic alterations suggest that most of these challenges will be overcome readily in the near future.
Nomenclature

Combining histopathological and molecular features into diagnoses necessarily results in portmanteau diagnostic terms and raises the need to standardize such terminology in as practical a manner as possible. In general, the 2016 CNS WHO decision was to approximate the naming conventions of the hematopoietic/lymphoid pathology community, which has incorporated molecular information into diagnoses in the past. As detailed below, CNS tumor diagnoses should consist of a histopathological name followed by the genetic features, with the genetic features following a comma and as adjectives, as in:

Diffuse astrocytoma, IDH-mutant and Medulloblastoma, WNT-activated.

For those entities with more than one genetic determinant, the multiple necessary molecular features are included in the name:

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

For a tumor lacking a genetic mutation, the term wildtype can be used if an official “wildtype” entity exists:

Glioblastoma, IDH-wildtype.

However, it should be pointed out that in most such situations, a formal wildtype diagnosis is not available, and a tumor lacking a diagnostic mutation is given an NOS designation.

For tumor entities in which a specific genetic alteration is present or absent, the terms “positive” can be used if the molecular characteristic is present:

Ependymoma, RELA fusion–positive.

For sites lacking any access to molecular diagnostic testing, a diagnostic designation of NOS (i.e., not otherwise specified) is permissible for some tumor types. These have been added into the classification in those places where such diagnoses are possible. An NOS designation implies that there is insufficient information to assign a more specific code. In this context, NOS in most instances refers to tumors that have not been fully tested for the relevant genetic parameter(s), but in rare instances may also include tumors that have been tested but do not show the diagnostic genetic alterations. In other words, NOS does not define a specific entity; rather it designates a group of lesions that cannot be classified into any of the more narrowly defined groups. An NOS designation thus represents those cases about which we do not know enough pathologically, genetically and clinically and which should, therefore, be subject to future study before additional refinements in classification can be made.

With regard to formatting, italics are used for specific gene symbols (e.g., ATRX) but not for gene families (e.g., IDH, H3). To avoid numerous sequential hyphens, wildtype has been used without a hyphen and en-dashes have been used in certain designations (e.g., RELA fusion–positive). Finally, as in the past, WHO grades are written in Roman numerals (e.g., I, II, III and IV; not 1, 2, 3 and 4).

Definitions, disease summaries and commentaries

Entities within the 2016 classification begin with a Definition section that itself starts with an italicized definitional first clause that describes the necessary (i.e., entity-defining) diagnostic criteria. This is followed by characteristic associated findings. For example, the definition of oligodendroglioma, IDH-
mutant and 1p/19q-codeleted includes a first sentence: “A diffusely infiltrating, slow- growing glioma with IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q” (which is the italicized, entity-defining criteria), followed by sentences such as “Microcalcifications and a delicate branching capillary network are typical” (findings that are highly characteristic of the entity, but not necessary for the diagnosis). The diagnostic criteria and characteristic features are then followed by the remainder of the disease summary, in which other notable clinical, pathological and molecular findings are given. Finally, for some tumors, there is a commentary that provides information on classification, clarifying the nature of the genetic parameters to be evaluated and providing genotyping information for distinguishing overlapping histological entities. Notably, the classification does not mandate specific testing techniques, leaving that decision up to the individual practitioner and institution. Nonetheless, the commentary sections clarify certain genetic interpretations, e.g., in what situations IDH status can be designated as wildtype (depending on tumor type and, in some instances, patient age) and what constitutes prognostically favorable 1p/19q codeletion (combined whole-arm losses, which in IDH-mutant and histologically classic tumors can be assumed even when only single loci on each arm have been tested by fluorescence in situ hybridization).

**Newly recognized entities, variants and patterns**

A number of newly recognized entities, variants and patterns have been added. Variants are subtypes of accepted entities that are sufficiently well characterized pathologically to achieve a place in the classification and have potential clinical utility. Patterns are histological features that are readily recognizable but usually do not have clear clinico-pathological significance.

**Diffuse gliomas**

The nosological shift to a classification based on both phenotype and genotype expresses itself in a number of ways in the classification of the diffuse gliomas.

Most notably, while in the past all astrocytic tumors had been grouped together, now all diffusely infiltrating gliomas (whether astrocytic or oligodendroglial) are grouped together: based not only on their growth pattern and behaviors, but also more pointedly on the shared genetic driver mutations in the IDH1 and IDH2 genes. From a pathogenetic point of view, this provides a dynamic classification that is based on both phenotype and genotype; from a prognostic point of view, it groups tumors that share similar prognostic markers; and from the patient management point of view, it guides the use of therapies (conventional or targeted) for biologically and genetically similar entities.

In this new classification, the diffuse gliomas include the WHO grade II and grade III astrocytic tumors, the grade II and III oligodendrogliomas, the grade IV glioblastomas, as well as the related diffuse gliomas of childhood.

This approach leaves those astrocytomas that have a more circumscribed growth pattern, lack IDH gene family alterations and frequently have BRAF alterations (pilocytic astrocytoma, pleomorphic xanthoastrocytoma) or TSC1/TSC2 mutations (subependymal giant cell astrocytoma) distinct from the diffuse gliomas. In other words, diffuse astrocytoma and oligodendrogliomas are now nosologically more similar than are diffuse astrocytoma and pilocytic astrocytoma; the family trees have been redrawn.

**Diffuse astrocytoma and anaplastic astrocytoma**

The WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas are now each divided into IDH-mutant, IDH-wildtype and NOS categories. For both grade II and III tumors, the great majority falls into the IDH-mutant category if IDH testing is available. If immunohistochemistry for
mutant R132H IDH1 protein and sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations are both negative, or if sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations alone is negative, then the lesion can be diagnosed as IDH-wildtype. It is important to recognize, however, that diffuse astrocytoma, IDH-wildtype is an uncommon diagnosis and that such cases need to be carefully evaluated to avoid misdiagnosis of lower grade lesions such as gangliogliomas; moreover, anaplastic astrocytoma, IDH-wildtype is also rare, and most such tumors will feature genetic findings highly characteristic of IDH-wildtype glioblastoma.

Finally, in the setting of a diffuse astrocytoma or anaplastic astrocytoma, if IDH testing is not available or cannot be fully performed (e.g., negative immunohistochemistry without available sequencing), the resulting diagnosis would be diffuse astrocytoma, NOS, or anaplastic astrocytoma, NOS, respectively.

Historically, the prognostic differences between WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas were highly significant.

Some recent studies, however, have suggested that the prognostic differences between IDH-mutant WHO grade II diffuse astrocytomas and IDH-mutant WHO grade III anaplastic astrocytomas are not as marked.

Nonetheless, this has not been noted in all studies. At this time, it is recommended that WHO grading is retained for both IDH-mutant and IDH-wildtype astrocytomas, although the prognosis of the IDH-mutant cases appears more favorable in both grades. Cautionary notes have been added to the 2016 classification in this regard.

Of note, two diffuse astrocytoma variants have been deleted from the WHO classification: protoplasmic astrocytoma, a diagnosis that was previously defined in only vague terms and is almost never made any longer given that tumors with this histological appearance are typically characterized as other more narrowly defined lesions; and fibrillary astrocytoma, since this diagnosis overlaps nearly entirely with the standard diffuse astrocytoma. As a result, only gemistocytic astrocytoma remains as a distinct variant of diffuse astrocytoma IDH-mutant.

Gliomatosis cerebri has also been deleted from the 2016 CNS WHO classification as a distinct entity, rather being considered a growth pattern found in many gliomas, including IDH-mutant astrocytic and oligodendroglial tumors as well as IDH-wildtype glioblastomas.

Thus, widespread brain invasion involving three or more cerebral lobes, frequent bilateral growth and regular extension to infratentorial structures is now mentioned as a special pattern of spread within the discussion of several diffuse glioma subtypes. Further studies are needed to clarify the biological basis for the unusually widespread infiltration in these tumors.

**Glioblastomas**

Glioblastomas are divided in the 2016 CNS WHO into glioblastoma, IDH-wildtype (about 90% of cases), which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients over 55 years of age.

(2) glioblastoma, IDH-mutant (about 10% of cases), which corresponds closely to so-called secondary glioblastoma with a history of prior lower grade diffuse glioma and preferentially arises in younger patients; and (3) glioblastoma, NOS, a diagnosis that is reserved for those tumors for which full IDH evaluation cannot be performed. The definition of full IDH evaluation can differ for glioblastomas in older patients relative to glioblastomas in younger adults and relative to WHO grade II and grade III diffuse gliomas: in the latter situations, IDH sequencing is highly recommended following negative
R132H IDH1 immunohistochemistry, whereas the near absence of non-R132H IDH1 and IDH2 mutations in glioblastomas from patients over about 55 years of age suggests that sequencing may not be needed in the setting of negative R132H IDH1 immunohistochemistry in such patients.

One provisional new variant of glioblastoma has been added to the classification: epithelioid glioblastoma. It joins giant cell glioblastoma and gliosarcoma under the umbrella of IDH-wildtype glioblastoma. Epithelioid glioblastomas feature large epithelioid cells with abundant eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli (often resembling melanoma cells), and variably present rhabdoid cells. They have a predilection for children and younger adults, typically present as superficial cerebral or diencephalic masses, and often harbor a BRAF V600E mutation (which can be detected immunohistochemically).

In one series, rhabdoid glioblastomas were distinguished from their similarly appearing epithelioid counterparts on the basis of loss of INI1 expression.

IDH-wildtype epithelioid glioblastomas often lack other molecular features of conventional adult IDH-wildtype glioblastomas, such as EGFR amplification and chromosome 10 losses; instead, there are frequent hemizygous deletions of ODZ3. Such cases may have an associated low-grade precursor, often but not invariably showing features of pleomorphic xanthoastrocytoma.

Glioblastoma with primitive neuronal component was added as a pattern in glioblastoma. This pattern, previously referred to in the literature as glioblastoma with PNET-like component, is usually comprised of a diffuse astrocytoma of any grade (or oligodendroglioma in rare cases) that has well-demarcated nodules containing primitive cells that display neuronal differentiation (e.g., Homer Wright rosettes, gain of synaptophysin positivity and loss of GFAP expression) and that sometimes has MYC or MYCN amplification; these tumors have a tendency for craniospinal fluid dissemination. About a quarter develop in patients with a previously known lower grade glioma precursor, a subset of which shows R132H IDH1 immunoreactivity in both the glial and primitive neuronal components.

From a clinical point of view, the recognition of this pattern may prompt evaluation of the craniospinal axis to rule out tumor seeding. Small cell glioblastoma/astrocytoma and granular cell glioblastoma/astrocytoma remain patterns, the former characterized by uniform, deceptively bland small neoplastic cells often resembling oligodendroglioma and frequently demonstrating EGFR amplification, and the latter by markedly granular to macrophage-like, lysosome-rich tumor cells. In both examples, there is a particularly poor glioblastoma-like prognosis even in the absence of microvascular proliferation or necrosis.

**Oligodendrogliomas**

The diagnosis of oligodendroglioma and anaplastic oligodendroglioma requires the demonstration of both an IDH gene family mutation and combined whole-arm losses of 1p and 19q (1p/19q codeletion). In the absence of positive mutant R132H IDH1 immunohistochemistry, sequencing of IDH1 codon 132 and IDH2 codon 172 is recommended. In the absence of testing capabilities or in the setting of inconclusive genetic results, a histologically typical oligodendroglioma should be diagnosed as NOS. In the setting of an anaplastic oligodendroglioma with non-diagnostic genetic results, careful evaluation for genetic features of glioblastoma may be undertaken. It is also recognized that tumors of childhood that histologically resemble oligodendroglioma often do not demonstrate IDH gene family mutation and 1p/19q codeletion; until such tumors are better understood at a molecular level, they should be included in the oligodendroglioma, NOS category. However, care should be taken to exclude histological mimics like pilocytic astrocytoma, dysembryoplastic neuroepithelial tumor and clear cell ependymoma.
**Oligoastrocytomas**

see Oligoastrocytoma.

**Pediatric diffuse gliomas**

In the past, pediatric diffuse gliomas were grouped with their adult counterparts, despite known differences in behavior between pediatric and adult gliomas with similar histological appearances. Information on the distinct underlying genetic abnormalities in pediatric diffuse gliomas is beginning to allow the separation of some entities from histologically similar adult counterparts.

One narrowly defined group of tumors primarily occurring in children (but sometimes in adults too) is characterized by K27M mutations in the histone H3 gene H3F3A, or less commonly in the related HIST1H3B gene, a diffuse growth pattern, and a midline location (e.g., thalamus, brain stem, and spinal cord). This newly defined entity is termed diffuse midline glioma, H3 K27M–mutant and includes tumors previously referred to as diffuse intrinsic pontine glioma (DIPG). The identification of this phenotypically and molecularly defined set of tumors provides a rationale for therapies directed against the effects of these mutations.

**Other astrocytomas**

Anaplastic pleomorphic xanthoastrocytoma, WHO grade III, has been added to the 2016 CNS WHO as a distinct entity, as opposed to the descriptive title of pleomorphic xanthoastrocytoma with anaplastic features in the past. Grading of a pleomorphic xanthoastrocytoma as anaplastic requires 5 or more mitoses per 10 high-power fields; necrosis may be present, but the significance of necrosis in the absence of elevated mitotic activity is unclear. Patients with such tumors have shorter survival times when compared to those with WHO grade II pleomorphic xanthoastrocytomas.

The grading of pilomyxoid astrocytoma has also been changed. While previously designated as WHO grade II, recent studies have shown extensive histological and genetic overlap between pilomyxoid and pilocytic astrocytomas, with some of the former maturing into the latter over time and less certainty that the pilomyxoid variant always follows a more aggressive course than a more classic appearing suprasellar pilocytic astrocytoma. For these reasons, it is not clear that pilomyxoid astrocytoma should automatically be assigned to WHO grade II and the suggestion was made to suppress grading of pilomyxoid astrocytomas until further studies clarify their behavior.

**Ependymomas**

While it was recognized that the grading of ependymomas according to existing WHO criteria is difficult to apply and of questionable clinical utility, a more prognostic and reproducible classification and grading scheme is yet to be published. As a result, the difficulty in assigning clinical significance to ependymoma histological grades is discussed in the grading sections of both the Ependymoma and Anaplastic Ependymoma chapters. Nonetheless, it is expected that continuing studies of the molecular characteristics of ependymoma will provide more precise and objective means of subdividing these tumors, allowing for more narrowly defined tumor groups. In the meanwhile, one genetically defined ependymoma subtype has been accepted: Ependymoma, RELA fusion–positive.

This variant accounts for the majority of supratentorial tumors in children. The specificity of L1CAM expression, a potential immunohistochemical surrogate for this variant, has yet to be fully elucidated. Lastly, one ependymoma variant, cellular ependymoma, has been deleted from the classification, since it was considered to overlap extensively with standard ependymoma.
Neuronal and mixed neuronal-glial tumours

The newly recognized entity diffuse leptomeningeal glioneuronal tumor is an entity known in the literature under a variety of similar terms, perhaps most notably as disseminated oligodendrogial-like leptomeningeal tumor of childhood.

These tumors present with diffuse leptomeningeal disease, with or without a recognizable parenchymal component (commonly in the spinal cord), most often in children and adolescents, and histologically demonstrate a monomorphic clear cell glial morphology, reminiscent of oligodendroglioma, although often with expression of synaptophysin in addition to OLIG2 and S-100.

An additional neuronal component can be detected in a subset of cases. The lesions commonly harbor BRAF fusions as well as deletions of chromosome arm 1p, either alone or occasionally combined with 19q.

However, IDH mutations are absent.

Nonetheless, the nosological position of these tumors remains somewhat unclear at the present time, with some pathological and genetic features suggesting a relationship to pilocytic astrocytoma or to glioneuronal tumors. The prognosis is variable, with tumors showing relatively slow growth but considerable morbidity from secondary hydrocephalus.

A newly recognized architectural appearance is the multinodular and vacuolated pattern that may be related to ganglion cell tumors. Reported as multinodular and vacuolating neuronal tumor of the cerebrum, these are low grade lesions that may even be malformative in nature.

They are comprised of multiple nodules of tumor with a conspicuous vacuolation, and the tumor cells show glial and/or neuronal differentiation, including ganglion cells in some cases. Further characterization of these lesions is needed to understand its nosological place among CNS neoplasms.

Medulloblastomas

The classification of medulloblastomas produced the greatest conceptual challenges in devising a marriage of histological and molecular classification schemes. There are long-established histological variants of medulloblastoma that have clinical utility (e.g., desmoplastic/nodular, medulloblastoma with extensive nodularity, large cell, and anaplastic) and it is now widely accepted that there are four genetic (molecular) groups of medulloblastoma: WNTactivated, SHH-activated, and the numerically designated “group 3” and “group 4”.

Some of these histological and genetic variants are associated with dramatic prognostic and therapeutic differences. Rather than providing a long list of the many possible histological–molecular combinations, the classification lists “genetically defined” and “histologically defined” variants, with the expectation that a pathologist with the ability to undertake the molecular classification will generate an integrated diagnosis that includes both the molecular group and histological phenotype. In this regard, it was emphasized that there is a group of the most clinically relevant integrated diagnoses.

This modular and integrated approach to diagnosis is novel, but likely represents a method that will become more common as knowledge of tumor genetics and phenotype-genotype correlation grows. It is also anticipated that such a modular approach will allow greater flexibility for future changes in classification as such knowledge expands.
Other embryonal tumors

The embryonal tumors other than medulloblastoma have also undergone substantial changes in their classification, with removal of the term primitive neuroectodermal tumor or PNET from the diagnostic lexicon. Much of the reclassification was driven by the recognition that many of these rare tumors display amplification of the C19MC region on chromosome 19 (19q13.42). C19MC-amplified tumors include the lesions previously known as ETANTR (embryonal tumors with abundant neuropil and true rosettes, but also referred to as embryonal tumors with multilayered rosettes), ependymoblastoma and, in some cases, medulloepithelioma.

In the 2016 CNS WHO, the presence of C19MC amplification results in a diagnosis of embryonal tumor with multilayered rosettes (ETMR), C19MC-altered. In the absence of C19MC amplification, a tumor with histological features conforming to ETANTR/ETMR should be diagnosed as embryonal tumor with multilayered rosettes, NOS, and a tumor with histological features of medulloepithelioma should be diagnosed as medulloepithelioma (recognizing that some apparently bona fide medulloepitheliomas do not have C19MC amplification).

Atypical teratoid/rhabdoid tumor (AT/RT) is now defined by alterations of either INI1 or, very rarely, BRG1. These alterations can be evaluated using immunohistochemistry for the corresponding proteins, with loss of nuclear expression correlating with genetic alteration (in the setting of adequate control expression). If a tumor has histological features of AT/RT but does not harbor either of the diagnostic genetic alterations, only a descriptive diagnosis of CNS embryonal tumour with rhabdoid features is available; in other words, the diagnosis of AT/RT requires confirmation of the characteristic molecular defect. The understanding of other embryonal tumors is undergoing changes, with an expectation that molecular markers could lead to more precise cataloging of these tumors and their subtypes. In the meanwhile, the 2016 CNS WHO has created a probable wastebasket category of CNS embryonal tumor, NOS that includes tumors previously designated as CNS PNET.

Nerve sheath tumors

The classification of cranial and paraspinal nerve sheath tumors is similar to that of the 2007 CNS WHO, although a few changes have been made. Given that melanotic schwannoma is both clinically (e.g., malignant behavior in a significant subset) and genetically (e.g., associations with Carney Complex and the PRKAR1A gene) distinct from conventional schwannoma, it is now classified as a distinct entity rather than as a variant. Hybrid nerve sheath tumors have been included in the 2016 CNS WHO because such tumors are increasingly being recognized in a variety of combinations; as such, this broad category was separated out as an entity, although it may well represent a group of tumors rather than one distinct subtype. Lastly, the 2016 CNS WHO now designates two subtypes of malignant peripheral nerve sheath tumor (MPNST): epithelioid MPNST and MPNST with perineurial differentiation. These were considered sufficiently distinct clinically to warrant designation as variants, whereas other subtypes such as MPNST with divergent differentiation (malignant Triton tumor, glandular MPNST, etc.) simply represent histologic patterns.

Meningiomas

The classification and grading of meningiomas did not undergo revisions, save for the introduction of brain invasion as a criterion for the diagnosis of atypical meningioma, WHO grade II. While it has long been recognized that the presence of brain invasion in a WHO grade I meningioma confers recurrence and mortality rates similar to those of a WHO grade II meningioma in general, prior WHO classifications had considered invasion a staging feature rather than a grading feature and opted to discuss brain invasion as a separate heading. In the 2016 classification, brain invasion joins a mitotic
count of 4 or more as a histological criterion that can alone suffice for diagnosing an atypical meningioma, WHO grade II. As in the past, atypical meningioma can also be diagnosed on the basis of the additive criteria of 3 of the other 5 histological features:

spontaneous necrosis, sheeting (loss of whorling or fascicular architecture), prominent nucleoli, high cellularity and small cells (tumor clusters with high nuclear:cytoplasmic ratio).

**Solitary fibrous tumor / hemangiopericytoma**

Over the past decade, soft tissue pathologists have moved away from the designation hemangiopericytoma, diagnosing such tumors within the spectrum of solitary fibrous tumors, whereas neuropathologists have retained the term hemangiopericytoma given its historical understanding and distinct clinicopathologic correlations, such as high recurrence rates and long-term risk of systemic metastasis. Nonetheless, both solitary fibrous tumors and hemangiopericytomas, including those occurring in the neuraxis, share inversions at 12q13, fusing the NAB2 and STAT6 genes, which leads to STAT6 nuclear expression that can be detected by immunohistochemistry. It has thus become clear that solitary fibrous tumors and hemangiopericytomas are overlapping, if not identical entities. For this reason, the 2016 CNS WHO has created the combined term solitary fibrous tumor / hemangiopericytoma to describe such lesions. It is recognized that this term is cumbersome and it is likely that it will be shortened in the next WHO classification of CNS tumors.

The creation of a single designation for tumors in the spectrum of low-grade solitary fibrous tumor and the higher grade lesions previously designated as hemangiopericytoma and anaplastic hemangiopericytoma created a grading challenge relative to other CNS tumors. The WHO classifications of CNS tumors have always included grading as a malignancy scale, with a specific grade assigned to each entity rather than multiple grades within an entity (i.e., glioblastoma is grade IV, whereas a ductal carcinoma of the breast can be assigned a grade within the diagnosis of ductal carcinoma). To address this challenge in the context of solitary fibrous tumor / hemangiopericytoma, the 2016 CNS WHO has broken with the typical WHO CNS tradition and assigns three grades within the entity of solitary fibrous tumor / hemangiopericytoma: a grade I that corresponds most often to the highly collagenous, relatively low cellularity, spindle cell lesion previously diagnosed as solitary fibrous tumor; a grade II that corresponds typically to the more cellular, less collagenous tumor with plump cells and “staghorn” vasculature that was previously diagnosed in the CNS as hemangiopericytoma; and a grade III that most often corresponds to what was termed anaplastic hemangiopericytoma in the past, diagnosed on the basis of 5 or more mitoses per 10 high-power fields. Nonetheless, some tumors with a histological appearance more similar to traditional solitary fibrous tumor can also display malignant features and be assigned a WHO grade III, using the cutoff of 5 or more mitoses per 10 high-power fields. Additional studies will, therefore, be required to fine-tune this grading system.

Nonetheless, it is hoped that this break from how CNS tumors were usually graded in the past will allow for greater flexibility in grading CNS tumors in the future, which may be important as molecular characterization improves (see discussion of IDH-mutant diffuse astrocytic tumors, above).

**Lymphomas and histiocytic tumours**

Given the changes that have occurred in the classification of systemic lymphomas and histiocytic neoplasms over the past decade, the 2016 CNS WHO has expanded these categories to parallel those in the corresponding Hematopoietic/Lymphoid WHO classifications.\[6\]
References


