Brain Tumor Pathology (2022) 39:47–50
https://doi.org/10.1007/s10014-022-00428-3

EDITORIAL

# The 2021 WHO classification of tumors, 5th edition, central nervous system tumors: the 10 basic principles

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Published online: 22 March 2022


## Introduction

The 2021 WHO classification of tumors of the central nervous system (CNS), 5th edition (WHO CNS 5) [24] is built on the previous, revised 4th edition, published in 2016 (WHO2016CNS) [14], which incorporated molecular information into the diagnosis of brain tumors for the first time, breaking with the century-old histogenetic classification [1, 15]. The basic concept underlying WHO2016CNS was rooted in the Haarlem Consensus Guidelines [11] that aimed to establish instructions for incorporating molecular findings into the diagnosis of brain tumors and define diagnostic entities as narrowly as possible using molecular information. WHO CNS 5 also adopted a series of recommendations of "the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT)" [2, 3, 5, 6, 16, 18–20] that facilitates a consensus review of novel diagnostically relevant data and determines how such information can be fit into future CNS tumor classifications. Based on the above volumes and articles, the 5th edition moved molecular diagnosis forward [24]. However, the combination of histology and molecular information used to diagnose and grade CNS tumors remains at the center of tumor taxonomy [22].

This editorial focuses on the basic principles behind the 5th edition rather than covering all revisions because the editorial board of the 5th edition has comprehensively summarized the essential points of WHO CNS 5 in another review article [22].

## Histogenetic vs. molecular classification

Brain tumor research over two decades has clearly shown that a molecular assessment is more effective than a traditional histogenetic assessment using immunohistochemistry and electron microscopy in characterizing a tumor entity and evaluating the biological behavior of brain tumors, especially neuroepithelial tumors [4, 12, 13]. Such knowledge has made the histogenetic terminology and nomenclature of brain tumors irrational, and thus WHO CNS 5 has finally eliminated a cell of origin definition from the "Essential diagnostic criteria" for diffuse gliomas. For example, the term "astrocytic glioma" or "diffuse glioma" replaced the traditional, generic term "astrocytoma." "Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted" needs not to possess oligodendroglial differentiation, and any diffusely infiltrating glioma with IDH mutation with the codeletion is diagnosed as such. This principle drastically reduced the provisional entities from the previous edition [14] and enabled restructuring of the tumor categories, particularly diffuse gliomas (Table 1).

## Integrated diagnosis

The layered reporting format, which is one of the critical principles introduced in the Haarlem consensus guidelines [13], presents a full range of diagnostic information, including histopathological features, CNS WHO grade, and molecular alterations (Table 2). Integrated assessment of all available information leads to the final diagnosis, prioritizing molecular information over histopathological features. This layered format became a part of the International Collaboration on Cancer Reporting (ICCR) dataset [21] and was recommended for pathological examinations in the clinical setting.

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**Table 1** Diffuse gliomas in WHO CNS 5

| | CNS WHO grade |
|---|---|
| Adult-type diffuse gliomas | |
| Astrocytoma, IDH-mutant | 2/3/4 |
| Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted | 2/3 |
| Glioblastoma, IDH-wildtype | 4 |
| Pediatric-type diffuse low-grade gliomas | |
| Diffuse astrocytoma, *MYB*-or *MYBL1*-altered | 1 |
| Angiocentric glioma | 1 |
| Polymorphous low-grade neuroepithelial tumor of the young | 1 |
| Diffuse low-grade glioma, MAPK pathway-altered | NA |
| Pediatric-type diffuse high-grade gliomas | |
| Diffuse midline glioma, H3 K27-altered | 4 |
| Diffuse hemispheric glioma, H3 G34-mutant | 4 |
| Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype | 4 |
| Infant-type hemispheric glioma | NA |

*NA* not assigned

## Essential and desirable diagnostic criteria

In addition to the definitions of tumor types, each chapter gave a box describing the "Essential and desirable diagnostic criteria" for each tumor type. The essential diagnostic criteria are the minimum requirements to establish a diagnosis, whereas the desirable diagnostic criteria are the ones that support a diagnosis, but are not essentially needed for the diagnosis.

## NOS and NEC diagnoses

In addition to the not otherwise specified (NOS) diagnosis, the not elsewhere classified (NEC) diagnosis has been adopted in WHO CNS 5 [19, 22]. An NEC suffix indicates that the necessary diagnostic testing has been successfully performed but that the results do not allow for a complete WHO diagnosis because of a mismatch between the clinical, histological, immunohistochemical, and/or genetic features. For example, the diagnosis of histologically malignant glioma in the cerebral hemisphere harboring H3.3p.K28M (K27M)-mutation would be "pediatric-type diffuse high-grade glioma, H3.3 K27-mutant, NEC". Nonetheless, since the diagnosis of NEC corresponds to what pathologists have called a "descriptive diagnosis," [22] the usage of NEC may differ according to the pathologist.

## Grading across vs. grading within types

Traditionally, the CNS tumor grades have been applied across different entities in the WHO classification [7, 8, 10, 17]. However, WHO CNS 5 employed within-tumor-type grading rather than across-different-tumor-type grading to conform with WHO grading in non-CNS tumor types [22]. Nonetheless, WHO CNS 5 endorses the term "CNS WHO grade" because CNS tumor grading still differs from other tumor grading systems. In addition, to clearly differentiate it from the previous grading system, WHO CNS 5 adopted Arabic numerals (1, 2, 3, 4) rather than Roman numerals (I, II, III, IV).

**Table 2** An example of layered report structure

| Cerebrum | |
|---|---|
| Integrated diagnosis | Diffuse high-grade glioma, IDH-wildtype, H3-wildtype, NEC |
| Histopathological diagnosis | Anaplastic oligoastrocytoma with microvascular proliferation |
| CNS WHO grade | Not assigned |
| Molecular information | IDH-wildtype, H3-wildtype, *TERT* promoter-wildtype, and *BRAF*-wildtype (Sanger sequencing), *BRAF* fusion-negative (Break apart FISH study), 1p/19q non-deleted (FISH study), *CDKN2A/B* non-deleted, *EGFR* not-amplified, and 7/10 chromosome copy number alterations-negative (MLPA) |

Cf. This is an example of a right frontal mass with contrast enhancement on MRI in a 43-year-old male. Of note, the usage of NEC may differ according to the pathologist

*CNS* central nervous system, *FISH* fluorescence in situ hybridization, *NEC* not elsewhere classified

## Combined histological and molecular grading

Since some molecular markers can provide robust prognostic information, some molecular parameters were added as biomarkers for grading in WHO CNS 5. Examples include (i) *CDKN2A/B* homozygous deletion in the grading of "astrocytoma, IDH-mutant,"[3] and (ii) *TERT* promoter mutation, *EGFR* amplification, and + 7/10- copy number changes for a diagnosis of glioblastoma, IDH wildtype, regardless of the presence or absence of high-grade histological features[2]. Because neither historical nor prospective data on the prognosis are available for the newly recognized tumors, the CNS WHO grade is not given to them [22].

## Pediatric-type vs. adult-type diffuse gliomas

WHO CNS 5 restructured diffuse gliomas into adult-type and pediatric-type diffuse gliomas [5, 9, 20], and the latter were subdivided into low-grade gliomas and high-grade gliomas (Table 1). Although the pediatric-type diffuse gliomas share overlying histology with their adult counterpart, the biology and genetics are distinctively different; they are generally indolent despite "anaplastic" histological features and lack IDH mutation and 1p/19q codeletion, the genetic hallmark of adult-type gliomas, but harbor characteristic genetic profiling such as MAPK-pathway alteration [23]. This distinction is essential to separating these two prognostically and biologically different sets of tumors, enabling improved care for both children and adults with CNS tumors. The definitions of pediatric-type and adult-type do not depend on the patient's age. Instead, they are defined based on representative molecular alterations, implicating that pediatric-type gliomas may occur in adults and vice versa [9].

## Use of type/subtype instead of entity/variant

In WHO CNS 5, type is used instead of entity and subtype is used instead of variant to harmonize the terminology with other organ systems. Only types are listed in the main classification, whereas subtypes are listed under individual sections. For example, meningioma is a single type in the classification, and all the subtypes and grades are documented individually within the meningioma chapter.

## Gene and protein nomenclature

WHO CNS5 uses the Hugo Gene Nomenclature Committee system for gene symbols and names, and the Human Genome Variation Society (https://www.hgvs.org/) recommendations for sequence variants. For histone sequence alterations, WHO CNS 5 uses the legacy protein numbering system in parentheses after the protein level variant description to avoid any confusion by clinicians ("prefix c." for sequence alteration and "prefix p." for protein sequence). For example, *H3-3A*:c.83A > T p.Lys28Met (K27M).

## DNA methylation profiling and newly recognized tumor types

Using a DNA methylation array, genome-wide profiling of DNA methylation patterns has become a powerful tool for the diagnosis and classification of CNS tumors, particularly those with atypical histology or discordant genetic features [4]. In WHO CNS 5, some new types, like "high-grade astrocytoma with piloid features," are defined only by DNA methylation profiling. However, the WHO did not recommend methylome profiling as a primary or routine diagnostic method because of general inaccessibility of the test; it remains a desirable diagnostic criterion.

In the current classification, a strict definition of tumor types eliminated ambiguous types from the previous classification, reducing the number of tumor types to 110, with 22 newly recognized tumor types identified by DNA methylation profiling.

## Conclusions

WHO CNS 5 moved molecular diagnostics forward, beyond the legendary histogenetic classification, adopting as much possible knowledge about the recent progress in neuro-oncological studies. However, it is still incomplete for characterizing each tumor's phenotype and identifying its biological behavior. Brain tumor classification remains an ongoing process as we move toward future precision medicine, and try to provide more precise and beneficial assessments for patients suffering from brain tumors.

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