short review

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# WHO classification of tumors of the nervous system: preview of the upcoming 5th edition

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**Summary** Identification of the underlying genetic and epigenetic alterations in an increasing number of tumors of the nervous system is contributing to a more clinically relevant classification. In the following article, the 7 cIMPACT-NOW publications, which adumbrate the upcoming 5th edition of the WHO Classification of Tumours of the Central Nervous Sytem are summarized.

**Keywords** Brain · Tumor · Molecular · WHO · Classification

The revised fourth edition of the World Health Organization (WHO) classification of brain tumors, published in 2016, introduced a major restructuring in the diagnostic approach to brain tumors. Although strictly histological criteria were informative for certain tumors, concern was being increasingly raised about the subjective nature of histopathological assessment. A classic example was the low interobserver concordance in the diagnosis of diffuse gliomas with overlapping astrocytic and oligodendroglial features. After the advent of the IDH (isocitrate dehydrogenase), 1p19q era, however, most diffuse gliomas fell into astrocytoma or oligodendroglioma categories, rendering the ambiguous oligoastrocytoma designation largely obsolete. During the last decade, comprehensive, high-throughput molecular profiling coupled with advances in machine learning further transformed the diagnosis of brain cancer by supplying data for more accurate prediction of outcome and response to therapy. For the first time, molecular parameters were being incorporated with histological features into a complementary, integrative format, refining the WHO classification of an increasing number of primary brain tumors [1].

Given the rapid pace of advancement in the biological sciences, it was not surprising that WHO 2016 was already out of date at the time of publication. The ongoing discovery of promising biomarkers and new drug targets further fueled the need to accelerate the revision process. Accordingly, cIMPACT-NOW (Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was created to convey timely updates and provide recommendations for future WHO publications [2].

To date, the consortium has published 7 position papers (Table 1) with the first update dedicated to clarifying the use of the term NOS (not otherwise specified) and NEC (not elsewhere classified). The NOS designation should be applied when diagnoses lack necessary diagnostic (e.g., molecular) information for a more specific classification. The NEC qualifier can be applied when there is a mismatch between histological features and molecular results. Alternatively, NEC can be used when diagnostic tests show noncanonical results, precluding assignment to a known WHO entity and therefore suggestive of a new/emerging tumor type [3].

After several case reports of H3K27 mutations in such diverse tumors as posterior fossa ependymomas [4], pilocytic astrocytomas and glioneuronal tumors [5], cIMPACT-NOW decided that a clarification was in order. Therefore, the second update recommended that the term “diffuse midline glioma, H3K27m” and the accompanying WHO grade 4 designation should be restricted to diffuse midline gliomas and not be applied to other tumors only harboring the mutation. The prognostic significance of a H3K27 mutation in a noncanonical location or tumor entity is still un-

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**Table 1** cIMPACT-NOW updates

| Update / year | Main topics | Highlights | Comments |
|---|---|---|---|
| 1/2018 | Nomenclature, NOS vs. NEC | NOS ("not otherwise specified") and NEC ("not elsewhere classified") | NOS: molecular testing not available<br>NEC: test results do not fit known tumor |
| 2/2018 | H3K27m | WHO grade 4 restricted to H3K27m diffuse midline gliomas | Other tumors harboring the H3K27mut, not necessarily aggressive |
| | Diffuse astrocytoma, IDHmut | IDHmut, ATRX loss, diffuse p53-positivity suffice for astrocytoma diagnosis | 1p19q analysis not essential to exclude oligodendroglioma |
| 3/2018 | Diffuse astrocytoma, IDHwt | When histological criteria of GBM not fulfilled: *CDKN2A/2B* deletion or EGFR-amplification or *TERT*-promotor mutation | Prognosis similar to GBM with any of the listed molecular criteria |
| 4/2019 | Pediatric diffuse gliomas | MYB, MYBL1, or FGFR1 alterations or BRAFV600E mut | Brain tumors in children beyond the scope of this article |
| 5/2020 | Grading, Arabic numbers | Arabic in lieu of Roman numerals | – |
| | Grading, IDHmut astrocytomas | Grade 2: no M, MVP, N, D<br>Grade 3: M<br>Grade 3: MVP and/or N and/or D | GBM refers only to IDHwt, H3wt astrocytomas |
| 6/2020 | New tumor entities and summary of earlier publications | PLNTY (polymorphous low-grade neuroepithelial tumor)<br>Astroblastoma, *MN1*-altered<br>Chordoid glioma, *PRKCA* D463H-mut<br>High-grade astrocytoma with piloid features | – |
| 7/2020 | Ependymomas | Myxopapillary, WHO Grade 2<br>Classified according to location and molecular profile | *Supratentorial*[a]<br>RELA (C11orf95)-fusion<br>YAP-fusion<br>*Posteriuor fossa*<br>Type A<br>Type B<br>*Spinal*<br>MYCN-amplified |

*M* mitoses, *MVP* microvascular proliferation, *N* necrosis, *D* CDKN2A/B deletions, *cIMPACT-NOW* consortium to inform molecular and practical approaches to CNS tumor taxonomy, *WHO* World Health Organization
[a]Supratentorial excluding subependymoma

clear. In the same update, the diagnosis of diffuse astrocytoma, IDH mutant was simplified by introducing diagnostic criteria that obviated the requirement for 1p19q molecular testing. Based on immunohistochemical results alone, IDH-mutant gliomas with evidence of loss of ATRX expression and concomitant p53 overexpression could be diagnosed reliably as astrocytoma [6].

According to cIMPACT-NOW 3, IDH-wild-type astrocytomas, WHO grades 2 and 3, can be considered to behave as de facto glioblastomas, when the following molecular criteria are fulfilled: EGFR amplification and/or whole chromosome 7 gain and whole chromosome 10 loss (+7/–10) and/or *TERT* promoter mutation. In other words, reliable molecular readouts have made it possible to predict outcome in biopsies that do not fulfill the histological criteria of glioblastoma [7].

The fourth update focused on breakthroughs in the classification of IDH-, H3-wildtype, mostly hemispheric, pediatric diffuse gliomas. Six new glioma subtypes were introduced, including diffuse glioma, *MYB*-altered, diffuse glioma, MYBL1-altered, diffuse glioma, FGFR1 TKD-duplicated, diffuse glioma, FGFR1-mutant, and diffuse glioma, BRAFV600E-mutant (without *CDKN2A/2B* deletion) and diffuse glioma, other MAPK pathway alterations. The upshot of this update was that diffuse gliomas in childhood carry distinct molecular alterations, despite histological similarities to adult gliomas. Appropriate molecular testing is therefore essential for accurate classification and the identification of potential therapeutic targets [8].

In the fifth update, IDH mutant astrocytomas were grouped into a separate category reflecting the less aggressive clinical course compared to their wildtype counterparts. In lieu of Roman numerals, Arabic numeral grades 2–4 were assigned, with grade 3 tumors showing "significant" mitotic activity. Because of prognostic implications, it was recommended that grade 3 tumors undergo testing for homozygous *CDKN2A/B* deletions. Tumors with homozygous *CDKN2A/B* deletions or microvascular vascular proliferation and/or necrosis should henceforth be classified as astrocytoma, IDH-mutant, WHO grade 4 and no longer as glioblastoma [9].

The sixth update outlined general principles that will guide future grading and classification. Minor nomenclature refinements were introduced, such as substituting "entity" and "variant" with "type" and "subtype". Four major recommendations summarized changes that will appear in WHO 2021. The first category comprised newly recognized types, subtypes, diagnostic criteria or family of tumors. An example is the newly recognized diffuse glioma, H3.3 G34-mutant with an overall longer survival compared to

classic IDH-wildtype glioblastoma. Another example is astroblastoma, *MN1*-altered, once again highlighting the combined histological–molecular approach [10].

Nomenclature modifications (category 2) addressed in the sixth update include the elimination of location for chordoid glioma ("of the third ventricle"). In addition, ependymomas should carry combined histological–molecular designations based on unique epigenetic and genetic signatures at different anatomic sites. The category of supratentorial ependymoma comprises the clinically aggressive *RELA*-fusion (C11orf95)-positive and YAP1-fusion-positive tumors, which are associated with a more favorable prognosis. Ependymomas arising in the posterior fossa fall into *pediatric-type/PFA* and *adult-type/PFB*, with the latter associated with a better prognosis [10].

Several existing types such as extraventricular neurocytoma and pilocytic astrocytoma (category 3) will not undergo any changes. The fourth category comprises entities with insufficient literature to provide a recommendation. Examples include pilocytic astrocytomas with anaplastic features defined by its methylation profile and various infantile hemispheric gliomas characterized by a specific molecular signature, e.g., tyrosine receptor kinase fusions such as *NTRK, MET, ALK* or *ROS1* [8].

cIMPACT-NOW 7 once again focuses on advances in the classification of ependymomas, with most of the changes already alluded to in the sixth update. In light of frequent recurrences, myxopapillary ependymoma has been upgraded to WHO grade 2. In addition, a new, clinically aggressive, molecular subgroup of spinal ependymoma, ependymoma *MYCN*-amplified, has been recognized [10, 11, 12].

Recent publications that have appeared since the last cIMPACT update further underscore the distinct molecular landscape of brain tumors in children. To date, four molecular subtypes of diffuse midline glioma with H3.1/3.2 K27-, H3.3 K27 mutations, EZHIP-overexpression and EGFR mutations have been reported [13]. Most EGFR-mutated tumors are bithalamic, whereas H3.1 K27 mutations favor the pons [14]. Polymorphous low-grade neuroepithelial tumor (PLTY) of the young is a newly recognized, epilepsy-associated tumor type with MAPK alterations found in children and young adults [15]. Two additional entities, the diffuse glioneuronal tumor with oligodendroglial features and nuclear clusters (DGONC) and myxoid glioneuronal tumor, have joined the growing list of glioneuronal and neuronal tumors [16].

In addition to pediatric tumors, the discovery of actionable targets in roughly one-third of gliomas emphasizes the importance of optimal tissue management for meeting the challenges of personalized medicine [17]. In the setting of limited tissue samples, there is increasing need for critical evaluation, perhaps in the multidisciplinary setting, of the optimal diagnostic algorithm, including choice of analytical methods and tissue allocation for studies. Patient age, histological diagnosis and tumor location are important factors for selecting the appropriate nucleic acid tests such as FISH, PCR, DNA and RNA sequencing. In fact, next-generation sequencing (NGS) is becoming widely accepted as a cost-effective method for evaluating multiple genes simultaneously.

For histologically ambiguous tumors, DNA-methylome profiling is another analytical procedure that can complement the diagnostic process. For example, infantile hemispheric gliomas, which are histologically diverse and harbor a variety of gene fusions, tend to align to a separate methylation class [18]. However, caveats persist regarding regulatory and yet to be determined methodological issues. In the case of *NTRK*-fusions, however, methylation profiling has not proven informative [19].

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