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Review

CIMPACT-NOW UPDATES AND THE 2021 WHO CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS: WHERE DOES IT LEAVE UNDERDEVELOPED NEUROPATHOLOGY CENTERS AND HOW TO REPORT DIFFUSE GLIOMAS

George S. Stoyanov[1*], Emran Lyutfi[2], Reneta Georgieva[3], Deyan Dzhenkov[1], Lilyana Petkova[1], Borislav D. Ivanov[4], Ara Kaprelyan[2], and Peter Ghenev[1*]

[1]*Department of General and Clinical Pathology, Forensic Medicine and Deontology, Faculty of Medicine, Medical University, Varna, Bulgaria*

[2]*Department of Neurology and Neuroscience, Faculty of Medicine, Medical University, Varna, Bulgaria*

[3]*Student, Faculty of Medicine, Medical University, Varna, Bulgaria*

[4]*Department of Clinical Medical Sciences, Faculty of Dental Medicine, Medical University, Varna, Bulgaria*

The classification of central nervous system tumors, first introduced by Bailey and Cushing in 1926, has been constantly updated by the World Health Organization. The latest fifth edition, introduced in 2021, although the bluebook was officially published in the first weeks of 2022, is the first classification to officially introduce histological and molecular grading criteria for the different nosological units based on mutation-oriented, evidence-based patient prognosis. So far, these changes have had no impact on patient treatment, despite the stratified patient risk and prognosis. As such, there has been little initiative for underfunded and underdeveloped neuropathological centers to introduce molecular diagnostic modalities, especially as they are of little use to other tumor groups. This has disadvantaged neuropathologists in such centers, especially when reporting the most common of these tumor groups – diffuse (high-grade) gliomas, as mutational status is key in these nosological units. Herein we review the changes in the classification system and suggest an integrated descriptive manner of reporting such tumors, allowing for the oncologist to initiate treatment, suggesting the necessary mutations to be evaluated and not misleading the patient that he was misdiagnosed upon consultation at a referral center. ***Biomed Rev*** **2021; 32: 31–36**

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*Correspondence to: georgi.geesh@gmail.com, peterghenev@yahoo.com

INTRODUCTION

Given the many controversies in the classification of central nervous system (CNS) tumors arising from the original Percival Bailey and Harvey Cushing classification of 1926, the World Health Organization (WHO), as a governing medical body, has since strived to introduce a unified evidence-based (as well as peer-reviewed) classification (1, 2). As a result of the efforts of 23 international centers and more than 300 pathologists, a unified classification was established between 1956 and 1979, primarily based on that of Bailey and Cushing, but with many changes to the concepts embedded in it (2). The first unified classification published in 1979 was followed by new editions in 1982 (second edition), 2000 (third edition), 2007 (fourth edition), 2016 (revised fourth edition) and the latest one from 2021 (fifth edition), although the official bluebook was released in early 2022 (3–6).

The 2021 classification is the first WHO classification, which in addition to purely morphological aspects in the diagnosis of CNS tumors, includes molecular and genetic criteria, gross (neuroradiology) data on tumor growth and location, as well as separating entities based on the age group of patients (Figs 1, 2). Furthermore, unlike previous classifications, which sometimes came decades from one another for the fifth edition, interim updates were introduced to inform on novel findings not present in the classification, in the form of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) updates (4, 5). cIMPACT-NOW updates, curated by members of the WHO CNS tumor editorial board, served as a gentle introduction to future guidelines in the new classification and have been well accepted by the neuropathology community, as well as underlining the importance of interim updates and integration of molecular and genetic data in tumor taxonomy, something that no other WHO classification has adopted as extensively as the CNS one.

CIMPACT-NOW UPDATES

The establishment of the consortium aims to introduce new knowledge in practice by publishing data based on clinical and molecular parameters of tumors of the nervous system. The consortium was formed shortly after the publication of the revised fourth edition (2016), itself a mildly modified version of the 2007 classification, with few changes and molecular markers introduced, despite the accumulated body of evidence.

Until the release of the 2021 WHO CNS tumor classification, cIMPACT-NOW had published a total of 7 reports:

(i) the first report strictly defines the use of NOS (not otherwise specified) and NEC (not elsewhere classified) terminology. As such, CNS tumors should be designated as NOS (e.g., glioblastoma multiforme, WHO grade IV, NOS) when no immunohistochemical and molecular

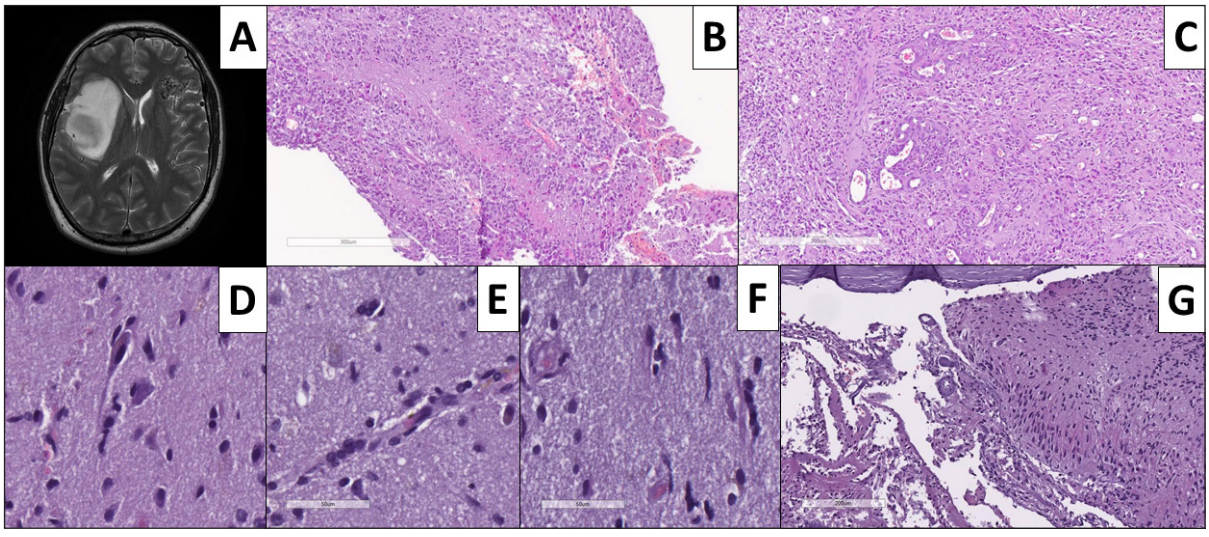

Figure 1. *Classical features require for* glioblastoma multiforme *diagnosis: diffuse tumor formation seen on neuroradiology, herein MRI (**A**); pathognomonic primary (pseudopalisadic necrosis) and secondary (glomeruloid vascular proliferation) Scherer figures (**B and C**); non-pathognomonic secondary Scherer figures (features of growth seen in other glial tumors as well) – neuronal satelitosis (**D**), vascular satelitosis (**E**), tractal/peryaxonal aggregation (**F**), and submeningeal palisading (**G**).*

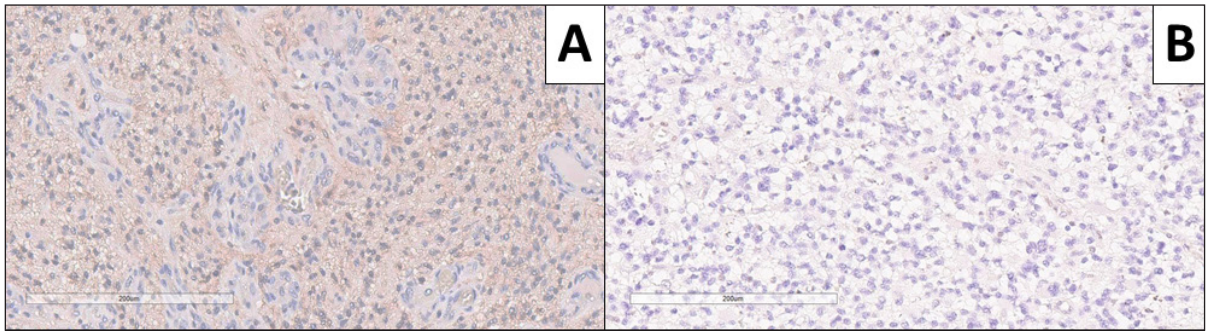

Figure 2. *Molecular features, as require by the WHO CNS 2021 guidelines: IDH R132H mutant phenotype as the basis of diffuse astrocytoma, WHO CNS grade 4 (A) and IDH-wildtype retaining its designation as* glioblastoma multiforme *in tumors with identical histomorphology (B).*

genetic tests have been performed to prove the mutations introduced in the classification, e.g., IDH, or if the results are of them are for one reason or another (fixation, processing of the material, atypical form of expression – nuclear or membrane, instead of cytoplasmic) are unreliable. Tumors in which the necessary or even a more comprehensive set of molecular and genetic tests have been performed, but the results do not correspond to any nosological unit in the classification, should be designated as NEC – a rare or emerging form of a tumor, whose genetic profile has not yet been defined and clarified in relation to clinical course and patient survival (7).

(i) the second report clarified that only glial tumors with astrocyte differentiation located along the midline with a mutation in H3K27m should be designated as diffuse midline glioma. This specification was introduced due to the presence of a similar mutation in other tumors close to the midline, such as subtentorial ependymomas, isolated cases of pilocytic astrocytoma and glioneuronal tumors, which have different clinical courses and the significance of this mutation in them is not specified, given their extreme rarity (8).

(i) the third report specifies molecular and genetic aspects for considering a morphologically low-grade glial tumor as a high-grade one. Such criteria are EGFR amplification and/or the presence of an additional 7 chromosome and loss of chromosome 10 (+ 7 / −10) and/or TERT promoter mutations, given the relatively closer clinical course of such tumors to glioblastoma multiforme than other tumors with similar morphology, without the described changes (9).

(i) the fourth report proposed several new diagnostic categories of diffuse pediatric gliomas, namely diffuse glioma, MYB-altered; diffuse glioma, MYBL1-altered; diffuse glioma with FGFR1 TKD duplication; diffuse glioma, FGFR1 mutant; diffuse glioma, BRAF V600E mutant (without CDKN2A / 2B deletion) and diffuse glioma with other alterations in the MAPK pathway. Thus, pediatric gliomas are primarily separated into their own group because of their different genetic profile and the different clinical course against the background of identical morphology with diffuse gliomas in adults (10).

(i) in the fifth report, the most significant number of changes in the classification of tumors of the CNS were proposed. With the idea of unifying the WHO CNS classification reporting with that of other classifications, tumor grading was suggested to be marked with Arabic (1-4) rather than the until then used Roman numerals (I-IV). Furthermore, IDH mutant tumors were separated in their own diagnostic category, and the morphological criteria for grade 3 tumors were specified – pronounced mitotic activity (Fig. 2). Testing for homozygous CDKN2A / B deletion has been proposed for such tumors, as IDH mutants with such a deletion have a significantly worse prognosis. As such, these changes introduced a significant shift in the most common glial tumor entry thus far, separating it into glioblastoma multiforme, WHO grade 4, as a tumor without an IDH mutation and diffuse astrocytoma, WHO grade 4 (thus far classified as glioblastoma), which must meet the following criteria: IDH mutation and microvascular proliferation and/or necrosis and/or homozygous deletion of CDKN2A / B (11) (Figs 2, 3). The newly introduced nosological entity has a better prognosis than glioblastoma and is identified in younger individuals, despite identical mor-

phology, but is still a more aggressive tumor than grade 3 designated entries.

(i) the sixth report introduced many nomenclature changes and clarified some of the principles for modifying future classifications by introducing new tumor types and subtypes. The new nosological units introduced were diffuse glioma, without mutation in IDH, H3.3 G34-mutant, which thus far was also reported as glioblastoma multiforme, but has a distinctly better prognosis as well as it occurs in younger individuals, and astroblastoma with alteration in MN1 (Figure 3). For some of the nosological units, the need to specify the location for the diagnosis has been eliminated (for example, choroidal glioma instead of choroidal glioma of the third ventricle). For ependymomas, a combined morphological-molecular diagnosis (integrated diagnosis) was introduced with new types – RELA-fusion (C11orf95) -positive and YAP1 fusion-positive supratentorial, as well as pediatric and adult subtypes of the subtentorial forms of these tumors. For some of the tumors, specifics for new molecular genetic alterations have been provided, which at this stage are with an unestablished role in patient prognosis (12).

(i) the latest seventh report has made minor clarifications for some of the new molecular profiles of tumors, such as introducing MYCN-amplified spinal ependymoma with an aggressive course and the reclassification of myxopapillary ependymoma as WHO grade 2 (13).

2021 WHO CLASSIFICATION OF HIGH-GRADE GLIOMAS

As cIMPACT-NOW members are designated WHO CNS tumor classification editors, the consortium updates were integrated and formed the basis of the 2021 WHO CNS tumor classification (3–5). Although drastic, these changes, compared to the previous classifications, are based on clinically significant and detectable changes in the phenotype of tumors (Fig. 3). Given their smooth implementation with cIMPACT-NOW reports, providing not only timely information to practicing neuropathologists but also time to adapt the diagnostic process before the official introduction of changes, adaptation to the new classification should not be a difficulty for many of the developed neuropathological centers (4). Finally, a large part of the innovations concern either previously introduced nosological units with a change in the name or rare subforms of tumors with a well-clarified diagnostic approach to them.

Concerning glioblastoma multiforme and the newly defined diffuse astrocytoma, IDH mutant, WHO CNS grade 4, given the partial presence of IDH in the previous revision and the well-known frequency and significance of the mutation, this change is cosmetic rather than functional and does not changes the diagnostic approach (Figure 1-3) (3,6). The changes in lower-grade astroglial tumors are more drastic with the introduction of molecular criteria for grading, which is why in the new classification, it should be noted as WHO

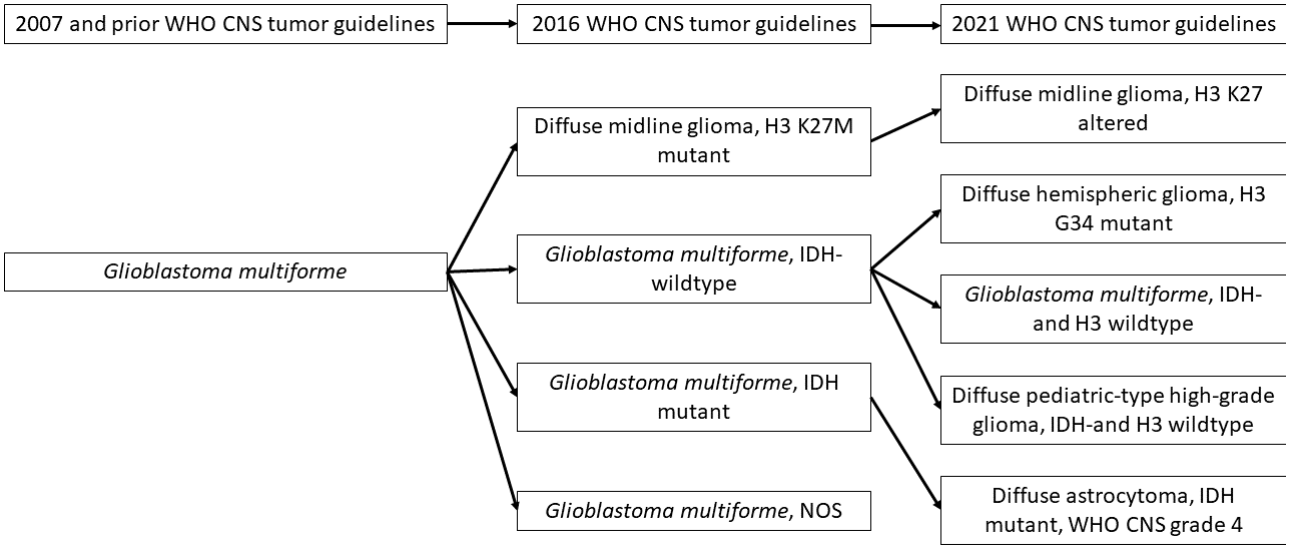

Figure 3. *The Darwinian evolution of reporting astrocytic tumors with glomeruloid vascular proliferation and/or pseudopalisadic necrosis. NOTE:* Glioblastoma multiforme*, NOS as per the 2016 guidelines is no longer in use (extinct term).*

CNS grade, given the integrated way of its placement. The change with the introduction of the pediatric group of diffuse gliomas, some of which so far belong to the group of glioblastoma multiforme, is a cosmetic modification rather than a functional one, and this should not be a diagnostic difficulty, given the rapid adaptation to midline gliomas introduced in the previous classification, which also morphologically resemble glioblastomas (Figure 3) (3).

FROM SCIENCE TO PRACTICE

The new guidelines are a needed update for practice, as they more strictly define the disease course and patient prognosis. However, despite these introductions, therapeutic modalities for the newly defined entries remain the same as in their previous incarnations – temozolomide (chemotherapy) and radiotherapy. Inevitably, however, new treatment guidelines will emerge for these entities with chemo and radiotherapy regimens doses modifications and new treatment options introduced. However, a big question remains of the histopathological reporting of such tumors in the absence of the classification-defined modalities for testing. While the previous classification introduced NOS and the current one still allows for its use, from a practical standpoint, the reporting of glioblastoma, NOS is no longer a viable option (Fig. 3). This is mainly because NOS is more suitable to entries that are defined morphologically and subtyped molecularly, such as ependymomas. For glial tumors, especially high-grade ones, as already mentioned, the diagnosis of glioblastoma can be placed molecularly with TERT promoter mutation, EGFR amplification, and +7/−10 copy number changes in IDH-wildtype diffuse astrocytomas.

This places minor and underfunded neuropathology labs in a peculiar situation: despite patient therapy being identical for the different nosological units, upon consultation at a referral center, the diagnosis can be changed, leading patients to believe they were severely misdiagnosed. Furthermore, reporting glioblastoma and lower grade astrocytic tumors as NOS can lead to bad science when studying future factors and establishing prognosis on a mixed group of tumor entries.

Hence a recommendation for histopathological reporting would be:

(i) using retrograde grading – e.g., ***glioblastoma multiforme, NOS, WHO grade IV (WHO 2016)*** – this approach, although showing the outdated methods of placing the diagnosis, will be of use both the oncology and radiotherapy department, as well as national and regional malignant tumor registries (as they historically take a long period to adapt to new classifications), but cannot be used to stratify patient prognosis and risk of disease progression (6).

(i) using minimal grading – e.g., ***diffuse astrocytoma, NOS*** – this approach, although technically correct based on histological criteria, will not allow proper inclusion into registries nor be of use to oncologists and radiotherapists (3).

(i) combined grading system – e.g., ***diffuse astrocytoma – glioblastoma multiforme, NOS as per the 2016 WHO classification*** – this method, although suffering from the drawback of the previous two ones, will on consultation in a referral center show that the neuropathologist reporting is aware of the changes of the classification, but is unable to evaluate mutations (3, 6).

(i) integrated descriptive diagnosis – e.g., ***diffuse astrocytoma with histological features of glioblastoma, WHO CNS grade 4, for molecular evaluation of IDH and H3*** – this method will not only allow for proper inclusion into registries and have sufficient information for oncologists to initiate treatment, but will also allow for consultation in genetic laboratories, without a designated neuropathologist, which upon testing can allow the pathologist who placed the initial diagnosis to properly classify – e.g., glioblastoma, IDH-wildtype, WHO CNS grade 4 or diffuse astrocytoma, IDH-mutant, WHO CNS grade 4. This method based on neuroradiology and patient age can further suggest the nosological units and pinpoint the minimal set of mutations to be evaluated – e.g., ***diffuse astrocytoma suggestive of midline glioma, WHO CNS grade 4, for molecular evaluation of H3 K27***. Furthermore, as histologically non-grade 4 tumors or ill-defined ones can obtain that grade and histogenesis through molecular workup, this method would allow for such tumors to be reported as ***diffuse astrocytoma with unclear WHO CNS grade (histological WHO CNS grade 3), for molecular evaluation of IDH, H3, CDKN2A/B and 1p/19q*** (3).

CONCLUSION

The updated neuropathology requirements introduced first through the cIMPACT-NOW reports and later integrated into the 2021 WHO CNS tumor classification, histopathological reporting of such tumors, especially for the most common

ones – diffuse gliomas, has become increasingly difficult for underdeveloped centers. The patient-oriented nosological units based on survival-significant mutations will inevitably improve clinical management of these relatively common conditions. However, significant care must be taken when reporting the tumors in these circumstances, with the goals of allowing registry inclusion for the patients, including sufficient information for the oncologist to initiate treatment as well as not misleading the patient that he was initially misdiagnosed if the case is consulted at a referral neuropathology laboratory. An optimal reporting system would be an integrated descriptive one, e.g., *diffuse astrocytoma with histological features of glioblastoma, for molecular evaluation of IDH and H3*, which specifies the larger tumor group and pinpoints the mutations needed for the identification of the proper nosological unit.

CONFLICT OF INTEREST STATEMENT

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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