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The anticipated revision of the grading criteria for adult isocitrate dehydrogenase–mutant diffuse glioma within the neuro-oncology community

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See the article by Appay et al. in this issue, pp. 1519–1528.

After the discovery of the isocitrate dehydrogenase (IDH) mutation, it has become well accepted that diffuse grades II and III gliomas in adults, which have long been defined by histology alone, should be biologically stratified by the presence or absence of an IDH mutation for more precise prognostication and clinical management. The 2016 updated fourth edition of the World Health Organization (WHO) classification of tumors of the central nervous system has therefore classified those gliomas into IDH-mutant and IDH-wildtype subgroups, with the latter considered to have a poor prognosis compared with the former.

While this molecular stratification has dramatically improved the classification of such gliomas, the grading schemes for new diagnostic classes remain unchanged. Indeed, the 2016 WHO update applies these same grading criteria for both IDH-mutant and IDH-wildtype gliomas.[1] Unfortunately, shortcomings with these legacy grading systems are evident[2,3]; the grading system based on histologic anaplasia, mitotic activity, and microvascular proliferation (MVP) and/or necrosis does not adequately correlate with the natural history, progression-free survival (PFS), or overall survival (OS). Several retrospective studies have shown that histologic grading based on the presence or absence of substantial mitotic activity may not adequately stratify IDH-mutant astrocytomas into the WHO grades II and III categories.[2,3] To provide a more meaningful risk stratification, several studies have tried to identify markers for aggressive clinical behavior in order to support a better therapeutic strategy.[4–9]

To address such issues in the 2016 WHO update, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) was established in 2016.[10] Recently, the cIMPACT-NOW Working Committee 1 proposed the grading of IDH-wildtype diffuse astrocytic gliomas, suggesting that histologic grades II/III IDH-wildtype gliomas with epidermal growth factor amplification, telomerase reverse transcriptase promoter mutations, or the combination of gain of chromosome 7 and loss of chromosome 10 could be considered "diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV."[10] However, no consensus on pathologic or molecular markers that could be incorporated into a more clinically relevant grading scheme for IDH-mutant gliomas has been reached.

In the present issue of *Neuro-Oncology*, Appay et al[11] show that cyclin-dependent kinase inhibitor 2A (CDKN2A) homozygous deletion is a strong adverse prognostic factor in diffuse malignant IDH-mutant gliomas, using 911 IDH-mutant gliomas from the POLA network, a dedicated program in France that has been established to homogenize the management of de novo adult high-grade glioma with an oligodendroglial component. Although the prognostic significance of CDKN2A loss in IDH-mutant astrocytomas has been demonstrated before, the findings of prognostic significance in anaplastic oligodendrogliomas is novel. They also show that no CDKN2A homozygous deletion was identified in an independent cohort of 40 grade II IDH-mutant gliomas, including 20 oligodendroglioma, IDH-mutant and 1p/19q-codeleted. In addition, they found that neither a retinoblastoma 1 (RB1) homozygous deletion nor cyclin-dependent kinase 4 (CDK4) amplification, which have been shown to be significant markers in diffuse astrocytomas, had prognostic value among IDH-mutant anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted.

In terms of the correlation with histologic malignant markers, among tumors lacking CDKN2A homozygous deletion (n = 450), the presence of MVP and/or necrosis was relevant for OS (P = 0.028), although not statistically significant for PFS (P = 0.085). In contrast, among tumors with CDKN2A homozygous deletion (n = 33), the presence of MVP and/or necrosis was relevant for neither PFS (P = 0.739) nor OS (P = 0.114).

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The molecular alterations previously studied using relatively large cohorts include CDKN2A/B homozygous deletion, CDK4 amplification, RB1 mutation/homozygous deletion, mutations of PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) or PIK3R1 (phosphoinositide-3-kinase regulatory subunit 1), platelet derived growth factor receptor A amplification, NMYC amplification, global hypomethylation, genomic instability, and chromosome 14 loss strategy.[4–9] Also evaluated have been proliferative activity, based on the mitotic count or Ki67 indices, and other morphologic features typical of a high grade that might stratify the risk better than the current criteria.

Although the results of this study are convincing overall, there is one point that is not consistent with the findings of previous studies in the literature; no previous study has successfully identified markers for distinguishing subgroups among IDH-mutant oligodendrogliomas and 1p/19q codeletion. Since the definition as well as the grading criteria for oligodendrogliomas and oligoastrocytomas are quite subjective in the WHO 2007 criteria of CNS tumors, which are primarily used by the POLA study focusing on high-grade gliomas with oligodendroglioma components, the actual inclusion criteria for this study may well differ from those of previous studies. For example, >25% oligodendroglioma components and a cutoff of 6 mitoses/10 high-powered fields have often been applied for grade III oligodendrogliomas and oligoastrocytomas, with the latter value being higher than that for anaplastic astrocytomas (1–2 mitoses present). Such a difference from the literature may be attributed, at least in part, to differences in the study cohort; for example, this cohort does not include grade II gliomas, which prevents the direct comparison of prognostic or predictive powers between oligodendrogliomas and anaplastic oligodendrogliomas lacking CDKN2A homozygous deletion, as well as making it difficult to compare the results of the present study with those in the literature.

Another concern of this study is the treatment heterogeneity, including the extent of surgical resection and adjuvant therapy regimen. The observation period (<120 mo) might not be long enough for an adequate evaluation of oligodendrogliomas without CDKN2A deletion.

However, despite such controversial issues concerning the design of this study, the group sufficiently showed that a CDKN2A homozygous deletion has prognostic significance in both anaplastic oligodendrogliomas and high-grade IDH-mutant astrocytomas and that MVP stratifies IDH-mutant gliomas lacking a CDKN2A homozygous deletion, suggesting that the integration of molecular information and traditional histologic findings is still essential for achieving maximum risk stratification of adult cases of IDH-mutant diffuse gliomas. The grading scheme for adult IDH-mutant as well as wildtype gliomas should therefore be revised in the next WHO update (fifth edition of the CNS Blue Book[10]).

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