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cIMPACT-NOW Update 5: Recommended Grading Criteria and Terminologies for IDH-mutant Astrocytomas

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Introduction

The diagnostic importance of IDH mutational status in diffuse gliomas was first formally recognized within the updated 4th edition of the WHO Classification of Tumours of the Central Nervous System (2016). Its introduction as a diagnostic marker was based on evidence that incorporation of biomarkers into an integrated diagnosis provided a more reproducible and clinically meaningful classification of diffuse gliomas in adults [20–22]. For IDH-mutant diffuse astrocytic gliomas, the integrated diagnostic entities (and corresponding grades) of the 2016 WHO Classification included: Diffuse Astrocytoma, IDH-mutant (WHO grade II), Anaplastic Astrocytoma, IDH-mutant (WHO grade III) and Glioblastoma, IDH-mutant (WHO grade IV). In contrast to IDH-mutant tumors, IDH-wildtype diffuse astrocytic gliomas are now recognized as distinct clinical and genetic entities that usually have much more aggressive clinical behavior, particularly in adults [5, 13]. While these molecular classifications represented a major step forward, grading schemes for the new diagnostic classes were not modified in parallel. The current grading criteria for diffuse astrocytic gliomas were developed prior to the understanding of molecularly distinct entities, yet the 2016 WHO update applies these same grading criteria for both IDH-mutant and IDH-wildtype gliomas [11, 14].

These legacy grading systems based on morphologic features (mitotic activity, anaplastic nuclear features, microvascular proliferation and necrosis) are not optimal [24, 27]. In particular, multiple retrospective studies have concluded that histologic grading criteria may not stratify risk for patients with IDH-mutant astrocytomas in the WHO grade II and III categories [1, 7, 24, 27, 33]. Yet, other studies have demonstrated that traditional grading schemes are still capable of stratifying risk for these patients [8, 30, 32]. In an attempt to improve risk stratification, several studies have investigated potential morphologic, proliferative or molecular markers that correlate with aggressive clinical behavior and could be incorporated into a more clinically relevant grading scheme [1, 2, 6, 7, 26, 30–32].

We evaluated the literature to determine whether there is sufficient evidence to define molecular genetic or other criteria that could reliably stratify risk among patients with IDH-mutant diffuse astrocytic gliomas or could identify those tumors that would behave most aggressively, with a clinical course corresponding to WHO grade IV. Among the molecular alterations considered were: *CDKN2A/B* homozygous deletion, *CDK4* amplification, *RB1* mutation or homozyous deletion, *PIK3CA* or *PIK3R1* mutations, *PDGFRA* amplification, *MYCN* amplification, global DNA methylation levels, genomic instability and chromosome

14 loss. We also considered whether there were thresholds of proliferative activity, based on mitotic count or Ki-67 indices, or other morphologic features typical of a high grade that might stratify risk better than current criteria. Finally, we considered potential future nosologies for IDH-mutant diffuse astrocytic gliomas in order to more clearly delineate these from IDH-wildtype diffuse gliomas. To achieve these goals, cIMPACT-NOW assembled a group of experienced neuropathologists and clinical neuro-oncologists as Working Committee 1 for Round 2 discussions, which held three teleconferences in an open manner similar to the discussions held at WHO consensus meetings. A subsequent meeting of cIMPACT-NOW in Utrecht, the Netherlands in September 2019 was used to further shape the recommendations and justifications of Working Committee 1.

Molecular Alterations Discussed for Grading of IDH-Mutant Diffuse Astrocytomas

CDKN2A/B homozygous deletion

Multiple studies have identified homozygous deletion of *CDKN2A/B* as a marker of poor prognosis in patients with IDH-mutant diffuse astrocytic gliomas [1, 2, 8, 16, 26, 30, 32, 33]. Initial observations were that both *CDKN2A/B* homozygous deletions and *CDK4* amplification were enriched among IDH-mutant astrocytomas that were associated with poor prognosis, and that this subset also showed lower levels of global DNA methylation (G-CIMP-low) [6]. Subsequent investigations of *CDKN2A/B* homozygous deletion as an independent marker in WHO grade II and III IDH-mutant astrocytic gliomas confirmed a strong association with shorter survival [7, 8, 26, 33]. A more recent study demonstrated that *CDKN2A/B* homozygous deletion was strongly associated with a poor prognosis in a cohort that included all grades of IDH-mutant astrocytomas (WHO grades II-IV) on univariable analysis [30]. In particular, *CDKN2A/B* homozygous deletions in histologic grade III IDH-mutant astrocytomas were associated with shorter patient survival, similar to WHO grade IV tumors [30]. Other investigations have corroborated these findings [2, 16, 30]. The frequencies of *CDKN2A/B* homozygous deletions reported in IDH-mutant astrocytic gliomas range from 0–12% in WHO grade II, 6–20% in WHO grade III and 16–34% in WHO grade IV tumors [2, 30, 32]. It should be noted that the prognostic associations reported for *CNKN2A/B* homozygous deletion have been based on retrospective cohorts with potentially confounding prognostic parameters, notably age and divergent patterns of care. Moreover, homozygous deletion at 9p21 not only targets the *CDKN2A/B* locus, but also other neighboring genes that have known or suspected tumor suppressive functions [3, 15, 29].

Alteration of other RB pathway genes

CDK4 amplification in IDH-mutant astrocytomas was associated with poor prognosis and its combination with chromosome 14 loss predicted an even shorter overall survival [7, 8]. Other studies have concluded that *CDK4* amplification was not associated with poor prognosis [2, 30]. Homozygous deletion of *RB1* was strongly associated with inferior overall survival among IDH-mutant astrocytomas on univariate analysis, but this finding was not corroborated in other investigations [2, 30]. In a multivariate analysis of two sizable patient cohorts, Aoki et al. demonstrated that altered RB pathway genes (*CDKN2A/B* homozygous deletion, *CDK4* amplification or *RB1* mutation), when considered together, were a strong and statistically significant predictor of poor prognosis in IDH-mutant astrocytoma patients [1]. When considered by themselves in this study, each of these markers was associated with a less favorable prognosis, although not significantly on univariate analysis. The prognostic role of less common RB pathway gene alterations, such as *CDKN2A/B* point mutation, *CDKN2A/B* promoter methylation or *CDK6* amplification remains unclear and deserves further study.

PIK3R1 and *PIK3CA* mutations

On multivariate analysis, *PIK3R1* mutations were an independent marker of poor prognosis in IDH-mutant astrocytomas of WHO grade II or III. *PIK3CA* mutations showed a strong trend towards shorter overall survival but were not an independent marker on multivariable analysis [1].

PDGFRA amplification

Multiple studies have demonstrated that *PDGFRA* amplification is associated with shorter survival among patients with IDH-mutant astrocytic gliomas, including a recent investigation showing its prognostic significance specifically in histologic grade II and III tumors on multivariable analysis [25, 30, 32]. Another study did not uncover this association [1].

MYCN amplification

MYCN amplification was associated with shorter overall survival in patients with IDH-mutant astrocytomas (WHO grades II-IV) on univariable analysis [30].

Genomic instability

Both high levels of copy number variations (CNV) and somatic mutations have been associated with higher histologic grade among IDH-mutant astrocytomas and with shorter overall survival in patients with WHO grade II or III IDH-mutant astrocytomas [1, 9, 28]. In a separate investigation, patients with IDH-mutant astrocytomas that displayed a high CNV level had shorter overall survival than those with low CNV level [30]. There are challenges in the comparison and interpretation of these investigations, since the thresholds for high CNV and somatic mutation varied [23].

Reduced global DNA methylation

In a study of 1,122 diffuse gliomas, a small subset of IDH-mutant diffuse astrocytic gliomas (WHO grades II-IV) were found to have globally reduced levels of DNA methylation (G-CIMP-low) relative to the majority of IDH-mutant astrocytomas, as well as a distinctive gene expression profile [6]. Half of these GCIMP-low gliomas corresponded to WHO grade IV and the other half were histologically WHO grade II or III. Patients with G-CIMP-low IDH-mutant astrocytomas had shorter overall survival than patients in the G-CIMP-high group. More than 75% of the G-CIMP-low tumors had alterations in RB pathway genes (*CDKN2A/B* homozygous deletion and *CDK4* amplification). Another study, focused exclusively on IDH-mutant glioblastoma, WHO grade IV, confirmed both the short survival of patients with G-CIMP-low tumors and the association with *CDKN2A/B* homozygous deletion [17].

Other genetic markers

Other genetic markers of interest did not show strong evidence for the ability to stratify risk among patients with IDH-mutant astrocytomas or predict WHO grade IV behavior. Larger or additional studies may provide stronger evidence in the future [6, 8, 12, 24, 30].

Mitotic activity and proliferation indices

The traditional method for stratifying risk among histologic grade II or III diffuse astrocytic gliomas has relied heavily on the identification of mitotic activity. The WHO 2016 indicates that "significant proliferative activity" distinguishes anaplastic astrocytoma, IDH-mutant, WHO grade III from diffuse astrocytoma, IDH mutant, WHO grade II [20]. Based on studies in the pre-WHO 2016 era, astrocytomas with ≥ 2 mitoses in the entire specimen have been shown to be associated with shorter survival than those with 0 or 1 mitoses and this threshold has therefore been used by practicing neuropathologists for the designation of WHO grade III [10, 11, 14]. Specimen size must also be considered. In a very small biopsy, one mitosis may be sufficient, whereas in very large specimens, greater mitotic activity may be necessary [20]. These thresholds for mitotic activity have not been corroborated by several studies of IDH-mutant cohorts [12, 24, 33]. However, others have demonstrated that traditional grading schemes can stratify risk among patients with grade II and III IDH-mutant astrocytomas, but with ample opportunity for improvement [8, 30, 32]. To date, there have been no studies that establish an alternative mitotic count that more reliably stratifies risk among histologic grade II and III IDH-mutant astrocytomas. Similarly, studies of proliferative index (e.g. based on Ki-67) have not identified criteria that unequivocally stratify risk among patients with IDH-mutant astrocytomas [12].

Summary of findings

The currently available evidence from multiple retrospective studies suggests that homozygous deletion of *CDKN2A/B* is associated with shorter survival in patients with IDH-mutant astrocytomas and that its presence corresponds to WHO grade IV clinical behavior. Alterations in other genes encoding members of the RB pathway, including *CDK4* amplification or *RB1* mutation/homozygous deletion, may also be markers of aggressive clinical behavior but the evidence is not as firmly established (e.g., fewer cases or fewer published studies). Several studies have demonstrated *PDGFRA* amplification as a marker of poor prognosis with potential for inclusion as a grading criterion with additional corroborating evidence. While mutations in *PIK3R1* and *PIK3CA*, as well as amplifications in *MYCN*, have been associated with shorter survival, additional cohorts are needed for validation. Genomic instability is a feature corresponding to poor prognosis in patients with IDH-mutant astrocytomas. However, the analyses and thresholds for clinical validation of genomic instability have not been firmly established for application to clinical practice. Similarly, G-CIMP-low DNA methylation pattern has been associated with shorter survival in IDH-mutant astrocytoma, but additional cohorts are needed for validation to more precisely define the G-CIMP-low methylation diagnostic profile as well as to assess the practicality of testing modalities. There is currently insufficient evidence to establish a new threshold of mitotic activity to discriminate histologic grade II and III IDH-mutant astrocytomas. Overall, with regard to clinical outcomes and grading criteria, we have been cautious in our interpretation of the literature, since most large studies on the relationship between genetic alterations and clinical outcomes have relied on retrospective cohorts in which patients had been treated differently depending on institution, era and histologic classification. Moreover, clinical follow-up times are limited in most studies, which is a particular weakness when assessing prognostic markers in patients whose median overall survival is beyond 10 years.

Proposed Terminology for next WHO classification

The terms used to classify the diffusely infiltrative gliomas are deeply rooted in history and based on presumed tumor cell lineage and levels of differentiation. For the diffuse astrocytic gliomas, we now understand that IDH-wildtype and IDH-mutant tumors represent distinct clinical and genetic entities, despite the similar terms used for their classification by the WHO (diffuse astrocytoma, anaplastic astrocytoma and glioblastoma). Terminologies that more clearly distinguish IDH-mutant and IDH-wildtype diffuse astrocytic gliomas are desirable. One suggestion was to reserve the term “glioblastoma” for those diffuse astrocytic gliomas that are IDH-wildtype and have histologic or genetic features predictive of a highly aggressive clinical behavior corresponding to WHO grade IV [4]. Diffuse astrocytic gliomas that are IDH-mutant would be graded based upon morphologic and genetic features that corresponded to WHO grade II, III or IV clinical behavior. The suggested terminologies, class definitions, and grading criteria for IDH-mutant astrocytomas are summarized in Table 1. We recognize that changes of this type may be viewed as controversial and will require further discussion in context of the next WHO classification, which is scheduled for later 2020 (see Supplemental Text for critiques and responses). Note the use of the Arabic numerals 2, 3 and 4, rather than the Roman numerals II, III and IV, that had traditionally been used for WHO CNS tumor grades; Arabic numerals are suggested in order to harmonize with WHO grading schemes of other tumor types and to reduce the possibility of introducing typographical and interpretive errors (i.e., the distinction of *2* vs *3* is less susceptible to error in a report than *II* vs. *III*).

Grading considerations for IDH-mutant astrocytomas.—IDH-mutant astrocytomas that lack significant mitotic activity, histologic anaplasia, microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletion are referred to as Astrocytoma, IDH-mutant, WHO grade 2. Patients with these tumors have a median overall survival greater than 10 years [2, 30]. An IDH-mutant astrocytoma that contains elevated mitotic activity and histologic anaplasia, yet lacks microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletion, currently fits into the designation of Astrocytoma, IDH-mutant, WHO grade 3. Recognizing that no validated published criteria exist for mitotic count cut-off values for grading IDH-mutant astrocytomas, “significant” mitotic activity remains the criterion to distinguish WHO grade 3 from grade 2 tumors. Most neuropathologists use a threshold of ≥ 2 mitoses within the entire specimen, or 1 mitosis in very small biopsies, while large specimen may require more [10, 14, 20]. The extent to which Astrocytoma, IDH-mutant, WHO grade 3 exhibits clinically more aggressive behavior relative to its

WHO grade 2 counterpart remains to be determined. It should be noted that future studies may refine mitotic thresholds for grading and may identify additional genetic alterations associated with more aggressive clinical behavior among WHO grade 2 and 3 IDH-mutant astrocytomas.

IDH-mutant astrocytomas with microvascular proliferation or necrosis or *CDKN2A/B* homozygous deletion, or any combination of these features, correspond to WHO grade 4. These tumors have been formerly considered as “Glioblastoma, IDH-mutant, WHO grade IV”. However, they are clinically and genetically distinct from glioblastoma, IDH-wildtype, and closely related to WHO grade 2 or 3 IDH-mutant astrocytomas. Thus, cIMPACT-NOW recommends that the WHO strongly consider discontinuing the term “Glioblastoma, IDH-mutant, WHO grade IV” and instead recommends referring to these tumors as “Astrocytoma, IDH-mutant, WHO grade 4”. Based on the strength of evidence, cIMPACT-NOW also recommends that *CDKN2A/B* homozygous deletion should be a WHO grade 4 criterion for IDH-mutant astrocytomas. Some studies have concluded that homozygous deletion of *CDKN2A/B* is associated with worse outcome even among patients with histologically defined WHO grade 4 IDH-mutant astrocytomas [16, 30]. Homozygous deletion can be determined by FISH, quantitative PCR, MLPA, microarray- or NGS-based methods. However, immunohistochemistry for p16 does not correlate well with deletion [26].

These recommendations represent the initial steps toward advancing our ability to distinguish clinically relevant subgroups of IDH-mutant astrocytomas at a diagnostic level, and in turn guide patient care and inclusion into clinical trials. In combination with the other cIMPACT-NOW updates, it is further anticipated that such recommendations will contribute to decisions guiding the 5th edition of the WHO brain tumor classification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

IDH-mutant Astrocytomas

Astrocytoma, IDH-mutant, WHO grade 2
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that is well differentiated and lacks histologic features of anaplasia. Mitotic activity is not detected or low*. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent.
Astrocytoma, IDH-mutant, WHO grade 3
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits focal or dispersed anaplasia and displays significant mitotic activity*. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent.
Astrocytoma, IDH-mutant, WHO grade 4
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits microvascular proliferation or necrosis or *CDKN2A/B* homozygous deletion or any combination of these features.

* = see text regarding mitotic count cut-off values