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REVIEW

cIMPACT-NOW: a practical summary of diagnostic points from Round 1 updates

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Abstract

cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was established to provide a forum to evaluate and recommend proposed changes to future CNS tumor classifications. From 2016 to 2019 (Round 1), cIMPACT published four updates. Update 1 clarified the use of the term NOS (Not Otherwise Specified) and proposed use of the additional term NEC (Not Elsewhere Classified). Update 2 issued clarifications regarding two diagnoses: *Diffuse Midline Glioma, H3 K27M-mutant* and *Diffuse Astrocytoma/Anaplastic Astrocytoma, IDH-mutant*. Update 3 proposed molecular criteria that could be used in the setting of an IDH-wildtype diffuse or anaplastic astrocytic glioma without histological features of glioblastoma to infer that the tumor would behave similarly to a grade IV glioblastoma. Update 4 suggested that, in children and young adults, subtypes of IDH-wildtype/H3-wildtype diffuse gliomas may have distinct clinical features in the setting of a *BRAF*^{V600E} mutation, *FGFR1* alteration, other MAPK pathway alteration, or a *MYB* or *MYBL1* rearrangement. The practical diagnostic relevance of these cIMPACT proposals is highlighted in this summary.

INTRODUCTION

cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was created under the sponsorship of the International Society of Neuropathology (ISN) in late 2016 to provide a forum to evaluate and recommend proposed changes to future CNS tumor classifications. While it was understood that the major impact on international brain tumor classification comes

through new editions of the WHO classification, it was hoped that this additional process would “see impact” in selected tumor types for periods between WHO classifications. Thus, cIMPACT-NOW updates are intended to provide guidance for diagnosticians and potentially inform future WHO classifications (3, 4).

In Round 1 (2016–2019), cIMPACT has published four updates, which are summarized below. Each update is the product of one of three cIMPACT-NOW Working

Committees, with vetting of the guidelines by all members of both the Steering Committee and Clinical Advisory Panel (see Acknowledgments for full rosters) as well as members of the ISN executive group. The following summaries are intended to provide practical diagnostic guidance for pathologists.

CIMPACT UPDATE 1

cIMPACT Update 1 (6), which came from Working Committee 3, clarified the use of the term NOS (Not Otherwise Specified) and proposed use of the additional term NEC (Not Elsewhere Classified). This distinction allows the ready separation of those diagnoses that result from lack of necessary diagnostic (e.g., molecular) information from those diagnoses that have had the required diagnostic testing but with the generation of non-diagnostic (i.e., for a WHO diagnosis) or negative results.

- For an **NOS** designation, diagnostic information (histological or molecular) necessary to assign more specific WHO diagnosis *is not available*.
- For an **NEC** designation, necessary diagnostic testing has been successfully performed, but the results do not readily allow for a WHO 2016 diagnosis. In some instances, this will be caused by a mismatch between clinical, histological, immunohistological and/or genetic features; in others, the results may support a new or emerging entity that is not yet included in the WHO classification.

Diagnostic relevance: The NOS designation provides an alert that a full molecular work-up has not been undertaken or was not successful. NEC diagnoses are similar to what pathologists have long referred to as “descriptive diagnoses”—in which the pathologist uses a non-WHO term to “describe” the tumor. The NEC designation simply provides a handy alert to treating neuro-oncologists that the tumor does not conform to a standard WHO diagnosis, despite the case having received an adequate pathological work-up. Importantly, NEC diagnoses are facilitated by the use of layered reports since such reports provide a ready means to display all of the histological and molecular data.

Some examples include:

- Whereas a histological oligodendroglioma that is IDH-mutant but has not been analyzed for 1p/19q status would be designated as *Oligodendroglioma, NOS*, a histological oligodendroglioma that is IDH-mutant with 1p deletion but intact 19q could be designated as *Diffuse glioma, IDH-mutant with 1p loss/19q retention, NEC*. (This is just an example, and analogous NEC diagnoses could be designated for other histological “oligodendrogliomas” showing different non-diagnostic genetic alterations).
- A high-grade diffuse astrocytic glioma with an H3 G34 mutation could be diagnosed using possible descriptive terms, such as *High-grade Astrocytic Glioma, H3 G34-mutant, NEC* or *Glioblastoma, IDH-wildtype and H3*

G34-mutant, NEC because this entity is not included in the current WHO classification, nor has terminology been determined for such an entity in a future classification. (Note that some nomenclatures use the designation G35 rather than G34 for the same residue.) If, on the other hand, this diagnosis is incorporated as an entity into a future WHO classification, the NEC designation would no longer be appropriate.

CIMPACT UPDATE 2

cIMPACT Update 2 (5) also came from Working Committee 3. It issued clarifications regarding two diagnoses: *Diffuse Midline Glioma, H3 K27M-mutant* and *Diffuse Astrocytoma, Anaplastic Astrocytoma, IDH-mutant*.

- The term *Diffuse Midline Glioma, H3 K27M-mutant* should be reserved for tumors that are diffuse (i.e., infiltrating), midline, gliomas and H3 K27M-mutant, and should not be applied to other tumors (e.g., ependymomas) that are H3 K27M-mutant.
- In the setting of a diffuse astrocytic-appearing WHO grade II or III glioma that has IDH mutation as well as loss of ATRX nuclear expression and/or strong, diffuse p53 immunopositivity, a diagnosis of *Diffuse Astrocytoma, IDH-mutant* or *Anaplastic Astrocytoma, IDH-mutant* can be rendered *in the absence of 1p/19q testing*.

Diagnostic relevance: The 2016 WHO classification states that H3 K27M mutations occur “exclusively” in diffuse midline gliomas, but these mutations have now been reported in other brain tumors. (Note that some nomenclatures use the designation K28 rather than K27 for the same residue.) The clinical significance of these mutations, however, is only understood well for those occurring in the setting of diffuse midline gliomas. For this reason, pathologists should reserve the specific diagnosis of *Diffuse Midline Glioma, H3 K27M-mutant* for tumors that meet all of the above diagnostic criteria. For a tumor that is H3 K27M-mutant but not a diffuse midline glioma, however, the mutation should be reported and an NEC designation should be considered.

Because the 2016 WHO classification introduced molecular parameters into tumor classification, there was considerable worry that some institutions would not be able to undertake full work-ups. cIMPACT Update 2 provides some relief in that context, since it states that a purely immunohistochemical work-up may yield a full diagnosis in the setting of a histological diffuse astrocytic glioma that is positive for IDH1 R132H and that also has loss of ATRX nuclear expression and/or strong, diffuse p53 immunopositivity—without the need for 1p/19q testing. Given that some institutions have access to 1p/19q testing but results may take a week or two to be finalized, the cIMPACT Update 2 should also decrease diagnostic turn-around time in these cases.

CIMPACT UPDATE 3

cIMPACT Update 3 (1) was from Working Committee 1. It determined molecular criteria that could be used in the setting of an *IDH-wildtype* diffuse or anaplastic *astrocytic glioma* without histological features of glioblastoma (i.e., microvascular proliferation and/or necrosis) to infer that the tumor would follow a clinical course more similar to a WHO grade IV glioblastoma.

- For diffuse and anaplastic astrocytic gliomas without IDH mutation, the finding of any or all of the following molecular criteria corresponds to WHO grade IV behavior and tumors can be referred to as *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV*:

- *EGFR* amplification

and/or

- *Whole chromosome 7 gain and whole chromosome 10 loss (+7/-10)*

and/or

- *TERT* promoter mutation

Diagnostic relevance: The 2016 WHO classification made clear distinctions between diffuse astrocytic gliomas that were IDH-mutant and those that were IDH-wildtype, with the general correlation that IDH-wildtype tumors carried a worse prognosis. However, some IDH-wildtype diffuse astrocytic gliomas do not carry a worse prognosis than IDH-mutant tumors, highlighting that the IDH-wildtype category is a mixed collection of tumors. cIMPACT Update 3 clarifies that a particular subset of IDH-wildtype diffuse astrocytic gliomas that lack microvascular proliferation and/or necrosis (i.e., those with one or more of the above three molecular alterations) have a prognosis that approximates that of a glioblastoma. The use of the recommended term (*Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV*) thus alerts the clinical neuro-oncology team to important prognostic and potentially therapeutic information.

CIMPACT UPDATE 4

cIMPACT Update 4 (2) came from Working Committee 2. It reviewed the status of IDH-wildtype/H3-wildtype diffuse gliomas that appear consistent with histological WHO grade II, focusing on those with a *BRAF^{V600E}* mutation, *FGFR1* alteration, or a *MYB* or *MYBL1* rearrangement, or other MAPK pathway alteration; such tumors tend to present in childhood. For these tumors, the Working Committee recommended the use of an integrated diagnosis to combine histologic and genetic features, as suggested in the following:

- Diffuse glioma, *MYB*-altered
- Diffuse glioma, *MYBL1*-altered
- Diffuse glioma, *FGFR1* TKD-duplicated
- Diffuse glioma, *FGFR1*-mutant
- Diffuse glioma, *BRAFV600E*-mutant (but without *CDKN2A/B* deletion)
- Diffuse glioma, other MAPK pathway alteration

Diagnostic relevance: As mentioned above under cIMPACT Update 3, the 2016 WHO classification made distinctions between diffuse astrocytic gliomas that were IDH-mutant and those that were IDH-wildtype, with the general interpretation that IDH-wildtype tumors carried a worse prognosis. In children and some young adults, however, there are IDH-wildtype and H3-wildtype diffuse gliomas with better outcomes. While it is likely that some IDH-wildtype and H3-wildtype diffuse gliomas with better outcomes remain to be discovered, cIMPACT Update 4 stated that those listed above are important to designate at the present time (preferably in a layered diagnosis and with an NEC designation for now) as distinct entities with prognostic and potentially therapeutic implications.

SUMMARY AND NEXT STEPS

cIMPACT has had a successful Round 1 of deliberations and publications, as summarized above. Following some changes in the Steering Committee, Clinical Advisory Panel and Working Committee rosters, cIMPACT has now embarked on a second round of deliberations. In Round 2, Working Committee 1 is addressing the possibility of novel grading approaches for IDH-mutant diffuse gliomas; Working Committee 2 is discussing ependymoma classification; and Working Committee 3 is formulating and defining “new” entities that should be considered for the next WHO classification. It is anticipated that these recommendations will emerge in advance of the next WHO update, which is the fifth Series, with the CNS Blue Book planned for late in 2020.

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Committee 3 [David Louis (chair), Tracy Batchelor, J. Gregory Cairncross, David Capper, Dominique Figarella-Branger, Caterina Giannini, M. Bea Lopes, Werner Paulus, Martin van den Bent, Pieter Wesseling, Wolfgang Wick].

DATA AVAILABILITY

Data sharing are not applicable to this article as no new data were created or analyzed in this study.

CONFLICTS OF INTEREST

The authors have no conflicts of interest regarding this publication.

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