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TERT promoter mutation: is it enough to call a WHO grade II astrocytoma IDH wild-type glioblastoma?

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See the article by Berzero et al. in this issue, pp. 955–966.

In 2018, the cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH wild-type (*IDH*-wt), with molecular features of glioblastoma, WHO grade IV"[1] reviewed the current literature and proposed a combination of molecular features that could be used to identify those *IDH*-wt diffuse (WHO grade II) or anaplastic (WHO grade III) astrocytomas that would behave aggressively with a clinical course similar to glioblastoma WHO grade IV. The consensus reached at that time included the following molecular alterations: *EGFR amplification or combined whole chromosome 7 gain and whole chromosome 10 loss (+7/–10) or TERT promoter mutation* (*pTERTmut*) as the minimal diagnostic molecular criteria. In this consensus paper, the authors acknowledged the following points: (1) the vast majority of *IDH*-wt diffuse astrocytic gliomas, which would qualify as having molecular features of glioblastoma WHO grade IV would correspond histologically to anaplastic astrocytoma, WHO grade III rather than diffuse astrocytomas, WHO grade II; (2) in The Cancer Genome Atlas (TCGA) Research Network, among 500 WHO grade II or III diffuse gliomas, only six *IDH*-wt were diffuse astrocytomas, WHO grade II, with *EGFR* amplification, +7/–10 or *pTERTmut*[2]; (3) *pTERTmut* occurred most commonly in association with +7/–10 or *EGFR* amplification, and the combination of *pTERTmut* with *EGFR* amplification and +7/–10 added specificity as a marker of grade IV behavior.[3] The occurrence of *pTERTmut* in other types of "*IDH*-wt" gliomas, from pleomorphic xanthoastrocytoma to ependymoma, also prompted particular caution regarding its use in isolation in defining a diffuse astrocytic glioma with molecular features of glioblastoma.

In 2020, the cIMPACT-NOW update 6[4] went one step further and proposed to simplify the nomenclature, including among criteria to diagnose a diffuse astrocytic glioma as glioblastoma, *IDH*-wt, WHO grade 4 microvascular proliferation *or* necrosis *or* one (or more) of the three genetic alterations (*pTERTmut*, *EGFR* gene amplification, +7/–10 chromosome copy number changes), thus facilitating entry into clinical trials. New data were brought in support of the view that survival of the patients with these tumors, including those with "*pTERTmut* only," was similar to patients with histologically classic glioblastoma, *IDH*-wt, WHO grade IV.[5]

In this issue, the study by Berzero et al.[6] further explores the issue of histological grading and tries to better define the outcome of patients with *IDH*-wt grade II diffuse gliomas with molecular alterations typical of *IDH*-wt glioblastoma in comparison to *IDH*-wt grade III tumors. Among 517 grade II gliomas, with known IDH1/2 and 1p/19q codeletion status, using strict selection criteria, the authors identified 47 (9%) diffuse astrocytoma *IDH*-wt grade II. MRI scans were reviewed and cases showing gross necrotic nodules of contrast enhancement, suggesting a higher-grade tumor, were excluded. In addition, the histological slides were independently reviewed by 2 experienced neuropathologists, and tumors graded using widely accepted criteria, also reviewed by the cIMPACT group in separating grade II and III *IDH*-mutant astrocytomas.[7] *IDH*-wt tumors, harboring *H3F3A* mutations were excluded. Twenty-nine (of 43) cases (67%) met the definition of molecular glioblastoma according to cIMPACT-NOW update. Median overall survival (OS) in this subset was 42 months, shorter than patients with *IDH*-wt grade II astrocytomas not meeting this definition (57 months), but significantly longer than patients with grade III *IDH*-wt gliomas with molecular features of glioblastoma (17 months) ($P < .0001$). Most WHO grade II tumors (62%) met the cIMPACT criteria for glioblastoma *IDH*-wt grade 4 because of isolated *pTERTmut* (16/26, 62%), and in this patient subset (n = 14) median OS was 88 months compared to 22 months in patients (n = 24) with similar WHO grade III tumors ($P = .002$).

Even though, inevitably, this study brings back the flaw of the subjectivity of the histological grading, ie, the distinction between grade II and grade III based on the number of mitoses, its conclusions are noteworthy: (1) histological grade is important for the prognostic stratification of *IDH*-wt lower-grade gliomas; and (2) patients with strictly defined astrocytoma *IDH*-wt grade II with isolated *pTERTmut* do not have the same prognosis of those with glioblastoma *IDH*-wt.

These conclusions may seem in contrast with the study by Tesileanu et al.[5] This study, however, as others before,[2,3] combined histological grade II and III astrocytomas *IDH*-wt and, although one could argue that most *IDH*-wt *pTERTmut* only

"lower-grade astrocytomas" in the study were grade II (15 of 22; 68%, with only 2 grade III and 5 NOS [not otherwise specified]), this was only the original diagnosis without neuropathological review.

The strength of the study by Berzero et al.[6] is the strict selection of grade II *IDH*-wt astrocytomas, with accurate radiological and pathological review. From a cohort of 517 WHO grade II glioma, they ultimately identified only 29 astrocytomas *IDH*-wt grade II, which met the definition of molecular glioblastoma according to cIMPACT-NOW update, among which 14 with *pTERTmut* in isolation. Such stringent selection was not applied in previous studies.

Grade II astrocytomas, *IDH*-wt with molecular features of glioblastoma, represent a small percentage of the whole population of patients bearing *IDH*-wt grade II and III astrocytomas and those which qualify for the diagnosis because *pTERTmut* only are even less frequent (<5%). Despite their small number, these patients with a median OS of 88 months should not be equated to those with glioblastoma, *IDH*-wt, WHO grade IV. The inclusion of these patients in clinical trials for therapeutic options specifically addressed to glioblastoma *IDH*-wt WHO grade IV may not be appropriate and may affect the study results.

While it may be too late for the results of this paper to be incorporated in the upcoming 2021 WHO classification for CNS Tumor, clinicians and pathologists should be aware of its conclusions. Histological grade is still useful for prognostic stratification of *IDH*-wt gliomas and *pTERTmut* in isolation in strictly defined grade II astrocytoma does not appear to be sufficient to assume that the tumor will behave as glioblastoma, wild-type (WHO CNS grade 4) as proposed in cIMPACT-NOW update 6.[4]

References

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