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Inclusion bias of patients with genetically different glioblastoma subgroups in clinical trials

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See the article by Cimino et al., pp. 1368-1373.

The revised fourth edition of the World Health Organization (WHO) classification of brain tumors from 2016 differentiates diffusely infiltrating malignant astrocytomas with necrosis and/or vascular proliferates into the 3 genetic subgroups isocitrate dehydrogenase (IDH) wild-type, IDH mutated, and H3K27M mutated.[1] In particular, the differentiation of the IDH status allows considerable clinical conclusions regarding the prognosis.[2,3] The largest molecular subgroup by far are patients with glioblastoma without IDH mutation. This subgroup can also be further differentiated on a molecular level. The "Heidelberg brain tumor classifier" currently contains about 6 epigenetic subgroups of glioblastomas without an IDH mutation.[4] If one analyzes these glioblastoma patients by expression profiling, then at least 4 molecular subgroups are found.[5,6] However, all these molecular classifications of glioblastomas without IDH mutation require a technically and thus also economically sophisticated infrastructure, which can currently be provided by only a few well-established neuro-oncological institutions. In addition, it has not yet been conclusively resolved whether these high-throughput methods can be used to identify prognostically relevant molecular subgroups. The demand is correspondingly high for further molecular differentiation of the large bunch of IDH wild-type glioblastomas using only a few markers to generate prognostic conclusions, which can also be investigated in an averagely equipped neuropathology.

The public availability of The Cancer Genome Atlas (TCGA) glioma datasets led to a flourishing of bioinformatics, which tried to identify especially prognostic patterns by applying different, partly newly developed algorithms. For example, clusters of different tumor groups could be visualized in a 2-dimensional space using the multidimensional scaling algorithm.[7] Driven by the idea that the complex TCGA datasets may also contain simple molecular subgroups, for the prognosis-relevant patterns these datasets were then analyzed further on the improved Oncoscape platform and extended to the German Glioma Network (GGN) cohort of glioblastomas.[8] Both TCGA and the GGN cohort are composed of glioblastoma patients predominantly selected by the availability of sufficient tissue and clinical follow-up data. Using this approach, a diagnostic algorithm for glioblastomas without IDH mutation was developed, which requires only a few molecular markers and thus enables a simple differentiation of prognostic subgroups. Molecular information is required regarding a gain of chromosome 1 and 19 and the amplification status of cyclin-dependent kinase 4 (*CDK4*) and murine double minute 2 (*MDM2*). The prognostically very poor subgroup W1 is characterized by the coamplification of *CDK4* and *MDM2*. Instead, there is no combined amplification of *CDK4* and *MDM2* and no gains on chromosome 1 or 19 in the prognostically intermediate subgroup W2; the best prognostic subgroup, W3, also shows no coamplification of *CDK4* and *MDM2* but gains on chromosome 1 or 19.[8]

In a next step, the authors asked whether the distribution frequency of subgroups W1, W2, and W3 can be found in the same way in glioblastoma cohorts of clinical trials evaluating the effect of a certain treatment.[9] It became evident that the distribution frequency of the prognostically worse groups W1 and W2 were clearly lower compared with the datasets of TCGA and the GGN, as patients of the prognostically best subgroup, W3, were preferably included in the 2 investigated clinical trials. The authors conclude that the trial design of phase II studies should already aim to achieve a balanced distribution of these 3 molecular subgroups. Otherwise, there is the risk that initially promising appearing results cannot become reproduced in phase III trials because only in such setting the broad diversity of glioblastoma patients might be sufficiently reflected. Overall, the current publication by Patrick Cimino et al[9] thus underlines the need for a more differentiated molecular characterization of glioblastomas and introduces a new aspect to the discussion as to why pharmaceuticals in phase II still often suggest interesting results that are no longer evident in a phase III trial.

It remains the responsibility of the scientific community to validate the simple model for the molecular subtyping of glioblastomas without IDH mutation on independent cohorts. It will

then be necessary to clarify how to interpret cases in which only *CDK4* or *MDM2* are amplified alone. Furthermore, the question will arise whether gains on chromosome 1 and 19 can also be sufficiently detected using established methods such as fluorescence in situ hybridization or digital PCR analyzing only circumscribed chromosomal areas. In addition, it will be important to clarify whether it is possible to examine the same chromosomal regions that are also investigated regarding deletions in oligodendrogliomas. If the proposed algorithm for molecular differentiation of glioblastomas without IDH mutation is confirmed and the resulting technical questions can be resolved, then it would be appropriate to include it in the next revision of the WHO classification of brain tumors.

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