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High-grade gliomas: A unique cohort? An overview of a complex and heterogeneous histomolecular classification system

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To the Editor.

I am writing to comment on the article “Dose escalation with simultaneous integrated boost for un-methylated multiple glioblastoma” by Ory Haisraely et al., published online ahead of print in Reports of Practical Oncology and Radiotherapy on 25 April [1]. While the study provides valuable insights into the treatment of high-grade multiple gliomas, I believe there are critical aspects that merit further discussion and consideration.

A notable theme that runs throughout the article is the interchangeable use of the terms “high-grade gliomas” and “glioblastomas”. While these terms are often interchanged in the current dialogue among colleagues, it's important to acknowledge that they cannot be considered synonymous according to the latest World Health Organization Classification of Tumours of the Central Nervous System, 2021 (WHO-CNS 2021). “High-grade glioma” is a broad, generic term that encompasses several malignant gliomas and lacks specificity in diagnostic categorisation. In contrast,

glioblastoma is a well-defined entity with precise histological and molecular characteristics [2]. Therefore, it's important to use precise terminology to accurately describe the type of glioma being studied to ensure consistency in diagnostic and therapeutic approaches.

Historically, glioma grading has been based on the St Anne-Mayo classification system, which assigns a grade primarily based on histological features such as cellular atypia, mitosis, necrosis, and/or endothelial proliferation [3]. In previous grading systems, low-grade tumours were generally considered to be grade 1 or 2 according to the St Anne-Mayo classification, while high-grade tumours were classified as grade 3 or 4. However, with advances in research and an increased understanding of the molecular biology of gliomas, it has been recognised that molecular characteristics play a critical role in prognosis and treatment response. This awareness has led to the integration of molecular markers, such as isocitrate dehydrogenase (IDH) mutation status and 1p/19q codeletion status, into diagnostic and classification criteria, resulting in a significant revision of glioma classification and grading, as well as the introduction of O-6 methylguanine DNA methyltransferase (MGMT) promoter methylation status as a prognostic parameter for temozolomide responders. This integration, first introduced in the penultimate World Health Organization classification of central nervous system tumours of 2016 [4], has been further extended in the latest WHO-CNS 2021 classification, while retaining the old concept that entities assigned to the new histo-molecular grade 1 or 2 are of low grade and entities assigned to the new histo-molecular grade 3 or 4 are of high grade.

According to the WHO-CNS 2021 classification, tumours of glial origin are divided into diffuse and circumscribed tumours. Diffuse gliomas are further subdivided into adult and paediatric types, each with distinct molecular profiles and clinical behaviours [2,5]. This classification system provides a more nuanced understanding of glioma pathogenesis and guides tailored treatment strategies.

A systematic approach to the topic of "high-grade gliomas" according to the WHO-CNS 2021 classification includes glial entities that are either completely high-grade or may contain high-grade subsets, as extrapolated and reported in Table 1.

This actual subdivision also leads to comment on the statement made in the article regarding the H3 K27 status and the H3 G4 status. The authors state that: *among the*

patients who were still stable or had a response, none had a mutation in histone K27M or H3 G34, which carry a worse prognosis [1], but their casistic shows an age range between 58 and 79 years, and these molecular features are associated with paediatric-type high-grade diffuse gliomas rather than adult-type ones. Therefore, discussing these markers in the context of adult patients with multiple high-grade gliomas may lead to misunderstandings, although it is in any case correct to point out that the two WHO CNS 2021 terms "adult-type" and "paediatric-type" do not categorically exclude the possibility that a tumour with morpho-molecular characteristics typical of a paediatric age ("paediatric-type") may arise in adulthood (or vice versa), as documented by some literature data [6]. But even more than for adult/paediatric classification or prognosis, the identification of the precise molecular alteration at histone H3 K27 has important therapeutic implications in diffuse midline gliomas, with the recent introduction of targeted therapy with ONC201 showing a positive response in both primary and recurrent cases of this molecular tumour type [7, 8].

Finally, a separate discussion should be devoted to another category of tumours, the mixed glio-neuronal tumours, which are almost exclusively low grade, but in their context recognise entities with possible (very rare) evolution of their glial component to high grade, such as ganglioglioma [2, 9].

In conclusion, the WHO-CNS 2021 highlights the importance of considering the wide heterogeneity in high-grade glioma classification from a morpho-molecular point of view, as a reflection of different clinical behaviour and response to treatment, allowing for more targeted and effective therapeutic strategies in the future.

Conflict of interest

Author declare no conflict of interest.

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Table 1.

Tumours categories	**Tumours entities**	**Grading (WHO 2021)**
Adult-type diffuse gliomas	Astrocytoma, IDH-mutant	2 or 3 or 4
	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	2 or 3
	Glioblastoma, IDH-wildtype	4
Paediatric-type diffuse high grade gliomas	Diffuse midline glioma, H3 K27-altered	4
	Diffuse hemispheric glioma, H3 G34-mutant	4
	Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	4
	Infant-type hemispheric glioma	High*
Circumscribed astrocytic gliomas	High-grade astrocytoma with piloid features	High*
	Pleomorphic xantoastrocytoma	2 or 3
	Astroblastoma, MN1-altered	Low or High*

*Definitive central nervous system (CNS) WHO grade not assigned