

Acta Neurochir (Wien). 2023 Mar 15. doi: 10.1007/s00701-023-05544-3. Online ahead of print.

Long-term survival in patients with IDH-wildtype glioblastoma: clinical and molecular characteristics

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PMID: 36920664 DOI: [10.1007/s00701-023-05544-3](https://doi.org/10.1007/s00701-023-05544-3)

Abstract

Backg round: Glioblastoma is an aggressive tumor that has a dismal prognosis even with multimodal treatment. However, some patients survive longer than expected. The objective of this study was to revisit patients diagnosed with glioblastoma according to the 2021 WHO classification and analyze clinical and molecular characteristics associated with long-term survival (LTS).

Methods: We retrospectively analyzed 120 IDH-wildtype glioblastomas operated on at our institution between 2013 and 2018. We divided them into LTS patients, surviving more than 3 years, and non-LTS patients, and then compared their features. Additionally, we performed DNA methylation-based brain tumor classification in LTS patients.

Results: Sixteen patients were long-term survivors. Age < 70 years, MGMT promoter methylation, extent of resection $\geq 95\%$, and administration of radiochemotherapy were associated with LTS ($P = 0.005$, $P < 0.001$, $P = 0.048$, and $P = 0.008$, respectively). In addition, when these factors were combined, the probability of LTS was 74% (95% CI: 62--84). The methylome analysis confirmed the

diagnosis of glioblastoma in the majority of the tested LTS patients. Regarding subtypes, 29% of cases were mesenchymal (MES), 43% were RTK1, and 29% were RTK2. Interestingly, RTK1 and RTK2 cases tended to have longer overall survival than MES cases ($P = 0.057$). Moreover, the only tested LTS patient with an unmethylated MGMT promoter had an "adult-type diffuse high-grade glioma, IDH-wildtype, subtype E" rather than a glioblastoma. This tumor was characterized by multinucleated giant cells and a somatic mutation in POLE.

Conclusions: We suggest that glioblastoma patients with a combination of favorable prognostic factors can achieve LTS in 74% of cases. In addition, methylome analysis is important to ascertain the type of glioma in LTS patients, especially when the MGMT promoter is unmethylated.

Keywords: Adult-type diffuse high-grade glioma, IDH-wildtype, subtype E; DNA methylation-based brain tumor classification; Extent of resection; Glioblastoma; Long-term survival; o(6)-methylguanine-DNA methyltransferase.

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