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Tumor-associated epilepsy at diagnosis in glioblastoma patients reveals an inflammatory molecular signature and is associated with better overall survival

Lilyana Dimova¹, Jenny Stritzelberger², Diyan Dimov³, Jonas Ort¹, Hussam Aldin Hamou¹, Hans Clusmann^{1 4}, Oliver Schnell⁵, Hajo Hamer², Florian Putz⁶, Stefanie Corradini⁶, Ludwig Singer⁷, Arnd Dörfler⁷, Franz Ricklefs⁸, Richard Drexler^{8 9}, Matthias Simon³, Dieter Henrik Heiland^{5 10 11}, Daniel Delev^{1 5}

Affiliations

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Abstract

Background: Glioblastoma (GB) is the most aggressive primary brain tumor in adults. Tumor-associated epilepsy at diagnosis (TAE) is common, yet its prognostic significance remains unclear.

Methods: We analyzed a retrospective multicenter test cohort of 855 GB patients (Aachen, Hamburg, Bielefeld) and validated findings in a prospectively collected cohort of 344 patients (Erlangen). Survival was assessed using multivariable Cox regression, propensity score matching, and interaction modeling of TAE and extent of resection (EOR). Molecular profiling included methylation-based classification, epigenetic deconvolution, and spatial transcriptomics.

Results: TAE was independently associated with improved survival (HR 0.81, 95% CI 0.69-0.99, $P = .036$, absolute survival advantage ~4-5 months). This effect was validated in the independent cohort (C-index 0.68 (95% CI 0.62-0.74) and persisted in propensity-matched analyses (HR 0.74, 95% CI 0.56-0.96, $P = .027$). Interaction modeling revealed that gross total resection (GTR) improved survival in both groups but particularly in patients with TAE (EOR interaction HR 0.69, 95% CI 0.49-0.99, $P = .041$). In this subgroup, partial resection provided no significant advantage over biopsy, whereas patients without seizures benefited incrementally from both partial resection and GTR. Molecular analysis demonstrated enrichment of the RTK II subtype, differentiated cell states, and an inflammatory microenvironment in glioblastoma with TAE; tumors without seizures displayed neuronal and stem-like features. Functional validation using ElectroGenomics showed that glioblastoma cortical slices with increased inflammatory score exhibited synchronization of action potentials characteristic for seizure-like epileptiform activity.

Conclusions: TAE at diagnosis is a favorable prognostic marker in GB, defining a biologically distinct subgroup. Seizure status modifies the prognostic effect of surgical resection, underscoring the importance of GTR particularly in patients presenting with TAE.

Keywords: Glioblastoma; methylation; overall survival; transcriptomics; tumor-associated epilepsy.

Plain language summary

Glioblastoma patients who present with seizures at diagnosis live significantly longer than patients without seizures. In this multicenter study of more than 1100 patients, we show that tumor-associated epilepsy identifies a biologically distinct glioblastoma subtype characterized by inflammatory and immune-related features. Seizure status also influenced the effect of surgery: complete tumor removal was particularly important in patients with seizures. These findings suggest that seizures are not merely a symptom of glioblastoma, but a clinically relevant biomarker that may help guide prognosis, surgical decision-making, and future personalized therapies.

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