J Neurooncol. 2025 Mar 6. doi: 10.1007/s11060-025-04994-2. Online ahead of print.

Characterizing the molecular and spatial heterogeneity of midline gliomas in adults: a single institution analysis

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PMID: 40048040 DOI: 10.1007/s11060-025-04994-2

Abstract

Purpose: Primary gliomas arising within midline structures of the central nervous system are associated with a worse prognosis compared with hemispheric gliomas. In adults, compared to their pediatric counterparts, adult midline gliomas are not as clearly characterized on the clinical behavior, prognostic factors, and treatment approaches for these diseases.

Methods: This retrospective cohort assessed all adult (≥ 18 years) patients from our institution with diffuse gliomas arising from midline structures at time of diagnosis (2014-2020). Molecular features characterized using immunohistochemistry, targeted next-generation sequencing, and chromosomal microarray analysis were collected. Patient characteristics were compared across groups using analysis of variance, Kruskal-Wallis, and the chi-square test as appropriate. Cumulative progression-free survival (PFS) and overall survival (OS) probabilities were estimated using the Kaplan-Meier method. Comparisons across groups were made using the log rank test.

Results: 79 patients were included in analysis, with a median follow-up of 22.5 months (range, 0.6-123). The mean age at diagnosis was 44.5 years (range, 19.4-76.4), and 51% (n = 40) were female. Thalamus/basal ganglia was the most common primary tumor location (47%), followed by the brainstem (30%), and cerebellum (23%). For the entire cohort, median PFS was 11.5 months (95% CI 9.4-20.1), and median OS was 25.5 months (95% CI 22.0-38.2). We grouped primary tumor types into four distinct diagnostic entities based on integrated histological and molecular features, which had survival differences (log-rank p = 0.007)-diffuse midline glioma, H3 K27-altered (17% with median OS 19.4 months); astrocytoma, IDH-wild type, not otherwise specified (42% with median OS 25.5 months); glioblastoma, IDH-wild type (24% with median OS 11.0 months); and astrocytoma, IDH-mutant (18% with OS 63.3 months). There were no cases of IDH-mutant tumors in the thalamus/basal ganglia. IDH-mutant tumors had better prognosis (OS: IDH-mutant 63.3 months, IDH-wild type 22.5 months, log-rank p = 0.003). Tumor enhancement and diffusion restriction at initial diagnosis was associated with worse prognosis (OS: enhancing 22.0 months, non-enhancing 64.5 months, log-rank p < 0.001; OS: restriction 20.3 months, no restriction 30.6 months, log-rank p = 0.028).

Conclusion: There is significant molecular heterogeneity between midline gliomas which has prognostic implications. These findings emphasize the need to molecularly characterize these tumors

to facilitate personalized treatment approaches.

Keywords: Brain tumor; Glioblastoma; Midline glioma; Molecular heterogeneity; Neuro-oncology; Prognosis.