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Surgical Management and Molecular Stratification in Adult Diffuse Midline Gliomas: A Multicenter Retrospective Cohort Study

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Abstract

Objective: Diffuse midline gliomas (DMGs) are highly aggressive and biologically heterogeneous malignancies in adults. Due to the deep-seated, eloquent anatomy of these lesions, the optimal surgical strategy remains controversial. The present multicenter study evaluates the impact of cytoreductive resection versus biopsy alone on overall survival (OS) and postoperative functional status in adult patients with DMGs.

Methods: We retrospectively reviewed a consecutive series of adult patients surgically treated for primary DMGs and an exploratory control cohort of 21 matched adult patients with non-midline gliomas was included for contextual comparison concerning clinical, molecular and radiological data.

Results: 21 patients with primary DMGs were identified. Interventions included 15 biopsies and 6 resections. Subgroup analysis revealed that surgical strategy did not significantly alter morbidity, with permanent deficits occurring in 53% of the biopsy group (8/15) vs. 50% of the resection group (3/6) (p=1.000). Molecular stratification showed a significantly higher incidence of permanent neurological deficits in the H3K27-mutated cohort compared to the H3K27-wildtype group (82% [9/11] vs. 22% [2/9], respectively; OR: 0.06, 95% CI: 0.01–0.57, p=0.022). The median OS for the entire midline cohort was 14 months, with no statistically significant difference between the biopsy and resection groups. In a multivariable Cox model adjusting for age, preoperative Karnofsky Performance Status (KPS), and H3K27 status, resection did not confer a survival advantage. Comparative analysis revealed no significant difference in survival distributions or functional outcomes between the midline cohort and the non-midline control cohort.

Conclusion: In adult DMGs, cytoreductive surgery did not yield a survival benefit over biopsy alone and was associated with a high rate of perioperative neurological morbidity. Diagnostic biopsy remains an appropriate and safe approach to achieve necessary histomolecular stratification, whereas radical resection should be selectively reserved for cases with favourable anatomical boundaries where cytoreduction can be achieved without causing unacceptable functional compromise.

Keywords: Diffuse midline glioma, H3K27 alteration, Biopsy, Surgical resection, Neuro-oncology

Introduction

Diffuse midline glioma (DMG) is an aggressive central nervous system malignancy predominantly affecting pediatric populations [37]. In adults, DMGs constitute a rare, biologically heterogeneous subgroup of gliomas for which evidence-based surgical guidelines remain sparse [3, 4, 9]. Current literature consists primarily of small, single-center series, reflecting it rarity and the profound technical challenges of accessing deep-seated, highly eloquent neuroanatomy. Consequently, clinical management has historically favored conservative strategies, often limited to diagnostic biopsy [5, 8, 12].

The definitive impact of the extent of resection (EOR) on overall survival (OS) and postoperative functional outcomes in adult DMG remains controversial [7, 13, 16]. To address the limitations of low epidemiological incidence, we conducted a multicenter retrospective study pooling data from three high-volume tertiary neurosurgical centers. This study evaluates the impact of surgical strategy (cytoreductive resection vs. biopsy alone) on OS and postoperative neurological morbidity in adult patients with DMGs.

Methods

Study Design and Clinical Assessment

This observational retrospective, multicenter cohort study evaluated adult patients surgically managed for primary midline gliomas between January 2019 and September 2025 across three tertiary referral centers. Inclusion criteria comprised: age ≥18 years, histologically verified midline glioma (thalamus, brainstem, spinal cord), surgical intervention (biopsy or cytoreductive resection), and complete clinico-radiological follow-up. Recurrent lesions or incomplete data were excluded. To contextualize outcomes, an exploratory control cohort of adult patients with non-midline gliomas, matched for baseline demographics and functional status, was established.

Functional status was graded using the Karnofsky Performance Status (KPS) preoperatively, at discharge, and during follow-up. Preoperative and early postoperative (≤72 hours) MRI protocols were performed using standard T1, T2, FLAIR, and contrast-enhanced sequences. Extent of resection (EOR) was determined via central neuroradiological review using RANO criteria, categorized as Gross Total Resection (GTR; no residual enhancement), Subtotal Resection (STR; <10% residual volume), or Partial Resection (PR; ≥10% residual volume).

Histomolecular and Statistical Analysis

Diagnoses were retrospectively harmonized to reflect contemporary WHO integrated histomolecular classification paradigms [38]. Molecular profiling evaluated H3K27 alteration, IDH mutation, ATRX expression, TP53 mutation, and MGMT promoter methylation.

Statistical analyses were performed via Python (v3.12.0) using pandas and Statsmodels. Continuous variables were tested for normality, expressed as median and interquartile range (IQR), and compared using the Mann–Whitney U test. Categorical data were evaluated via Fisher's exact test (reported as Odds Ratios [OR] with 95% Confidence Intervals [95% CI]). Overall survival (OS), calculated from index surgery to death or last follow-up, was evaluated using Kaplan–Meier curves, the log-rank test, and univariable/multivariable Cox proportional hazards regression models. All tests were two-sided, and significance was set at $P < 0.05$.

Ethical Considerations

This study adhered to the Declaration of Helsinki. Given its retrospective nature and data anonymization, formal ethics committee approval was obtained or waived in accordance with institutional regulations at each participating center. Informed consent for surgical treatment and subsequent data utilization was obtained from all patients during routine clinical practice.

Results

Cohort Characteristics and Surgical Outcomes

The study enrolled 21 adult patients with midline diffuse midline gliomas (DMGs; 6 females, 15 males; mean age 43.3 years) located in the brainstem (n=11), thalamus (n=7), and spinal cord (n=3). 19 lesions were high-grade (11 H3K27-altered, 8 IDH-wildtype glioblastomas) and 2 were low-grade. Interventions included 15 biopsies and 6 resections (1 GTR, 2 STR, 3 PR). The matched control cohort comprised 21 non-midline glioma patients (11 males, 10 females; mean age 56.3 years; 18 IDH-wildtype glioblastomas, 3 low-grade gliomas) managed via 2 biopsies and 19 resections (Table 1).

Postoperative neurological deterioration occurred in 8 of 21 (38%) midline patients, including 1 surgical mortality. The median cohort KPS shifted from 80 preoperatively to 75 postoperatively, with 5 patients experiencing a significant decline ($\Delta KPS \leq -10$) and 3 improving. Adjuvant therapies included concurrent chemoradiation (n=9, 43%), alternative radiotherapy (n=4, 19%), and palliative chemotherapy (n=1, 5%). Comprehensive comparative data for the surgical and molecular subgroups are consolidated in Table 2 and all surgical strategies, postoperative functional outcomes, and adjuvant treatment data are summarized in Table 3.

Survival Data

Thirteen deaths occurred during follow-up (8 biopsy, 5 resection). The median OS for the midline cohort was 14 months. Stratification by baseline status demonstrated a median OS of 8 months for KPS ≥ 70 versus 2 months for KPS <70.

No significant survival differences were found between biopsy and resection (11 vs. 6 months; log-rank χ^2=1.64 , P = 0.200; univariable HR: 2.09, 95% CI: 0.64–6.86, P = 0.224) or between H3K27-altered and H3K27-wildtype tumors (8 vs. 7 months; log-rank χ^2=2.56, P = 0.109; HR: 0.39, 95% CI: 0.11–1.34, P = 0.135) (figure 1-2). In a multivariable Cox model (N=21, events = 12), resection trended toward higher hazard (HR: 2.45, 95% CI: 0.61–9.88) and H3K27 mutation trended toward lower hazard (HR: 0.30, 95% CI: 0.06–1.53), without reaching statistical significance. All survival data are summarized in Table 4.

Midline vs. Non-Midline Control Cohort

Comparative analysis (n=42; 29 deaths) showed a median OS of 14 months for the midline cohort versus 15 months for controls (log-rank χ^2=0.052, P = 0.820; univariable HR: 0.91, 95% CI: 0.41–2.03, P = 0.825) (figure 3). Survival rates at 12 and 24 months were 57.5% vs. 61.5% and 30.8% vs. 17.9%, respectively. Preoperative (P = 0.136) and postoperative (P = 0.089) KPS comparisons between cohorts were non-significant (Table 5-6).

Discussion

The Surgical Dilemma: Biopsy vs. Resection

Surgical management of primary adult midline gliomas occupies a controversial space in neuro-oncology [5] (Table S1-S2-S3). Historically deemed "no-man's land" [8], modern microneurosurgical corridors have rendered cytoreductive resections feasible [6]. However, this study highlights a critical paradox: surgical resection did not yield a survival benefit over stereotactic or open biopsy (6 vs. 11 months, P = 0.224) (figure 1), trending instead toward a higher hazard ratio (HR: 2.45) in multivariable modeling. This finding aligns with recent multicenter evidence indicating that cytoreduction in adult H3K27-mutated gliomas has a limited impact on overall survival [7].

Crucially, recent clinical breakthroughs have further shifted the therapeutic paradigm toward less invasive strategies immediately at disease onset. Recent data from the international Phase III ACTION trial evaluating frontline paradigms demonstrate that introducing Dordaviprone (Modeyso) in newly diagnosed, H3K27M-mutant diffuse midline glioma patients right after standard radiotherapy—but prior to recurrence—significantly extends median overall survival compared to historical controls [40]. Because this small-molecule antagonist exhibits potent clinical efficacy early in the disease course, obtaining a definitive molecular blueprint at first presentation has become far

more critical than attempting an aggressive surgical cytoreduction. Consequently, a safe, stereotactic biopsy is often sufficient and highly preferable to radical resection at new onset. Biopsy minimizes early perioperative morbidity while successfully securing the tissue architecture required for contemporary histomolecular profiling, thereby granting patients immediate access to frontline targeted protocols [40]. When tumor margins are infiltrative and embedded in eloquent structures (such as the thalamus or brainstem), aggressive resection risks severe neurological fragmentation without modifying the overarching biological trajectory of the disease, especially in an era where molecularly driven therapies are becoming available at the very start of treatment. This is partially encoded in our resection cohort by the early perioperative morbidity and a surgical mortality event, which precipitously drops the early survival curve.

Molecular Influence and Structural Vulnerability

A striking finding in our analysis was that H3K27-mutated tumors exhibited a significantly higher rate of permanent neurological deficits postoperatively compared to their wildtype counterparts (9/11 vs. 2/9, $P = 0.022$). This implies that the H3K27 alteration does not merely dictate long-term survival, but directly influences immediate tissue vulnerability. H3K27-altered diffuse midline gliomas are notoriously characterized by a highly infiltrative, permissive growth pattern that disrupts white matter tracts without causing early macroradiological mass effect [9,10]. Consequently, what may radiologically appear as a resectable tumor volume represents an intricate web of functional neural tissue interwoven with neoplastic cells, making structural damage during cytoreduction almost inevitable.

Interestingly, despite this aggressive biology, H3K27 status did not significantly alter overall survival compared to midline wildtype lesions (8 vs. 7 months, $P = 0.109$). This underscores that adult midline gliomas possess an unfavorable prognosis across the board, where anatomical localization itself dictates a restrictive survival ceiling, overshadowing traditional hemispheric molecular advantages like IDH status or MGMT methylation [13,15].

Midline vs. Non-Midline Biology

To contextualize these outcomes, our study utilized a matched non-midline control cohort. The lack of a statistically significant survival difference between midline lesions and hemispheric counterparts (14 vs. 15 months, $P = 0.820$) offers a profound insight into glioma biology. While the surgical approach to the midline is infinitely more complex and burdened by higher transient or permanent deficits [5,16], the long-term survival vector is ultimately governed by integrated histomolecular characteristics [4,38]. Once a high-grade biological profile is established, systemic and local failure

occurs at a comparable temporal rate, regardless of whether the index lesion arose in the eloquent cortex or the intrinsic brainstem. This highlights the critical need to shift the therapeutic paradigm from aggressive physical debulking toward novel targeted molecular and cellular therapies, such as GD2-CAR T-cell infusions or specific microenvironmental modulators, which bypass anatomical restrictions [20, 39, 41].

Further Study and Limitations

Several limitations of this study should be acknowledged. First, its retrospective design introduces inherent selection bias regarding the surgical strategy (biopsy vs. resection), which was non-randomized and driven by tumor location, baseline functional status, and surgical risk. Despite retrospective harmonization, minor variations in surgical execution and adjuvant protocols across the three centers could not be entirely ruled out. Second, the small sample size reflects the clinical rarity of adult diffuse midline gliomas and limits the statistical power of our analyses, particularly for multivariable modeling and H3K27-altered subgroup stratifications. Consequently, these statistical trends should be interpreted with caution. Larger, prospective multi-institutional studies are required to validate our findings.

Conclusion

In primary adult midline gliomas primary an aggressive cytoreductive surgical resection does not confer a significant survival advantage over safe stereotactic biopsy, while potentially carrying a higher burden of persistent neurological deficits in H3K27-altered phenotypes. In the burgeoning era of precise neuro-oncological medicine—exemplified by frontline targeted approaches like Dordaviprone—the primary surgical objective must pivot from maximum physical debulking toward safe tissue acquisition. Maximizing functional preservation via a tailored biopsy ensures that patients maintain a higher performance status, allowing them to safely transition to contemporary, mutation-specific therapeutic protocols.

Data availability Data or information needed to reproduce the findings presented are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The protocol was approved by Institutional Review Board – Comitato Etico Territoriale CET.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors have no relevant financial or non- financial interests to disclose.

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Thalamic Gliomas

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
Enomoto et al., 2020	Adult midline gliomas	23 (14 thalamic)	11	58.2 months	NA	Small sample size, in adults no no significant difference in prognosis with the presence or absence of H3K27M-mutant, unlike that seen in children.

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
Broggi et al., 2024	Adult DMG / Thalamic	3 / 487	3	5 months	NA	Single case series + literature review
Ryba et al., 2024	Adult DMG	70 (35 thalamic)	24	14 months	NA	Location and pre- and postoperative KPS, as well as ATRX status, impact overall survival significantly in H3 K27M-mutant glioma. Furthermore, resection provided no significant survival benefit compared with biopsy.
Ferroli et al., 2023	Thalamic gliomas Mixed cohort	56	9	17 months	NA	The surgery group showed a better OS compared to the biopsy group
Dono et al., 2020	Adult DMG	9 (2 thalamic)	3	19 months	NA	adult DMGs have different oncogenic drivers

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
						compared to nonmidline high-grade gliomas.
Schulte et al., 2020	Adult DMG	60 (34 thalamic)	60	27.6 months	9.6 months	H3 K27M-mutant DMG represents a heterogeneous disease with regard to outcomes, sites of origin, and molecular pathogenesis in adults versus children.
Palmisciano et al., 2021	Adult thalamic gliomas	617	82	19.7% 2 year survival rate	9 months	Complete surgical resection is associated with improved survival rates but is not always feasible. H3K27M-mutant is associated with worse survival and a more aggressive

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
						approach should be considered for mutant neoplasms.
Grimaldi et al., 2022	Adult thalamic gliomas	38	4	15.6 months	7.1 months	Long-term survival is observed in young patients with limited symptoms and H3K27M mutation compared to wild-type.
Li et al., 2020	Adult thalamic gliomas	58	Not systematically tested	16 months	NA	The OS and PFS of adult patients with thalamic glioma were not significantly different between patients in the surgical group and in the IMRT group.

Table S1. Summary of published studies on adult thalamic gliomas. **Abbreviations:** OS, overall survival; PFS, progression-free survival; DMG, diffuse midline glioma; KPS, Karnofsky Performance Status; ATRX, alpha-thalassemia/mental retardation syndrome X-linked; IMRT, intensity-modulated radiotherapy; NA, not available.

Brainstem Gliomas

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
Enomoto et al., 2020	Adult midline gliomas	23 (8 brainstem)	11	58.2 months	NA	Small sample size, in adults no no significant difference in prognosis with the presence or absence of H3K27M-mutant, unlike that seen in children.
Ius et al. 2023	Adult brainstem gliomas	748	Not systematically tested	9.99 HGG, 111.3 LGG	NA	Literature review, not possible to aggregate data to demonstrate time differences in survival among different degrees of resection.

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
Ryba et al., 2024	Adult DMG	70 (35 brainstem)	24	14 months	NA	Location and pre- and postoperative KPS, as well as ATRX status, impact overall survival significantly in H3K27M-mutant glioma. Furthermore, resection provided no significant survival benefit compared with biopsy.
Dono et al., 2020	Adult DMG	9 (4 brainstem)	3	19 months	NA	adult DMGs have different oncogenic drivers compared to nonmidline high-grade gliomas.
Schulte et al., 2020	Adult DMG	60 (5 brainstem)	60	27.6 months	9.6 months	H3K27M-mutant DMG represents a heterogeneous disease with regard to outcomes, sites of origin, and molecular

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
						pathogenesis in adults versus children.
Guillamo et al., 2001	Adult brainstem gliomas	48	Not systematically tested	5.4 years	NA	adult brainstem gliomas are different from the childhood forms and resemble supratentorial gliomas in adults.

Table S2. Summary of published studies on adult brainstem gliomas. **Abbreviations:** OS, overall survival; PFS, progression-free survival; DMG, diffuse midline glioma; KPS, Karnofsky Performance Status; ATRX, alpha-thalassemia/mental retardation syndrome X-linked; IMRT, intensity-modulated radiotherapy; NA, not available.

Spinal Cord Gliomas

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
Enomoto et al., 2020	Adult midline gliomas	23 (1 spinal cord)	11	58.2 months	NA	Small sample size, in adults no significant difference in prognosis with the presence or

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
						absence of H3K27M-mutant, unlike that seen in children.
Dono et al., 2020	Adult DMG	9 (2 spinal cord)	3	19 months	NA	adult DMGs have different oncogenic drivers compared to nonmidline high-grade gliomas.
Schulte et al., 2020	Adult DMG	60 (10 spinal cord)	60	27.6 months	9.6 months	H3K27M-mutant DMG represents a heterogeneous disease with regard to outcomes, sites of origin, and molecular pathogenesis in adults versus children.
Watanabe et al., 2024	Spinal cord gliomas Mixed cohort	279	279	24 months	14 months	Outcomes for DMG-SCs are poor overall but appear to be favorable compared to intracranial DMGs

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
Corazzelli et al., 2025	Spinal cord gliomas Mixed cohort	80	Not systematically tested	14.88 ± 17.75	NA	gross total resection did not provide a significant survival benefit in PscGB, while earlier surgery and adjuvant chemoradiotherapy were associated with improved outcomes.
Li et al., 2025	Spinal cord gliomas Mixed cohort	582	Not systematically tested	15 months	NA	Lower WHO tumor grade, younger age group, and undergoing GTR surgery are important protective factors for the prognosis of patients with primary spinal intramedullary astrocytoma.
Wong et al., 2013	Adult spinal cord astrocytomas	89	Not systematically tested	18 months (?)	NA	Adjuvant radiotherapy and age at diagnosis did not have a significant

Study (year)	Population	N (Adults)	H3K27-mutant	Median OS	Median PFS	Notes
						influence on survival.

Table S3. Summary of published studies on adult spinal cord gliomas. **Abbreviations:** OS, overall survival; PFS, progression-free survival; DMG, diffuse midline glioma; KPS, Karnofsky Performance Status; ATRX, alpha-thalassemia/mental retardation syndrome X-linked; IMRT, intensity-modulated radiotherapy; NA, not available.

Characteristic	Midline glioma cohort (n = 21)	Non-midline control cohort (n = 21)
Age, mean (years)	43.3	56.3
Sex, n (%)		
Male	15 (71.4)	11 (52.3)
Female	6 (28.6)	10 (47.6)
Tumor location, n (%)		
Thalamus	7 (33.3)	–
Brainstem	11 (52.4)	–
Spinal cord	3 (14.3)	–
Eloquent brain areas	21 (100)	15 (71.4)
Corpus callosum involvement	–	3 (14.3)

Histopathology, n (%)		
High-grade glioma	19 (90.5)	18 (85.7)
Low-grade glioma	2 (9.5)	3 (14.3)
Glioblastoma, IDH-wildtype	8 (38.1)	18 (85.7)
Diffuse midline glioma H3K27-mutant	11 (52.4)	–
Surgical management		
Biopsy	15 (71.4)	2 (10.5)
Resection	6 (28.6)	19 (90.5)

Table 1. Baseline demographic, clinical, and pathological characteristics of the study cohorts. **Abbreviations:** IDH, isocitrate dehydrogenase; H3K27, histone H3 lysine 27; n, number.

Clinical Metric	**Biopsy (n=15)**	**Resection (n=5)***	**H3K27-Wildtype (n=9)**	**H3K27-mutant (n=11)***	**P-value**
Preoperative KPS (Median)	80.0	75.0	70.0	80.0	0.615 (Surg) / 0.624 (Mol)
Postoperative KPS (Median)	80.0	70.0	75.0	70.0	1.000 (Surg) / 0.443 (Mol)
Median ΔKPS (Post vs Pre)	0.0	0.0	—	—	0.255 (Surg)
Transient Deficits (n; %)	5 (33.3%)	2 (40.0%)	3 (33.3%)	4 (36.4%)	1.000 (Surg) / 0.406 (Mol)
Permanent Deficits (n; %)	4 (26.7%)	2 (40.0%)	2 (22.2%)	9 (81.8%)	1.000 (Surg) / 0.022 (Mol)

Surgical Complications (n; %)	3 (20.0%)	1 (20.0%)	2 (22.2%)	2 (18.2%)	1.000 (Surg) / 0.642 (Mol)

Table 2. Comparison of functional outcomes according to surgical strategy and H3K27 status. *Note: Denominators reflect patients with available longitudinal functional data. "Surg" indicates the p-value for the Biopsy vs Resection comparison; "Mol" indicates the p-value for the H3K27-Wildtype vs Mutant comparison bold P-values indicate statistical significance ($P < 0.05$). **Abbreviations:** KPS, Karnofsky Performance Status; Surg, surgical comparison; Mol, molecular comparison.

Variable	Midline glioma cohort (n = 21)	Non-midline control cohort (n = 21)
Surgical strategy, n (%)		
Biopsy	15 (71.4)	2 (10.5)
Resection	6 (28.6)	19 (90.5)
Extent of resection (EOR), n (%)		
Gross total resection (GTR)	1 (16.7)	16 (84.2)
Subtotal resection (STR)	2 (9.5)	2 (10.5)
Partial resection (PR)	3 (14.3)	1 (5.2)
Functional outcome (KPS)		
Preoperative KPS, median (IQR)	80 (70-80)	80 (70-90)
Postoperative KPS at discharge, median (IQR)	75 (65-80)	90 (65-95)
KPS worsening ≥10 points, n (%)	5 (23.8)	3 (14.3)

Adjuvant treatment, n (%)		
Chemotherapy (CHT)	1 (4.7)	–
RT + CHT	9 (42.9)	13 (61.9)
RT	–	1 (4.7)
RT + other treatments	4 (19.05)	1 (4.7)

* *Extent of resection is reported only for patients undergoing tumor resection.*

Table 3. Surgical strategy, perioperative morbidity, and functional outcomes. Abbreviations: EOR, extent of resection; GTR, gross total resection; STR, subtotal resection; PR, partial resection; KPS, Karnofsky Performance Status; RT, radiotherapy; CHT, chemotherapy; IQR, interquartile range.

Variable	No. of patients	Deaths, n (%)	Median OS (months)	HR (95% CI)	p-value
Entire cohort	21	13 (61.9)	14	–	–
Surgical strategy					
Biopsy	15	8 (61.5)	11	Reference	–
Resection	6	5 (38.5)	6	2.45	0.207
Extent of resection (EOR)*					
Gross total resection (GTR)	1	1 (7.7)	28		
Subtotal resection (STR)	2	1 (7.7)	9.5		
Partial resection (PR)	3	3 (23.1)	3		

Age at diagnosis					
≤ median	11	5 (38.5)	6	Reference	–
> median	10	8 (61.5)	8.5	1	0.933
Baseline KPS					
≥70	20	13 (100)	8	0.47	0.149
<70	1	–	2	Reference	–
H3K27 alteration status					
H3K27-mutant	11	4 (30.8)	8	0.30	0.147
H3K27–wildtype	10	9 (69.2)	7	Reference	–

Table 4. Overall survival analysis according to clinical, surgical, and molecular variables.

* Extent of resection analysis is limited to patients undergoing tumor resection.Hazard ratios are derived from univariate Cox proportional hazards models. A p-value < 0.05 was considered statistically significant. Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; EOR, extent of resection; GTR, gross total resection; STR, subtotal resection; PR, partial resection; KPS, Karnofsky Performance Status.

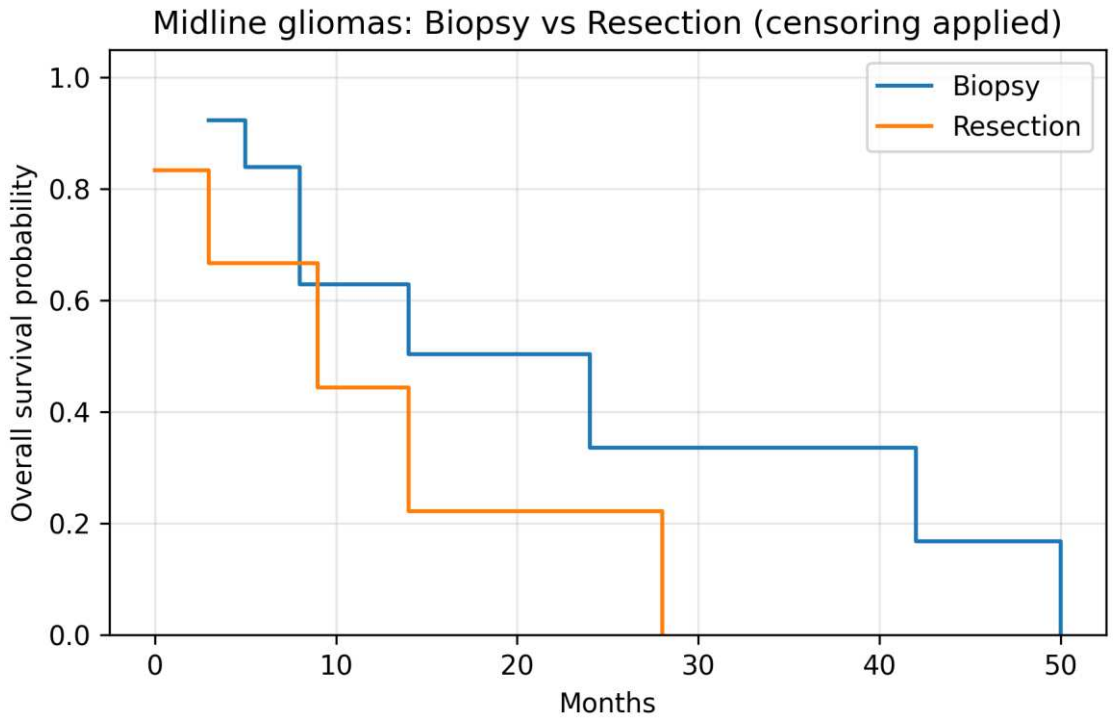


Figure 1. Kaplan–Meier overall survival curves comparing biopsy and resection in patients with midline gliomas. Kaplan–Meier curves were compared with a log-rank test (χ^2=1.64, p=0.200; N=21, events=13). Univariable Cox regression (resection vs biopsy): HR 2.09 (95% CI 0.64–6.86), p=0.224. Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval.

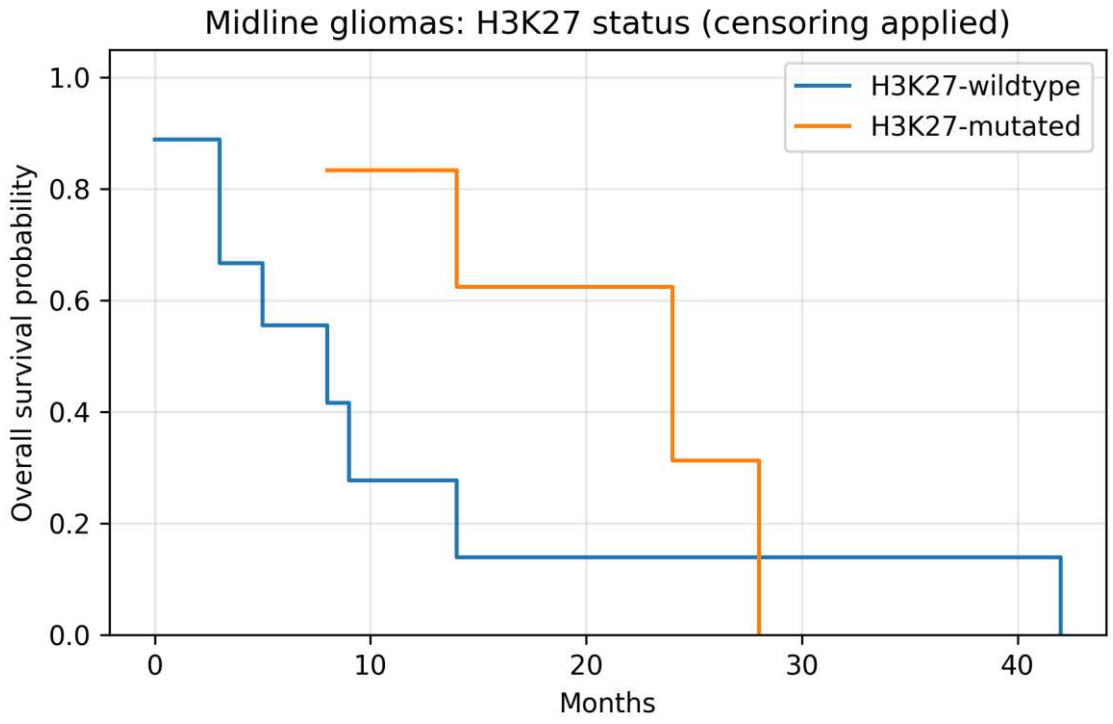


Figure 2. Kaplan–Meier overall survival curves according to H3K27 status in patients with midline gliomas. Kaplan–Meier curves were compared with a log-rank test (χ^2=2.56, p=0.109; N=21, events=12). Univariable Cox regression (H3K27 mutation yes vs no): HR 0.39 (95% CI 0.11–1.34), p=0.135. Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval.

Variable	HR	95% CI	p
Resection (vs biopsy)	2.45	0.61–9.88	0.207
Age	1.00	0.93–1.06	0.933
Pre-op KPS	0.47	0.17–1.31	0.149
H3K27 mutation (yes vs no)	0.30	0.06–1.53	0.147

Values should be interpreted as follows:

- **< 1**: protective factor;
- **> 1**: unfavorable prognostic factor;
- **= 1**: neutral/no effect.

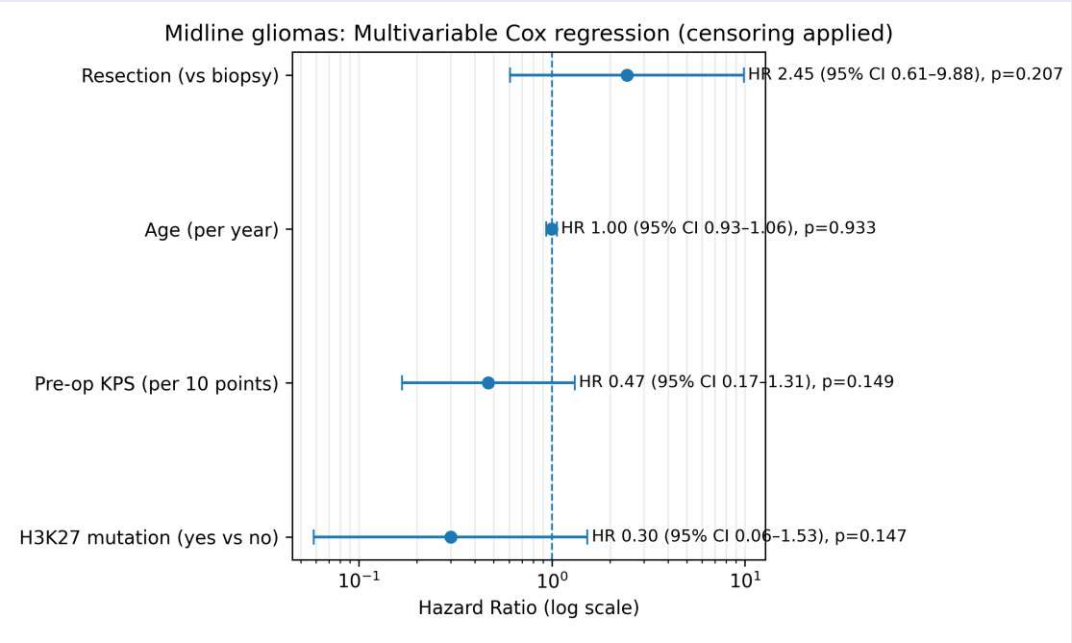


Table 5. Multivariable Cox proportional hazards regression analysis of overall survival in patients with midline gliomas. A multivariable Cox proportional hazards model was fitted (N=21, events=12) including procedure, age, pre-operative KPS, and H3K27 status. Survival sample: n=42 (events=29); Midline n=21, Control n=21. Log-rank test: χ^2=0.05, p=0.820. Univariable Cox (Control vs Midline): HR=1.09, 95% CI 0.49–2.43, p=0.825. Abbreviations: HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Status.

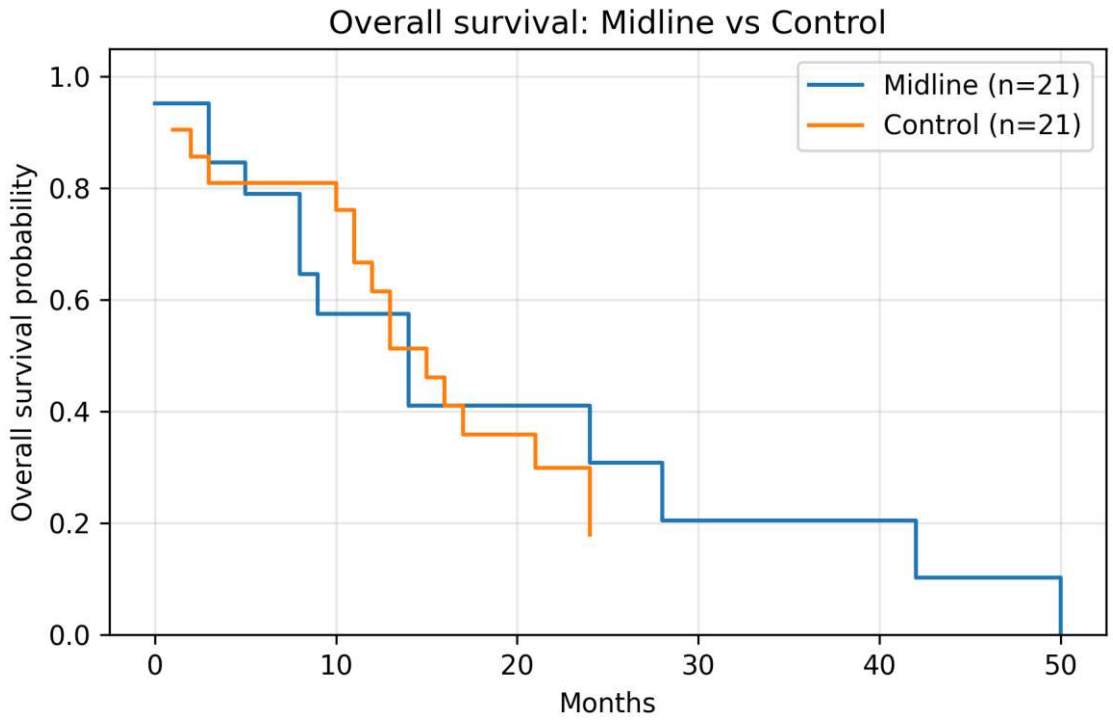


Figure 3. Kaplan–Meier overall survival curves comparing patients with midline gliomas and non-midline glioma controls. **Abbreviations:** OS hazard ratio; CI, confidence interval

KPS outcome (median)	Midline	Control	Median diff (Mid–Ctrl)	95% CI	p
Pre-op KPS	80.0 (n=21)	80.0 (n=21)	0.0	-20.00–0.00	0.136

Post-op KPS	75.0 (n=20)	90.0 (n=21)	-15.0	-20.00–10.00	0.089
Delta KPS	0.0 (n=20)	0.0 (n=21)	0.0	-10.00–0.00	0.122

Table 6. Comparison of preoperative, postoperative, and change in Karnofsky Performance Status between midline and control cohorts. Abbreviations: KPS, Karnofsky Performance Status; CI, confidence interval.