Survival analysis of adult midline-located gliomas: Does the H3K27 alteration in adult midline- located gliomas actually indicate a poor prognosis?

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Abstract

Purpose

Although pediatric diffuse midline gliomas (DMGs) have been studied extensively, and midline-located gliomas (MGs) with H3K27 alterations in children have been shown to have a poor prognosis, few researchers have assessed adult DMGs. We aimed to identify factors affecting the prognosis of adult MGs. This was the first study to investigate the prognosis of adult DMGs according to histological grade and was the largest study to investigate the survival of adult patients with DMGs.

Methods

We reviewed the charts of adult patients diagnosed with MG after undergoing resection or biopsy at our institution between 2010 and 2020. The Gehan–Breslow–Wilcoxon test was used for univariate survival analysis, and the Cox regression proportional hazard model was used for multivariate survival analysis.

Results

Among the 125 adult MGs identified, 45 (36.0%) showed H3K27 alterations. The survival analysis performed on 125 adult MGs indicated that a low histological grade, Karnofsky performance score (KPS) ≥ 80, and age ≤ 60 years were associated with significantly better survival. After adjusting for age, the difference in survival between the H3K27-alteration and wildtype groups was not significant. In the survival analysis of 45 patients with DMG, low histological grade, KPS ≥ 80, total resection, and concurrent chemoradiation therapy were associated with significantly better survival.

Conclusion

Adult MGs did not show a poor prognosis due to H3K27 alterations, unlike pediatric cases. The prognosis of adult MGs is based on the histological grade, age, KPS, adjuvant treatment, and extent of tumor resection.

Introduction

Since the first pontine glioma was described in 1926, diffuse intrinsic pontine gliomas (DIPGs) have long been considered fatal tumors that are difficult to remove surgically because of their critical location.[1] The difficulties in acquiring tumor tissue also limited the development of immunohistochemical techniques for midline-located diffuse gliomas. However, with advancements in surgical techniques and the accumulation of clinical experience, it has become possible to acquire tissues of midline-located glioma (MG) through surgical resection or stereotactic biopsy,[2–8] allowing histological diagnosis and gene studies using the obtained tumor tissue and facilitating research on midline-located diffuse

gliomas. Many such studies have shown that pediatric DIPGs with the H3K27 alteration have a worse prognosis than wildtype pediatric DIPGs. Therefore, in the 2016 WHO classification, diffuse midline glioma (DMG) was defined as “an infiltrative midline high-grade glioma with predominant astrocytic differentiation and a K27M mutation in either H3F3A or HIST1H3B/C” and classified as grade IV.[9, 10]

Although multiple studies have identified the prognosis for pediatric DMG, adult DMGs are less well-studied. Moreover, the clinical significance of H3K27 alterations in adult DMG is still controversial,[9, 11–14] and no previous study has revealed the differences in prognosis according to the histological diagnosis in adult DMGs. In this study, we investigated the effects of H3K27 alterations in adult MGs. We also aimed to identify the factors affecting survival in adult patients with MGs and DMGs.

Methods

Study population

The medical records of patients over 20 years of age with MG diagnosed between January 2010 and December 2020 were reviewed retrospectively. Preoperative magnetic resonance imaging (MRI) was performed at least once before surgery, and glioma location was determined using MRI. Tumor invading the following structures were considered MGs: basal ganglia, thalamus, midbrain, pons, and medulla oblongata. A DMG was defined as an infiltrative midline high-grade glioma with predominant astrocytic differentiation and K27M mutation in either H3F3A or HIST1H3B/C. Based on the recommendations of the cIMPACT consortium, pilocytic astrocytoma and ependymoma were excluded from the definition of DMG.[15] Data on patient demographics, tumor characteristics, surgery type, adjuvant treatment, and survival period were obtained. If the tumor was surgically removed, the extent of resection was classified as total or non-total.

Immunohistochemistry

All cases were reviewed by neuropathologists (SHK) to obtain a histological diagnosis and molecular profile of the tumor. Histologically diagnosed DMG was graded from II to IV according to the 2016 WHO classification, which reflects the histological characteristics. The H3.3 K27M mutation was examined by immunohistochemistry (IHC) and pyrosequencing. Pyrosequencing for identification of the H3.3 gene (H3F3A K27M and G34V) was performed according to previously described methods.[16] IHC was performed with a Ventana BenchMark XT autostainer (Ventana Medical System Inc., Tucson, Arizona, USA) according to the manufacturer’s protocol. The anti-histone H3 antibody, K27M mutant (ABE 419, 1:300 dilution, Millipore, Burlington, Massachusetts, USA), and anti-histone H3 antibody, K27me3 (07-449, 1:300 dilution, Millipore), were used as antibodies. As our institution has been regularly testing for H3K27M mutations in MGs since July 2015, we could determine whether H3K27M mutations were present simply by reviewing the medical records. However, regular tests for H3K27M mutation were not conducted from January 2010 to June 2015. Therefore, in cases where the H3K27M mutation was not

tested, pyrosequencing was performed using formalin-fixed paraffin-embedded tissues to confirm the H3K27M mutation. Additional molecular profiles such as 1p/19q co-deletion, IDH mutation, MGMT hypermethylation, and EGFR amplification were also examined.

Statistical analysis

The IBM SPSS Statistics package version 25 (IBM Corp.) was used for statistical analysis. We performed a survival analysis to determine whether the survival period of patients with MGs differed in relation to characteristics such as tumor location, histological grade, extent of resection, age, and Karnofsky performance status (KPS). The Gehan–Breslow–Wilcoxon test was used for univariate survival analysis, and the Cox regression proportional hazard model was used for multivariate survival analysis. Chi-square test, Fisher's test, and Student's t-test were performed to determine statistically significant differences in the demographic and tumor features between the two groups.

Results

Midline-located gliomas

We identified 125 adult MGs. The mean follow-up duration was 21.0 months (range: 1–125 months), and 96 patients (76.8%) died during the follow-up and investigation periods. In 80 (64.0%) patients, the tumors involved the thalamus or basal ganglia; in 39 (31.2%) patients, they involved the brainstem; and in 6 (4.8%) patients, they extensively involved the brainstem, thalamus, and basal ganglia. Forty-five (36.0%) patients were diagnosed with DMG due to H3K27 alterations. The demographic data and tumor characteristics of MGs are detailed in Table 1.

Table 1
Demographics and tumor characteristics of midline-located gliomas.

Group	**(N = 125)**
Age (years)	48.6 ± 15.2
Sex	
Female	61 (48.8%)
Male	64 (51.2%)
Right/Left	
Right	49 (39.2%)
Left	51 (40.8%)
Bilateral	25 (20.0%)
Tumor location	
Brainstem	39 (31.2%)
Thalamus or Basal ganglia	80 (64.0%)
Extensive involvement	6 (4.8%)
Surgery type	
Biopsy	60 (48.0%)
Resection	65 (52.0%)
Extent of resection	
Partial	75 (60.0%)
Subtotal	31 (24.8%)
Total	19 (15.2%)
Karnofsky Performance Status	76.3 ± 10.2
Histological grade (2016 WHO classification)	
II	14 (11.2%)
III	38 (30.4%)
IV	73 (58.4%)
H3K27 alteration	45 (36.0%)

We performed a survival analysis to determine whether the survival of patients with MGs differed according to tumor location, histological grade, age, KPS, and presence of H3K27 alteration. The survival period did not differ significantly according to tumor location or left/right position ($p = 0.662$, $p = 0.568$) (Fig. 1a, b). In comparisons based on histological grade, the median survival of grade II MG (45.8 months) was significantly better than that of grade III (19.5 months, $p = 0.011$) and grade IV (15.6 months, $p = 0.002$) tumors (Fig. 1c). However, no significant difference was observed in the median survival between grade III and IV MGs ($p = 0.198$). Patients aged ≤ 60 years showed significantly better median survival than those aged > 60 years (21.4 vs. 12.6 months, $p = 0.005$) (Fig. 1d). Patients with KPS ≥ 80 had significantly better median survival than those with KPS < 80 (22.1 vs. 11.7 months, $p = 0.001$) (Fig. 1e).

Surprisingly, the H3K27 alteration group showed significantly better median survival than the wildtype group in patients of all ages (23.1 vs. 15.9 months, $p = 0.040$) (Fig. 1f). However, as the H3K27 alteration group showed a significantly younger age and higher KPS, H3K27 alteration could not be considered to show a direct positive effect on survival (Table 2). To correct for the difference in age and KPS between the two groups, we limited the analysis to those aged 30–60 years, and the findings revealed no significant difference between the survival of the H3K27 alteration and wildtype groups ($p = 0.121$) (Fig. 1g). Moreover, in this age range, no significant difference was observed in the factors affecting survival between the H3K27 alteration and wildtype groups (Table 2).

Table 2
Comparison of demographics and tumor characteristics between H3K27M mutation and H3 wildtype group

	All age			**30 ≤ Age <60**		
	H3 wildtype (N = 80)	**H3K27M mutation** (N = 45)	p-value	**H3 wildtype** (N = 43)	**H3K27M mutation** (N = 29)	p-value
Age (years)	54.1 ± 13.1	38.8 ± 13.9	**< 0.001**	47.9 ± 7.7	45.8± 8.2	0.278
Sex			1.000			0.768
Female	39 (48.8%)	22 (48.9%)		25 (58.1%)	15 (51.7%)	
Male	41 (51.2%)	23 (51.1%)		18 (41.9%)	14 (48.3%)	
Right/Left			0.282			0.349
Right	31 (38.8%)	18 (40.0%)		20 (46.5%)	12 (41.4%)	
Left	36 (45.0%)	15 (33.3%)		17 (39.5%)	9 (31.0%)	
Central	13 (16.2%)	12 (26.7%)		6 (14.0%)	8 (27.6%)	
Tumor location			0.057			0.180
Brainstem	19 (23.8%)	20 (44.4%)		9 (20.9%)	12 (41.4%)	
Thalamus or Basal ganglia	57 (71.2%)	23 (51.1%)		32 (74.4%)	16 (55.2%)	
Extensive	4 (5.0%)	2(4.4%)		2 (4.7%)	1 (3.4%)	
Surgery type			**0.028**			0.102
Biopsy	32 (40.0%)	28 (62.2%)		17 (39.5%)	18 (62.1%)	
Resection	48 (60.0%)	17 (39.5%)		26 (60.5%)	11 (37.9%)	
Extent of resection			0.732			1.000
Total	11 (13.8%)	8 (17.8%)		7 (16.3%)	4 (13.8%)	

	All age			30 ≤ Age <60		
Non-total	69 (86.2%)	37 (82.2%)		36 (83.7%)	25 (86.2%)	
Karnofsky Performance Status	75.1 ± 11.6	78.4 ± 6.7	**0.045**	75.4 ± 12.4	77.6 ± 6.9	0.331
Histological grade			0.786			0.332
Low (II)	8 (10.0)	6 (13.3)		5 (11.6)	6 (20.7)	
High (III,IV)	72 (90.0)	39 (86.7)		38 (88.4)	23 (79.3)	

Variables with *p* values less than 0.10 in the univariate survival analysis were included in the Cox regression model (Table 3). Therefore, histological grade, age, KPS, and presence of H3K27 alteration were used as covariates in the Cox regression model for MG. The results indicated that histological grade (lower histological grade as the reference; hazard ratio [HR], 3.556, 95% confidence interval [CI], 1.533–8.245, $p = 0.003$), age (≤ 60 years as the reference; HR, 1.914; 95% CI, 1.192–3.073, $p = 0.007$), and KPS (< 80 as the reference; HR, 0.521; 95% CI, 0.341–0.798; $p = 0.002$) were significantly associated with survival. As predicted, the Cox regression model showed that H3K27 alteration had no significant impact on survival.

Table 3
COX regression model of midline-located glioma and diffuse midline glioma

Variable		HR (90% CI)	*p*
Midline glioma	**Histological grade**		
	Low (II)	1.000 (Reference)	
	High (III,IV)	3.556 (1.533–8.245)	**0.003**
	Age		
	≤60	1.000 (Reference)	
	>60	1.914 (1.192–3.073)	**0.007**
	KPS		
	<80	1.000 (Reference)	
	≥ 80	0.521 (0.341–0.798)	**0.002**
	H3K27		
	Wildtype	1.000 (Reference)	
	Alteration	0.984 (0.610–1.586)	0.946
Diffuse midline glioma	**Histological grade**		
	Low (II)	1.000 (Reference)	
	High (III,IV)	6.765 (1.308–34.991)	**0.023**
	KPS		
	<80	1.000 (Reference)	
	≥ 80	0.406 (0.181–0.909)	**0.028**
	Extent of resection		
	Non-total	1.000 (Reference)	
	Total	0.255 (0.070–0.928)	**0.038**
	Adjuvant treatment		**0.001**
	RTx only	1.000 (Reference)	
	CCRT	0.177 (0.049–0.642)	**0.008**
	Non	13.447 (0.746–242.496)	0.078

KPS: Karnofsky performance scale ,RTx: Radiotherapy, CCRT: Concurrent chemoradiation therapy

We additionally analyzed whether the survival rates differed between the H3K27 alteration group and the H3 wildtype group at each histological grade. As mentioned above, patients aged 30–60 years were included to control for other variables affecting survival. For each histological grade of MG in adults aged 30–60 years, H3K27 alteration did not significantly affect the survival (grade II, $p = 0.439$; grade III, $p = 0.220$; grade IV, $p = 0.077$) (Online Resource 1). No significant differences were observed in the factors that could affect survival at each histological grade (Online Resource 2).

Diffuse midline gliomas

Among the 125 patients with MG, we identified 45 patients with H3K27 alterations, and their tumors were defined as DMGs. The median survival time of adult patients with DMG was 23.0 months. The demographic data and tumor characteristics of the 45 patients with DMG are summarized in Table 4.

Table 4
Demographics and tumor characteristics of diffuse midline gliomas

Group	**(N = 45)**
Age (years)	38.8 ± 13.9
Sex	
Female	22 (48.9%)
Male	23 (51.1%)
Right/Left	
Right	18 (40.0%)
Left	15 (33.3%)
Bilateral	12 (26.7%)
Tumor location	
Brainstem	20 (44.4%)
Thalamus or Basal ganglia	23 (51.1%)
Both	2 (4.4%)
Surgery type	
Biopsy	28 (62.2%)
Resection	17 (37.8%)
Extent of resection	
Partial	31 (68.9%)
Subtotal	6 (13.3%)
Total	8 (17.8%)
Histological grade (2016 WHO classification)	
II	6 (13.3%)
III	19 (42.2%)
IV	20 (44.4%)
Karnofsky Performance Status	78.4 ± 6.7
Adjacent treatment	

RTx: Radiotherapy, CCRT: Concurrent chemoradiation therapy

Group	(N = 45)
CCRT	38 (84.4%)
RTx	6 (13.3%)
Non	1 (2.2%)
RTx: Radiotherapy, CCRT: Concurrent chemoradiation therapy	

We also performed survival analysis to identify factors influencing survival in patients with DMG. The median survival did not differ according to tumor location in the DMG ($p = 0.141$, $p = 0.226$) (Fig. 1h, i). Patient age did not significantly affect survival ($p = 0.631$) (Fig. 1k). When classified according to histological grade, the median survival of grade II DMG was 52.7 months, which was significantly higher than that of grade III (15.7 months, $p = 0.005$) and grade IV (33.0 months, $p = 0.041$) (Fig. 1j). However, there was no significant difference in the median survival between histological grade III and grade IV DMG ($p = 0.246$). When classified into histological low-grade (grade II) and high-grade (grades III and IV) groups according to histological findings, no significant intergroup differences were observed in factors that could affect survival (Online Resource 3).

Patients with KPS ≥ 80 had significantly better survival than those with KPS < 80 (median survival, 31.8 vs. 11.5, $p = 0.023$) (Fig. 1l). Patients who had tumors completely removed had significantly better survival rates than those who did not (median survival, 57.1 vs. 19.5 months, $p = 0.016$) (Fig. 1m). Patients with DMG who received concurrent chemoradiation therapy (CCRT) showed significantly better survival than those who received radiation therapy alone (median survival, 31.4 vs. 7.8 months, $p = 0.009$) (Fig. 1n). No significant differences were observed in the factors affecting survival between the KPS ≥ 80 and KPS < 80 groups, between the total resection and non-total resection groups, and between the CCRT and the radiotherapy groups (Online Resource 4–6).

Variables with a *p*-value less than 0.10 in the survival analysis were included in the Cox regression model (Table 3). Thus, the histological grade, KPS, extent of resection, and adjuvant treatment were used as covariates in the Cox regression model of DMG. The results indicated that histological grade (lower histological grade as the reference; HR, 6.765; 95% CI, 1.308–34.991; $p = 0.023$), KPS (< 80 as the reference; HR, 0.406; 95% CI, 0.181–0.909; $p = 0.028$), extent of resection (non-total as the reference; HR, 0.255; 95% CI, 0.070–0.928), and adjuvant treatment (radiotherapy as the reference; HR, 0.177; 95% CI, 0.049–0.642) were significantly associated with survival.

The immunohistological features of the 45 adult DMGs are presented in Online Resource 7. IDH mutation was assessed in 39 out of 45 adult patients with DMG, and one (2.6%) of them had an IDH1R132H mutation (Online Resource 8). TERT promoter mutation status was evaluated in 22 of 45 patients with DMG, and TERT promoter mutation was confirmed in one patient (4.5%). H3K27 alterations were

frequently associated with p53 mutation (56.1%, 23/41) and ATRX mutation (79.4%, 27/34) and were not associated with EGFR amplification (0/34) and MGMT promoter methylation (0/32).

Discussion

In this study, we attempted to identify the factors affecting the survival of adult patients with MG, including H3K27 alterations and histological grade. Our study has the advantage of being the largest study to analyze the survival of adult DMG according to histological grade.

Survival of adult patients with midline-located glioma

Several papers have already shown that the pediatric DMG has a poor prognosis with a median survival of 6.9–12.5 months.[11,17,18] However, in adults, no studies have revealed whether MGs with the H3K27 alteration have a worse prognosis than those with the H3 wildtype.[13,19] Rather, in some papers, a better prognosis was seen with the H3K27 alteration than with non-mutant MGs.[14] A previous study on spinal cord glioma also reported that K27M mutation patients showed significantly longer overal survival than K27M negative patients.[20] In our study, the median survival of adult patients with DMG was 23.1 months, indicating a better prognosis than the previously reported catastrophic prognosis of pediatric DMG.[11,17,18] A combination of the results of previous studies and our study indicated that H3K27 alterations in adults may have different meanings from those in children. Therefore, in this study, we aimed to identify factors affecting the prognosis of MG, including H3K27 alterations.

Histological low grade, age ≤60 years, and KPS ≥80 showed significantly better survival, suggesting that the characteristics of MGs are not different from those of gliomas located in known general locations (Fig. 1c, d, e). In the analysis based on histological grade, the difference between grades II and III and between grades II and IV was significant, but the difference between grades III and IV was not significant. With a larger sample size, a significant difference may be observed between grades III and IV. Contrary to previous studies in children showing that H3K27 alteration is associated with a worse survival in MG, in our study, the H3K27 alteration group in adult patients with MGs of all ages showed significantly better survival (Fig. 1f). However, it is too soon to say that H3K27 alteration is a good prognostic factor, as the H3K27 alteration group included patients who were young and had a high KPS, as shown in Table 2. Therefore, to minimize the effect of confounders on survival, we performed survival analysis by limiting the age to 30–60 years. The H3K27 alteration group did not show a significant difference in survival (Fig. 1g). Therefore, we concluded that the H3K27 alteration in adults was not associated with a good prognosis but also did not lead to a worse survival.

Survival of patients with adult DMG

The area where pediatric DMG frequently invades is slightly different from that frequently invaded by adult DMG. The most common location of H3K27-altered DMGs in children is the pons.[18,21,22] However, in our study, adult DMGs were most commonly located in the thalamus or basal ganglia, which is consistent with previous reports (Table 4).[13,19,23] Moreover, because MGs are difficult to surgically

resect or biopsy because of their critical location, they may be diagnosed and treated only by radiological findings without tissue acquisition for pathological diagnosis. In our institution, tissue from all MGs, including brainstem gliomas, was obtained by biopsy or surgical removal from July 2015.[24] Therefore, the status of the H3K27 mutation could be determined using this tissue. However, prior to 2015, when the significance of molecular diagnosis was not understood, tissue confirmation for MGs was not routinely carried out. As a result, the number of DMGs located in the brainstem may be underestimated.[25,26]

Previous small series of adult DMG patients have shown variable prognoses, with median survival periods of 19.6 months (n=21),[19] 8.4 months (n=13),[17] 17.6 months (n=18),[14] and 4.0 months (n=29).[13] We suggest that this diversity in median survival of adult patients with DMG could be attributed to the grouping of several histological spectra into one group called DMG. Therefore, we tried to identify the factors affecting the survival of DMG, including histological grade, through survival analysis, as we did for MGs. Similar to MGs, the tumor location did not significantly affect survival, consistent with the results of the study by Karremann et al., who argued that the H3K27M mutant midline-location glioma showed similar survival in all anatomical locations.[18]

Several studies have failed to show superiority when comparing different treatment regimens, such as CCRT, radiotherapy alone, or chemotherapy alone.[27,28] In this study, we compared survival according to adjuvant treatment in DMG. Patients with DMG who received CCRT showed significantly better survival than those who received radiation therapy alone. Therefore, vigorous adjuvant therapy for MGs should be considered.

Among DMGs, no significant difference was observed in survival between histological grades III and IV, consistent with the results of previous studies.[18,21] However, histological grade II DMG showed significantly better survival than histological grades III and IV in our study. The prognosis has not been reported to vary according to the histological grade of adult DMG. As previous studies showed that pediatric DMG has a poor prognosis regardless of histological grade, H3K27 alterations in adults may have different meanings from those in children. Fortunately, in the recently published 2021 WHO classification, pediatric-type diffuse gliomas have been moved to a separate category, distinct from adult-type diffuse gliomas. However, MGs with H3K27 alteration, pediatric-type diffuse high-grade gliomas, still exists in adults, and has completely different characteristics from the MG with H3K27 alteration in children.

The survival rate associated with complete tumor removal was significantly higher than that when the tumor was not completely removed (Fig. 1m). Acceptable complications and better survival can be obtained by performing maximal safe resection in MG.[29-34] We demonstrated that even in DMGs, better survival can be achieved by applying maximal safe resection. In many cases, complete removal of the tumor is impossible owing to its critical location. In our study, total resection was achieved in only 17.8% (8/45) of the patients, highlighting the need for appropriate patient selection through a detailed radiological review.

As reported previously, H3K27 alterations are frequently associated with p53 overexpression,[12,13,35,36] and are not associated with IDH mutation,[13,14,19,37] EGFR amplification,[38,19] and MGMT promoter methylation.[13,38,19] These findings support the hypothesis that telomere maintenance in H3K27M mutant gliomas seems to result mainly from alternative lengthening of telomeres through ATRX mutations.[12,39] Similarly, in our study, MGMT promoter methylation was not observed in patients with DMG. However, Karisa et al. reported that MGMT promoter methylation status could be assessed in five out of 18 adult patients with DMG and was confirmed in one patient.[14] Moreover, in our study, IDH1R132H was confirmed in one (2.6%) patient. Coexistence of IDH mutations with H3K27 modifications is extremely rare and has not been previously reported. The authors double-checked to rule out errors in the genetic test, and both mutation in the case was clear (Online Resource 8). And TERT promoter mutation was confirmed in one (4.5%) patient, consistent with the results of previous studies reporting that TERT promoter mutations are rare but are observed in DMG.[19]

Limitations

The limitations of this study include its retrospective design. First, as the poor prognosis of H3K27 mutation in children was revealed, our institution has obtained tumor tissue for H3K27 mutation testing in all MG patients since July 2015. However, not all MG tissue acquisitions were made prior to 2015. Therefore, this study may have a selection bias.

Second, although our study was the largest to examine the survival of adult DMG, bias may still occur owing to the relatively small number of patients. If the study is conducted with a larger sample size, it may be possible to confirm a significant survival difference between histological grade III DMG and histological grade IV DMG, which was not revealed in this study.

Third, in 60 (48.0%) patients, tumor tissue was obtained through biopsy. As the amount of tissue obtained through biopsy was much smaller than that obtained through resection, there is a possibility of incorrect histological diagnosis (including underestimation of histological grade).

Conclusions

Unlike pediatric MGs, adult MGs did not show a poor prognosis with the H3K27 alteration. The prognosis of adult MGs was related to the histological grade, age, KPS, adjuvant treatment, and extent of tumor resection.

Declarations

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Competing interests

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

Author contributions

In-Ho Jung: Original draft, data curation, formal analysis, methodology

Jihwan Yoo: Data curation, formal analysis

Jaejoon Lim: Resources, Review & editing

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Seok-Gu Kang: Resources

Se Hoon Kim: Resources, Data curation, Supervision

Jong Hee Chang: Resources, Supervision, Conceptualization

All authors read and approved the final manuscript.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital (4-2022-0716).

Consent to participate

The requirement for written consent from the patients was waived, as this was a retrospective study.

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Figures

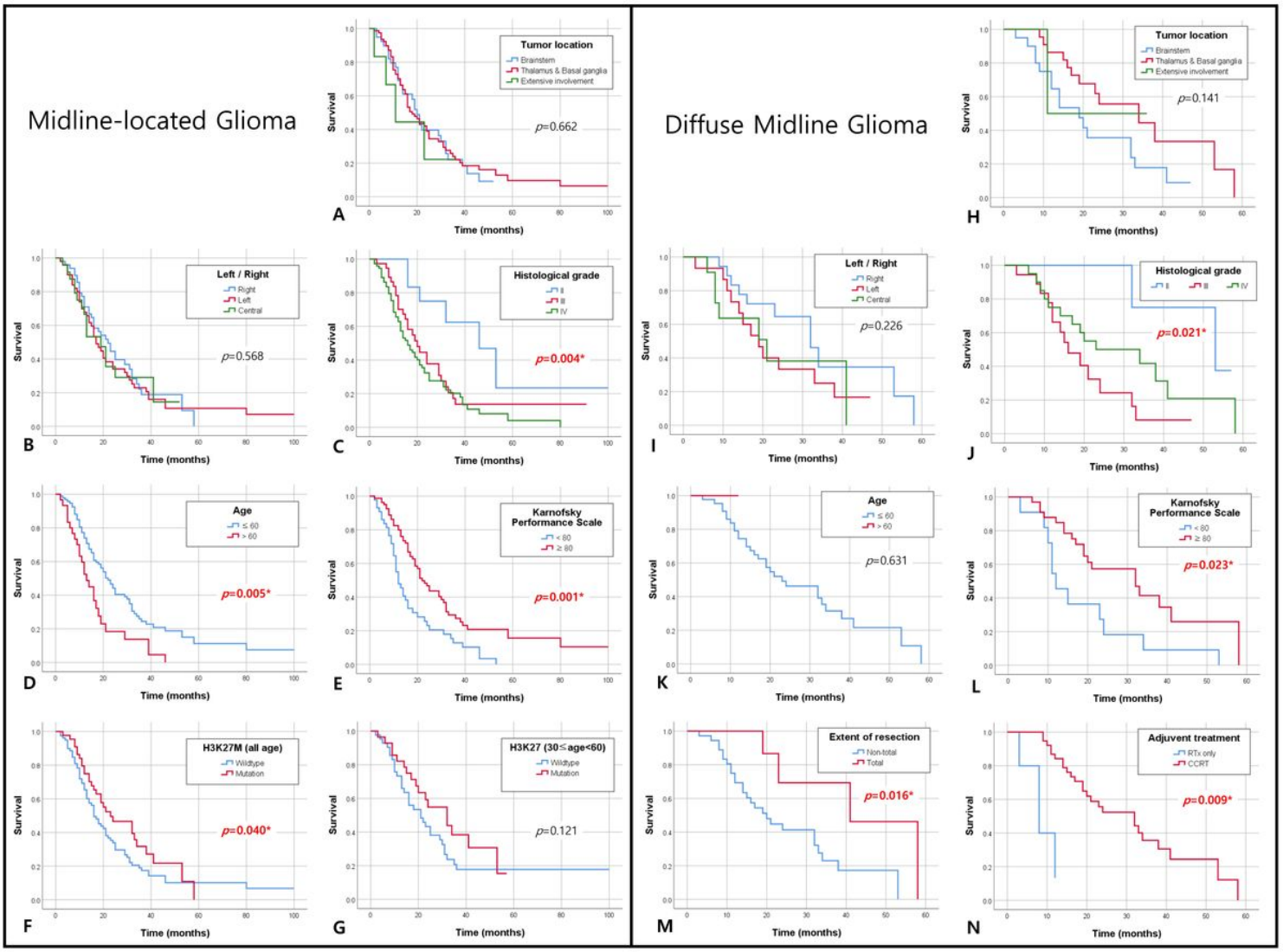

Figure 1

Survival analysis of 125 patients with midline-located gliomas (MGs) in relation to tumor location, histological grade, age, Karnofsky performance status (KPS), and presence of H3K27 alteration **(a-g)**. **a, b**: Patients with MGs showed no significant difference in survival according to tumor location (p=0.662) or left/right position (p=0.568). **c**: When classified according to histological grade, the median survival of patients with grade II MGs was 45.8 months, which was significantly higher than that of patients with grade III gliomas (19.5 months, p=0.011) and grade IV (15.6 months, p=0.002) gliomas. However, there was no significant difference between patients with grade III and IV MGs (p=0.198). **d**: Patients aged ≤ 60 years had significantly higher median survival than those aged > 60 years (21.4 vs. 12.6, p=0.005). **e**: Patients with KPS ≥ 80 had significantly higher median survival than those with KPS < 80 (22.1 vs. 11.7 months, p=0.001). **f**: Surprisingly, the H3K27 alteration group showed significantly higher median survival than the wildtype group in adult MGs of all ages (23.1 vs. 15.9 months, p=0.040). However, as the H3K27 alteration group showed a significantly younger age and higher KPS, the findings do not indicate that the H3K27 alteration had a direct positive effect on survival. **g**: To correct for the differences in age and KPS

between the two groups, we limited the analysis to patients aged 30–60 years. The analysis showed no significant difference between the survival of the H3K27 alteration and wildtype groups (p=0.121).

Survival analysis of 45 patients with diffuse midline glioma (DMG) in relation to tumor location, histological grade, age, Karnofsky performance status (KPS), extent of resection, and adjuvant treatment **(h-n)**. **h, i**: As in MG, median survival showed no difference related to tumor location (p=0.141, p=0.226). **j**: The median survival of histological grade II DMG was 52.7 months, which was significantly higher than that of grade III (15.7 months, p=0.005) and grade IV (33.0 months, p=0.021) DMGs. However, there was no significant difference in the median survival between histological grade III and grade IV DMGs (p=0.293). **k**: Patient age did not significantly affect survival (p=0.631). **l**: Patients with KPS ≥ 80 had significantly better survival than those with KPS < 80 (median survival, 31.8 vs. 11.5, p=0.023). **m**: Patients who underwent complete tumor removal had significantly better survival than those who did not (median survival, 57.1 vs. 19.5 months, p=0.016). **n**: Patients with DMG who received concurrent chemoradiation therapy showed significantly better survival than those who received radiation therapy alone (median survival, 31.4 vs. 7.8 months, p=0.009).

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