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RESEARCH

Clinical and molecular characteristics of thalamic gliomas in adults: prognostic impact of *TERT* promoter mutation

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Abstract

Background Adult thalamic gliomas (ATGs) are rare and biologically heterogeneous tumors. Although the 2021 World Health Organization (WHO) classification designates all diffuse midline gliomas (DMGs), H3-altered, as grade 4, accumulating evidence suggests that adult thalamic DMGs may exhibit more indolent clinical behavior, compared with glioblastomas or pediatric DMGs. In this study, we aimed to characterize the clinical, radiological, pathological, and molecular features of ATGs and identify clinically relevant prognostic markers, with particular focus on H3K27M and *TERT* promoter (*TERTp*) mutations.

Methods We retrospectively analyzed 45 adult patients (≥18 years) who underwent surgical resection or biopsy for ATGs between 2007 and 2023. Clinical, radiological, pathological, and molecular data were collected, and prognostic factors for overall survival were evaluated.

Results Patients with thalamic DMG demonstrated significantly longer overall survival (OS) than those with glioblastoma (median OS, 24.6 vs. 12.4 months; $p=0.035$). In multivariate Cox regression analysis adjusted for age, WHO grade, H3K27M status, and *TERTp* status, *TERTp* mutation emerged as an independent predictor of poor survival (hazard ratio [HR], 1.81; $p=0.026$), whereas H3K27M mutation was not significantly associated with outcome (HR, 0.93; $p=0.77$). Younger age (<45 years) was independently associated with longer OS, and WHO grade 4 with shorter survival; however, the survival curves overlapped substantially across histological grades.

Conclusions In ATGs, *TERTp* mutation was an independent predictor of poor survival and provided prognostic information beyond H3K27M status. These findings support incorporating *TERTp* status into risk stratification for ATGs.

Keywords Adult thalamic glioma · Diffuse midline glioma · H3K27M mutation · *TERT* promoter mutation · Prognosis

Introduction

Adult thalamic gliomas (ATGs) are rare tumors arising in deep midline structures. Their infiltrative growth and limited resectability make their clinical management challenging. Historically, most thalamic gliomas have been classified as high-grade astrocytomas, with surgery followed by chemoradiotherapy serving as the standard treatment approach [1, 2]. Prior reports indicate that > 80% of thalamic tumors are astrocytic and approximately half are histologically malignant, emphasizing their generally unfavorable prognosis [1, 2].

In the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS), diffuse midline glioma (DMG), H3-altered, is uniformly designated as CNS WHO grade 4 regardless of patient age or anatomical location [3]. However, large clinical

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series have demonstrated that H3K27M-mutant DMGs in children carry a uniformly dismal prognosis, with median survival typically less than 1 year [4]. In contrast, accumulating clinical evidence suggests that the clinical behavior of H3K27M-mutant DMGs varies considerably based on anatomical location, with thalamic tumors showing particularly heterogeneous outcomes, including in adults. A recent individual-patient meta-analysis suggested anatomical differences in survival among H3K27M-mutant DMGs, with thalamic tumors showing a trend toward better outcomes than brainstem (pontine) lesions [5]. Multiple multi-institutional studies similarly reported that adult thalamic DMGs do not uniformly display aggressive behavior classically associated with pediatric DMG and may even demonstrate outcomes comparable to or better than those of adult glioblastoma [6–8]. These findings collectively suggest that the current WHO grade 4 designation may not fully capture the biological heterogeneity of adult thalamic DMGs.

Genomic investigations have further highlighted the biological divergence between adult and pediatric midline gliomas. Adult DMGs show a distinct molecular landscape characterized by higher frequencies of *TERT* promoter (*TERTp*) mutations and lower frequencies of pediatric-type alterations, such as *ACVR1* mutations [9–12]. Several studies have suggested that *TERTp* mutations act as major prognostic drivers in adult midline gliomas, whereas the prognostic effect of H3K27M appears to be attenuated in adults [11, 13]. Moreover, H3K27M-mutant ATGs have been repeatedly shown to follow a more indolent course, compared with brainstem DMG or pediatric H3K27M-mutant tumors [14–16].

Collectively, these observations highlight the need for a better understanding of the clinical and molecular determinants of prognosis in ATGs. Despite substantial advances, the relative contributions of key molecular alterations, particularly H3K27M and *TERTp* mutations, to clinical outcomes in ATGs remain unclear.

In this study, we retrospectively analyzed a cohort of patients with ATGs to characterize their clinical, radiological, pathological, and molecular features. We further sought to identify prognostic markers with particular attention to the roles of H3K27M and *TERTp* mutations.

Materials and methods

Patients and samples

This retrospective study included data from 45 consecutive patients (median age, 45 years; range, 18–74 years) who underwent surgical resection or biopsy of thalamic tumors at our institution between January 2007 and November 2023. All cases were histologically reviewed and reclassified as CNS WHO grade 2–4 gliomas, according to the 2021 WHO Classification of Tumors of the CNS [3].

The clinical and radiological data collected included age at diagnosis, sex, histological subtype, CNS WHO grade, tumor laterality, maximum tumor diameter, presence of contrast enhancement, pre- and postoperative Karnofsky Performance Status (KPS) score, presenting symptoms, presence of hydrocephalus, extent of tumor resection, postoperative adjuvant therapy, and survival outcomes.

Among the 31 patients with contrast-enhancing tumors on gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI), gross total resection was defined as 100% removal of the enhancing area, and subtotal resection as >95% removal. For the 14 patients without contrast enhancement, the extent of resection was assessed based on the hyperintense area observed on T2-weighted MRI. The maximal tumor diameter was measured on preoperative MRI using the contrast-enhancing lesion on T1-weighted imaging in enhancing tumors and the hyperintense area on T2-weighted imaging in non-enhancing tumors. Tumors were classified as thalamic gliomas when the dominant tumor bulk was centered in the thalamus, including bithalamic lesions, even in cases with partial extension into adjacent structures.

Progression-free survival (PFS) was defined according to the Response Assessment in Neuro-Oncology criteria [17] as the interval from surgery to radiological progression. Overall survival (OS) was defined as the time from surgery to death from any cause.

This retrospective study was approved by the Ethics Committee of Tokyo Women's Medical University (approval no. 3540-R6) and was conducted in accordance with the Declaration of Helsinki. As only pseudonymized medical records were used, the requirement for written informed consent was waived by the ethics committee.

Pathological and molecular analyses

Formalin-fixed paraffin-embedded tumor tissues were examined using hematoxylin and eosin staining, followed by molecular and genetic analyses for integrated diagnosis according to the CNS WHO 2021, as previously described [18–20]. Tumor grading was primarily determined by histopathological characteristics in accordance with the WHO CNS 2021 criteria, including mitotic activity, microvascular proliferation, and necrosis, with available molecular findings incorporated for integrated diagnosis. Tumors lacking histological features of glioblastoma and without available molecular evidence of glioblastoma-defining alterations, including *TERT* promoter mutation or *EGFR* amplification, were classified as WHO grade 2 or 3 despite being *IDH*-wild-type, according to the WHO 2021 classification framework.

Immunohistochemistry (IHC) for *IDH1* p.R132H, p53, and *ATRX* was performed using an automated staining system (Histostainer, Nichirei Biosciences, Tokyo, Japan). The primary antibodies were anti-*IDH1* p.R132H (DIA-H09; Dianova, Hamburg, Germany), anti-p53 (DO-7; Nichirei Biosciences), and anti-*ATRX* (HPA001906; Sigma-Aldrich, St. Louis, MO, USA). Ki-67 labeling indices were assessed using an MIB-1 antibody (Dako, Santa Clara, CA, USA). O6-methylguanine-DNA methyltransferase (MGMT) expression was evaluated according to previously established criteria [21]. MGMT promoter methylation status was not routinely available in this retrospective cohort; therefore, MGMT status was evaluated based on immunohistochemical expression.

The chromosomal statuses of 1p and 19q were determined by fluorescence in situ hybridization using 1p36 and 19q13 probes (Vysis; Abbott Molecular, Abbott Park, IL, USA), and the signal ratios were calculated using standard analytical criteria [22]. Genomic DNA was extracted from representative tumor areas using the QIAamp DNA formalin-fixed paraffin-embedded Tissue Kit (QIAGEN, Venlo, Netherlands). Targeted Sanger sequencing (Eurofins Genomics, Kanagawa, Japan) was performed for *IDH1/2*, *TERTp*, and *BRAF*. Mutations affecting lysine 27 in the histone H3 genes (*H3F3A* and *HIST1H3B*) were analyzed by sequencing and IHC for H3 p.K27M and H3 p.K27me3.

IHC for H3 p.K27M and H3 p.K27me3 was carried out using anti–H3 p.K27M (rabbit monoclonal; Sigma-Aldrich, St.Louis, MO, USA, SAB5600095; 1:2000) and anti–H3 p.K27me3 (rabbit monoclonal; Cell Signaling Technology, Danvers, MA, USA, #9733; 1:500) antigens after antigen retrieval in citrate buffer (pH 6.0) at 100 °C for 40 min. Detection was performed using the Histofine MAX-PO (MULTI) system (Nichirei Biosciences). Tumors positive for the K27M mutation in either gene were classified as H3K27M-mutant.

Copy number variations in *EGFR*, *CDKN2A/B*, and chromosomes 7 and 10 were assessed by multiplex ligation-dependent probe amplification as part of routine pathological evaluation; however, these data were not available for all patients and were therefore excluded from the current prognostic analyses.

Statistical analysis

Differences between the groups were evaluated using Fisher's exact test for categorical variables and Welch's t-test for continuous variables. Age was dichotomized at 45 years, which was the median age of the cohort.

Survival curves were estimated using the Kaplan–Meier method, and differences between the curves were evaluated using the log-rank test.

Univariate and multivariate analyses of PFS and OS were performed using the Cox proportional hazards model, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Given the limited cohort size, the multivariate model was intentionally restricted to four clinically and biologically relevant covariates (age, WHO grade, H3K27M status, and *TERT* promoter mutation status) to minimize overfitting. Treatment-related variables were not incorporated into the final multivariate model because of substantial treatment heterogeneity and the absence of statistically significant associations in univariate analyses.

Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using JMP Pro version 17 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 45 patients with ATGs were included in this study (median age, 45 years; range, 18–74 years; male/female, 28/17) (Table 1). The median preoperative KPS score was 70 (range, 40–100). Tumors had a median maximal diameter of 37 mm (range, 23–63 mm) and were located in the right thalamus in 15 patients, the left thalamus in 22, and bilaterally in 8.

Gadolinium enhancement on preoperative MRI was observed in 31 patients (69%), and hydrocephalus was observed in 29 (64%). Surgical resection was performed in 31 patients (69%), including 29 gross total and 2 subtotal resections, whereas 14 patients underwent biopsy. According to the 2021 WHO classification, 2, 7, and 36

Table 1 Clinical, radiological and molecular characteristics of 45 adult patients with thalamic glioma

Variable	Value ($N=45$)
Age, y, median (range)	45 (18–74)
Sex, M/F	28/17
KPS, median (range)	70 (40–100)
Tumor diameter, mm, median (range)	37 (23–63)
Laterality (rt/lt/bilateral)	15/22/8
Contrast enhancement (+/-)	31/14
Hydrocephalus (+/-)	29/16
Surgical procedure (resection/biopsy)	31/14
Extent of resection (GTR/STR)	29/2
WHO grade (2/3/4)	2/7/36
IDH1/2 (mutant/wildtype)	0/45
H3K27M (mutant/wild-type)	19/26
TERT promoter (mutant/wild-type)	13/32
ATRX (loss/retain)	8/34
Follow-up, mo, median (range)	16.4 (2.2–76.3)
PFS, mo, median	9.5
OS, mo	24.5

Data are presented as median (range)

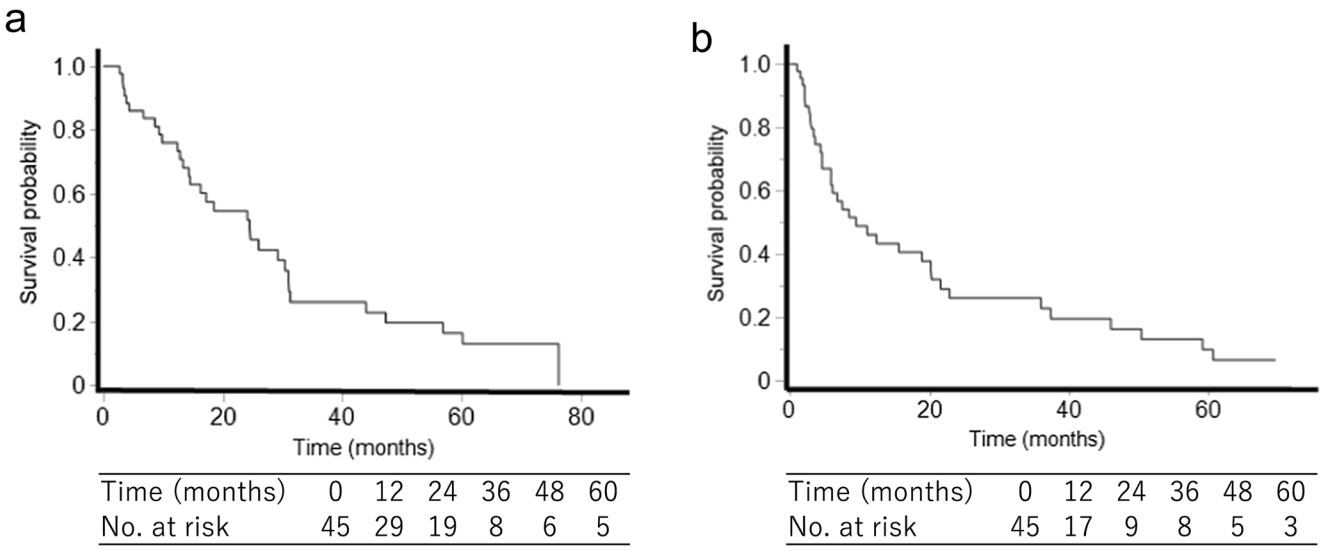

Fig. 1 Kaplan–Meier curves of overall survival and progression-free survival in 45 adult patients with thalamic gliomas (**a**) Overall survival (OS) The median OS for the entire cohort is 24.5 months (95% confidence interval [CI], 14.3–31.0) (**b**) Progression-free survival (PFS) The median PFS is 9.5 months (95% CI, 5.9–12.2)

tumors were classified as grades 2, 3, and 4, respectively. The median follow-up period was 16.4 months (range, 2.2–76.3 months). The median PFS was 9.5 months (95% CI, 5.9–12.2), and the median OS was 24.5 months (95% CI, 14.3–31.0) (Fig. 1).

Molecular and histopathological findings

IHC and molecular analyses demonstrated that all 45 tumors were *IDH*-wildtype. H3K27M mutations were present in 19 tumors (42%), whereas 26 (58%) were H3-wild-type. *TERTp* mutations were identified in 13 tumors (29%), and *ATRX* loss was observed in 8 of 44 evaluated patients (18%). BRAF V600E mutation was detected in 2 of 39 tested patients (5%). Co-occurrence of H3K27M and *TERTp* mutations was rare (1 patient, 2%), indicating that these alterations define largely distinct molecular subsets.

Histopathologically, all tumors exhibited astrocytic morphology without oligodendroglial components. Loss of H3K27me3 expression was consistently observed in H3K27M-mutant tumors, confirming the diagnosis of DMG, H3-altered. In contrast, H3-wild-type tumors retained H3K27me3 expression and were classified as *IDH*-wildtype astrocytic tumors according to the 2021 WHO CNS classification, based on histological features such as mitotic activity, microvascular proliferation, and necrosis, together with available molecular findings. In patients lacking histological features of glioblastoma and without available molecular alterations strongly defining glioblastoma, tumors were classified as WHO grade 2 or 3 astrocytomas (NOS) despite being *IDH*-wildtype. The detailed molecular profiles are summarized in Table 2.

Table 2 Molecular and immunohistochemical findings of 45 adult patients with thalamic gliomas

Molecular alteration	*n* (%)
IDH1/2 mutation	0 (0%)
H3K27M mutation	19 (42%)
TERTp mutation	13 (29%)
ATRX loss ($n=44$)	8 (18%)
BRAF V600E mutation ($n=39$)	2 (5%)

ATERTp, *TERT* promoter. Note: ATRX and BRAF analyses were performed on 44 and 39 patients, respectively

Survival outcomes

The median OS of the entire cohort was 24.5 months (95% CI, 14.3–31.0), and the median PFS was 9.5 months (95% CI, 5.9–12.2). Patients with H3K27M-mutant tumors tended to have longer OS than did those with H3-wild-type tumors (median OS: 24.6 vs. 14.5 months); however, this difference did not reach statistical significance (log-rank $p=0.27$). In contrast, the *TERTp* mutation was a strong predictor of poor prognosis.

Patients with *TERTp*-mutant tumors had a markedly shorter OS (9.3 months) than did those harboring *TERT*-wild-type tumors (29.2 months; log-rank $p=0.0049$) (Fig. 2).

Analysis by WHO grading showed a tendency toward longer OS for grade 2/3 tumors compared with that for grade 4 tumors (median OS: 31.3 vs. 24.1 months); however, this difference was not significant (log-rank $p=0.27$), likely due to the small number of grade 2/3 cases ($n=7$). To further clarify the prognostic impact of molecular alterations, we

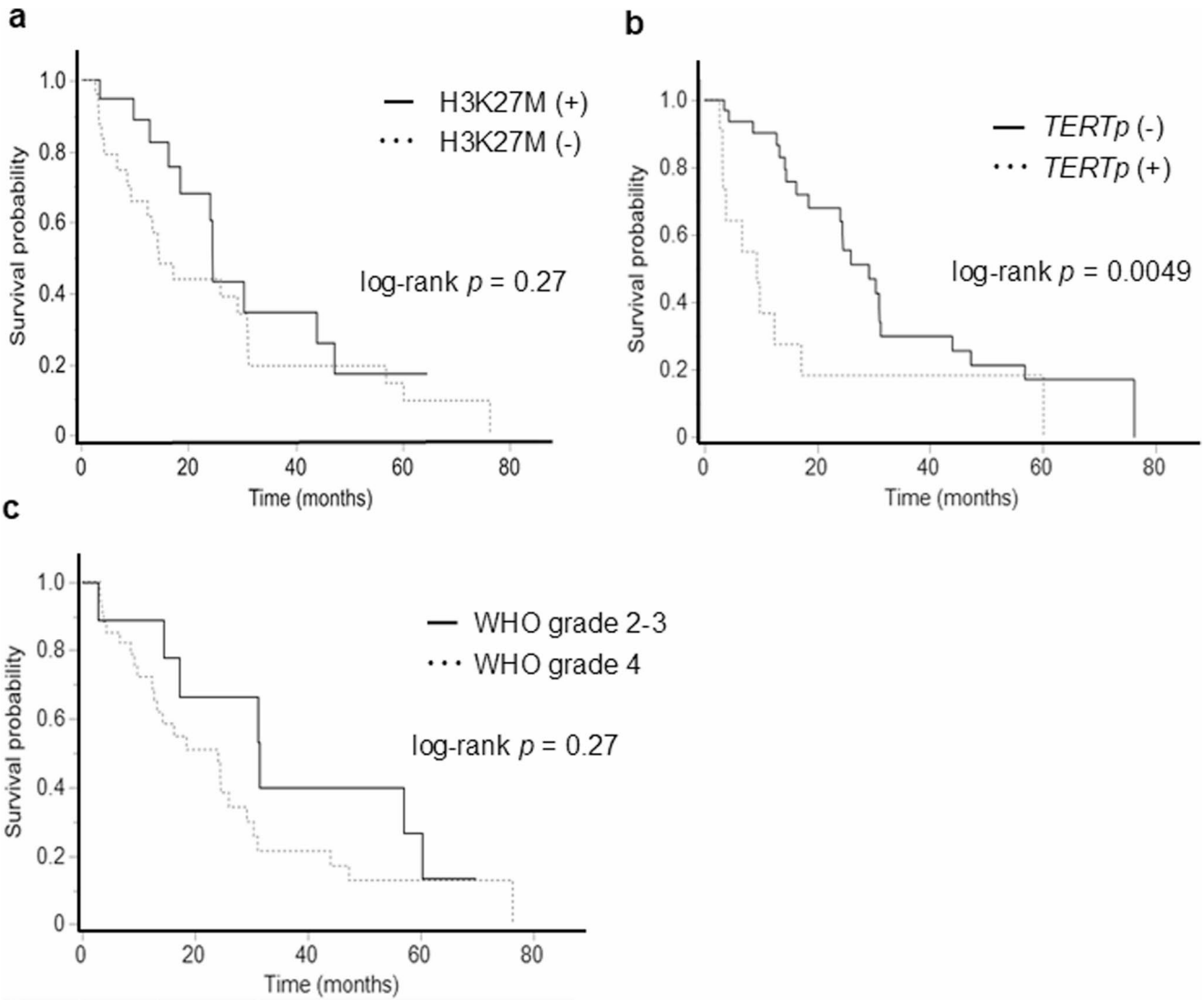

Fig. 2 Kaplan–Meier overall survival curves stratified by molecular and histopathological factors (**a**) H3K27M mutation status Patients with H3K27M-mutant tumors (solid line) show a trend toward longer OS, than those with H3-wild-type tumors (dotted line), although the difference was not significant (log-rank $p=0.27$) (**b**) *TERT* promoter mutation Patients with *TERT* promoter-mutant tumors (dotted line) had a significantly shorter OS than did those with *TERT* promoter-wild-type tumors (solid line) (median OS: 9.3 vs. 29.2 months; log-rank $p=0.0049$) (**c**) WHO grade classification Patients with WHO grade 2/3 tumors (solid line) tended to have a longer OS, than those with grade 4 tumors (dotted line), although the difference was not significant (log-rank $p=0.27$)

stratified patients according to the combined H3K27M and *TERTp* status (Fig. 3).

Among the three major groups, H3K27M(+)/*TERTp*(–), H3K27M(–)/*TERTp*(–), and H3K27M(–)/*TERTp*(+), a significant difference in OS was observed (log-rank $p=0.035$). As expected, the H3K27M(–)/*TERTp*(+) subgroup showed the poorest survival, whereas the wild-type groups showed more favorable outcomes. There was only a single patient with a double mutation (H3K27M(+)/*TERTp*(+)); therefore, this group was excluded from the group analysis because of the extremely small sample size.

Prognostic factors for survival

Univariate and multivariate analyses were performed to identify prognostic factors for OS (Table 3). Univariate Cox analysis identified older age (≥45 years) and *TERTp* mutations as significant predictors of poor OS. In contrast, the WHO grade, H3K27M mutation status, tumor diameter, extent of resection, and adjuvant therapy were not significantly associated with survival in the univariate analysis.

In the multivariate Cox regression model adjusted for age, WHO grade, H3K27M status, and *TERTp* mutations, three

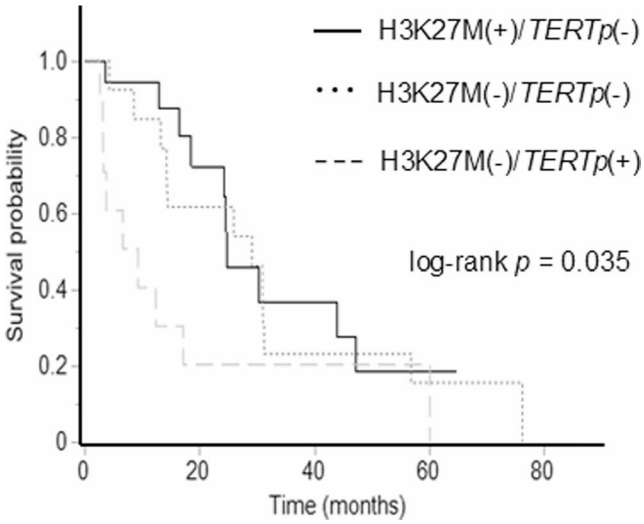

Fig. 3 Kaplan–Meier overall survival curves stratified by the combined H3K27M and *TERT* promoter (*TERTp*) mutation status Patients were assigned to three molecular subgroups based on their H3K27M and *TERTp* mutation status: H3K27M-mutant/*TERTp*-wild-type (solid line), H3K27M-wild-type/*TERTp*-wild-type (dotted line), and H3K27M-wild-type/*TERTp*-mutant (dashed line) Overall survival differs significantly among the three groups (log-rank $p = 0.035$), with the *TERTp*-mutant/H3K27M-wild-type subgroup demonstrating the poorest prognosis We excluded one patient harboring both mutations (H3K27M+/*TERTp*+) from the plot because of the extremely small sample size

Table 3 Univariate and multivariate analyses of prognostic factors for overall survival in 45 adult patients with thalamic glioma

Factor	Progression-free survival		Overall survival	
	Univariate (*P*)	Multivariate (*P*)	Univariate (*P*)	Multivariate (*P*) (HR [95% CI])
Age (<45 vs. ≥45 y)	0.489	0.529	0.0017	0.013 (0.53 [0.31–0.87])
WHO grade (2–3 vs. 4)	0.089	0.014	0.258	0.001 (0.41 [0.22–0.72])
H3K27M mutation (no vs. yes)	0.846	0.690	0.261	0.77 (0.93 [0.61–1.52])
TERTp mutation (yes vs. no)	0.331	0.177	0.012	0.026 (1.81 [1.07–3.13])

variables remained independent prognostic factors for OS. Specifically, compared with patients aged≥45 years, those aged<45 years had a significantly lower risk of death (HR 0.53, 95% CI 0.31–0.87; $p = 0.013$), indicating that older age was associated with shorter survival. Similarly, compared with patients with WHO grade 4 tumors, those with grade 2/3 tumors exhibited a lower risk of death (HR 0.41, 95% CI 0.22–0.72; $p = 0.001$). Importantly, *TERTp* mutation also remained a strong independent predictor of poor prognosis (HR 1.81, 95% CI 1.07–3.13; $p = 0.026$). H3K27M mutation status was not significantly associated with OS in either the univariate or multivariate analyses, highlighting that *TERTp* mutation exerts a stronger prognostic impact than H3K27M mutation status in ATGs.

Discussion

In this analysis, we identified several clinically meaningful observations that contributed to a refined understanding of tumor behavior in this deep-seated, surgically constrained region. The median OS of 24.5 months observed in our cohort was consistent with historical and contemporary reports of ATGs, which generally describe intermediate outcomes between hemispheric glioblastoma and pediatric DMG [2, 4, 23].

A key finding was that the H3K27M mutation was not associated with poorer survival in this cohort. This observation contrasts strongly with pediatric DMG, in which the H3K27M mutation is a defining hallmark of uniformly aggressive behavior [11, 13]. Prior clinical series similarly demonstrated that H3K27M-mutant ATGs exhibit markedly more favorable outcomes than do pediatric H3K27M-mutant tumors and adult brainstem DMGs [6, 14, 15]. Several biological mechanisms have been proposed, including age-dependent differences in precursor cell lineage, tumor epigenetic context, co-occurring *TP53* or *ATRX* alterations, and the more diverse methylation subclasses observed in adult midline glioma [16, 24]. Taken together, our findings support an emerging view that the H3K27M mutation in adults, particularly in the thalamus, may not confer the uniformly dismal prognosis characteristic of pediatric DMG. Given the limited cohort size, particularly after molecular stratification, the study may have been underpowered to detect moderate prognostic effects associated with H3K27M status. Therefore, the absence of statistical significance should be interpreted cautiously.

In contrast, the *TERTp* mutation demonstrated a strong and consistent association with poor survival. Recent studies have suggested that diffuse *IDH*-wildtype gliomas with isolated *TERTp* mutations might be biologically distinct entities and should not automatically be classified as glioblastoma in the absence of additional high-grade histological or molecular features [25, 26]; however, even within this biological heterogeneity, our findings indicate that *TERTp* mutation remains a strong adverse prognostic factor in ATGs. Accordingly, patients with *TERTp*-mutant tumors demonstrated a significantly shorter OS, and *TERTp* mutation remained an independent prognostic factor in multivariate analysis. These results are concordant with prior genomic studies showing that *TERTp* alterations drive telomerase reactivation and genomic instability and are among the strongest molecular predictors of adverse

outcome in adult *IDH*-wildtype diffuse gliomas [27, 28]. Co-occurrence of H3K27M and *TERTp* mutations was rare in this cohort, and the limited number of co-mutated cases precluded meaningful analysis of potential biological interactions between these alterations. Nevertheless, prior genomic studies have suggested that H3-driven and *TERT*-driven gliomas may represent biologically distinct molecular subtypes within adult midline gliomas [29]. Combined molecular stratification (H3+/*TERTp*–, H3–/*TERTp*–, H3–/*TERTp*+) demonstrated three prognostically distinct groups, with the *TERTp*-mutant group showing the worst survival. This pattern highlights the importance of incorporating *TERTp* status in addition to H3 status when performing risk stratification of ATGs.

Although gross total resection suggested improved outcomes, its deep location and proximity to critical structures frequently limit the extent of resection in ATGs. This surgical limitation has been consistently emphasized in earlier case series [2, 4, 23]. In our cohort, the extent of resection was not a significant factor, suggesting that prognosis in this location may be influenced more strongly by underlying molecular determinants than by surgical extent.

Similarly, although the WHO grade 4 designation traditionally indicates a poor prognosis, tumors classified as grade 2/3 and grade 4 exhibited substantially overlapping survival curves in our cohort. This finding aligns with prior observations that histological grade alone may not fully capture the biological behavior of midline gliomas [5, 24, 30]. Although Kaplan–Meier analysis demonstrated substantial overlap in survival between WHO grade 2/3 and grade 4 tumors, WHO grade retained prognostic significance in multivariate analysis, indicating that histological grade remains clinically relevant when interpreted alongside molecular factors. Importantly, molecular markers, particularly *TERT* promoter mutation status, provided additional prognostic stratification beyond histological grading, suggesting that integrated molecular assessment may further refine risk stratification in ATGs.

An additional clinically relevant observation was that the two tumors harboring both *TERTp* mutations and negative MGMT immunohistochemical expression exhibited extremely poor survival (< 3 months). This pattern is consistent with established evidence from adult glioblastoma, suggesting that the combination of *TERTp* mutation and unfavorable MGMT status may be associated with treatment resistance and poor clinical outcome [27, 31]. Although our sample size was small, this finding reinforces the need for intensified monitoring and potential eligibility for clinical trials in this high-risk subgroup. The status of chromosome 10 loss was not uniformly available in this retrospective cohort and was therefore not incorporated into the present analysis. Given the reported association between chromosome 10 loss and MGMT gene status in *IDH*-wildtype glioblastoma, future studies integrating copy number alterations and MGMT promoter methylation data may further clarify the biological interaction between *TERTp* mutation and MGMT status.

This study has limitations inherent to its retrospective design, single-institution setting, and modest sample size, especially within specific molecular subgroups, such as *TERTp*-mutant or double-altered tumors. Incomplete molecular characterization according to contemporary standards also limits the granularity of molecular subgrouping. Treatment heterogeneity across the study period, including variations in surgical strategy, adjuvant therapy, and salvage treatment, may have influenced survival outcomes and introduced residual confounding, which should be considered when interpreting the prognostic impact of molecular alterations. In addition, PFS assessment may have been affected by variability in imaging surveillance protocols and response assessment practices over the 16-year study period. DNA methylation profiling and Enhancer of Zeste Homolog Inhibitory Protein evaluation were not routinely available during the study period and therefore could not be incorporated into the present analysis. Moreover, molecular alterations including EGFR amplification, chromosome 7 gain/10 loss, and CDKN2A/B deletion were not uniformly available across the cohort, limiting comprehensive integrated molecular classification according to contemporary standards. Furthermore, MGMT immunohistochemistry was used as a surrogate because promoter methylation data were not uniformly available; however, immunohistochemical MGMT expression does not fully correlate with true MGMT promoter methylation status. Therefore, findings regarding the subgroup with combined *TERTp* mutation and unfavorable MGMT status should be interpreted cautiously. Given the anatomical constraints of the thalamus, heterogeneity in the extent of resection and baseline functional status is inherent to ATGs and reflects real-world clinical practice. Nevertheless, the strengths of this study include a relatively comprehensive molecular evaluation and consistent pathological review of a relatively large cohort with ATGs, a tumor population that remains underreported.

In conclusion, our findings highlight the heterogeneous nature of ATGs and demonstrate that prognosis is strongly influenced by molecular alterations, particularly *TERTp* mutations, in addition to conventional histological grading. *TERTp*-mutant tumors represent a distinctly high-risk subset and should be incorporated into prognostic assessment and risk stratification. Adult thalamic H3K27M-mutant tumors may not uniformly demonstrate the aggressive clinical behavior characteristic of DMGs; however, larger multi-institutional studies are needed to clarify the prognostic significance of H3K27M status in this population.

Incorporating molecular markers into diagnostic evaluations and risk stratification is essential for optimizing the management of adult midline gliomas. Future multi-institutional genomic studies are crucial for refining these molecular classifications.

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Author contributions Conceptualization: Shunsuke Tsuzuki; Data curation: Shunsuke Tsuzuki, Yoshihiro Muragaki, Masayuki Nitta, Kenta Masui, Takashi Komori, Taiichi Saito, Takashi Maruyama, Shunichi Koriyama, Buntou Ro, Takakazu Kawamata; Formal analysis: Shunsuke Tsuzuki; Investigation: Shunsuke Tsuzuki, Masayuki Nitta; Writing – original draft: Shunsuke Tsuzuki; Writing – review & editing: Kenta Masui, Shunsuke Tsuzuki, and all other authors; Supervision: Yoshihiro Muragaki, Takakazu Kawamata.

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Data availability The data supporting the findings of this study are not publicly available due to ethical and privacy restrictions and are available from the corresponding author upon reasonable request.

Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tokyo Women's Medical University (approval no. 3540-R6).

Consent to participate The requirement for written informed consent was waived because only pseudonymized clinical data were used.

Consent to publish Not applicable.

Clinical trial number Not applicable.

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

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