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CLINICAL STUDY

Surgical treatment and survival outcome of patients with adult thalamic glioma: a single institution experience of 8 years

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Abstract

Purpose Given the rarity in the population with adult thalamic gliomas (ATGs), comprehensive characteristics, treatments and survival outcome are not well characterized. This study was conducted to investigate the comprehensive characteristic and treatment of ATGs and identify the prognostic factors associated with overall survival (OS).

Methods A retrospective analysis of newly diagnosed ATGs who underwent surgical resection consecutively was conducted. Survival analysis of OS was performed by Kaplan–Meier analysis. Cox proportional hazard model was used to investigate the possible prognostic factors associated with OS.

Results A total of 102 patients with ATG were enrolled in this study. The median age was 41 years (range 18–68 years). There were 56 (54.9%) males. Sixty-two patients (60.8%) had glioblastoma (GBM). Among these patients, 46 patients (45.1%) had GTR/NTR, 50 patients (49.0%) had STR and 6 patients (5.9%) had PR. Postoperatively, 71.6% of these patients received adjuvant therapy. The median OS was 13.6 months (range 1 week–75 months). COX regression analysis revealed that ATG patients with longer duration of symptoms ($p=0.024$), better pre-KPS ($p=0.045$), maximal resection ($p=0.013$), or lower tumor grade ($p=0.002$) had longer OS, and these predictors are considered as independent prognostic factors. Survival analysis showed that ATGs with GTR/NTR plus chemoradiotherapy had significant OS advantage compared with other treatment regimens.

Conclusions This study comprehensively summarized the characteristics, treatments and survival outcomes of ATGs in the largest sample size. Maximal surgical resection can bring survival benefit. Combined-modality therapy regimen of GTR/NTR plus chemoradiotherapy may be better beneficial for OS than other regimens.

Keywords Adult thalamic glioma · Diffuse midline glioma · H3K27M · Surgical resection · Survival analysis · Thalamic tumor

Introduction

Thalamic gliomas (TGs) are relatively rare tumors, accounting for approximately 1–5% of all intracranial tumors. Most of these tumors commonly occur in children, but extremely unusual in adults, which constitutes for an incidence of about

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2–5% and 1%, respectively [1–4]. Majority of TGs belong to astrocytoma type and are unilaterally involved [1, 3, 5]. The optimal treatment strategies for TGs in children and adults remains unclear until now. Traditionally, surgical resection of these tumors has been a great challenge for neurosurgeons and are inoperable due to their deep anatomical location, proximity to critical structures with important neurological functions [6, 7] and associated with high risks of severe postoperative complications [8–10]. Based on these drawbacks, biopsy is the primary choice to obtain tissue samples for histopathological diagnosis and to guide subsequent therapy [3, 8–12]. Over several decades, with the advancements in neuroimaging, microsurgery and intraoperative assistant techniques, surgical resection of thalamic lesions has been the treatment option with acceptable complications and considered it as a benefit for survival [13–18]. However, there were only a few studies till date on surgical resection of adult thalamic glioma (ATG) with the inclusion of small sample size [16] and there were no definitive reports present on surgical resection of exclusive ATG patients in significant numbers at present. The investigation of ATG patients in a larger population can assist in well-defining the characteristics, management and survival outcomes of ATG. We herein described and summarized the characteristics and management strategies of patients with ATG, and identified prognostic factors that might influence the overall survival (OS) of this rare subset of tumors in larger sample size.

Methods

Patient cohort

This is a retrospective cohort study in which newly diagnosed ATG patients in our hospital between August 2009 and October 2017 were enrolled. All patients underwent surgical resection consecutively and were confirmed by two senior neuropathologists. Tumors involved in thalamus and adjacent structures simultaneously were also included. Patients were excluded if: (1) age < 18 years old, (2) the tumors are mainly involved in the adjacent structures, such as basal ganglia, midbrain, ventricles, hypothalamus or pineal region, with little or without any thalamic involvement, or (3) the clinical records of basic and survival data were not available. Informed consent was provided by all patients or their family members. Our Institutional Review Board (IRB) approved the ethics committee review for this retrospective study.

Preoperative evaluation and management

All patients with ATG underwent brain magnetic resonance imaging (MRI) examination and other evaluation preoperatively. Surgical resection with an assisted microscope was performed to remove the tumors by two senior neurosurgeons. Appropriate surgical approaches were selected individually according to the anatomical location of tumors and principle of protecting significant structures. The extent of resection (EOR) was evaluated through volumetric measurements by postoperative MRI (post-MRI) within 24–72 h after surgery, and if not (9 patients, 8.8%), by intraoperative evaluation of surgeons. According to volumetric analysis by post-MRI, gross total resection (GTR) was defined as no residual of tumor, near total resection (NTR) defined as > 90% removal, subtotal resection (STR) defined as 80–90% removal, and partial resection (PR) defined as < 80% removal. The obtained tissue samples were then used for pathological examination and molecular subtyping. Postoperative adjuvant therapies including radiotherapy and chemotherapy were administrated according to the pathologic diagnosis and EOR.

Date collection and follow up

Clinical characteristics, radiological features, treatments, and survival data of included patients were recorded and collected. All neurological and histological reports were interpreted by two senior neuroradiologists and neuropathologists, respectively.

Statistical analysis

Statistical analysis was performed by using statistical software Stata (version 15.0, StataCorp LLC) and GraphPad Prism 7 (version 7, San Diego, California). Continuous variables were presented as means ± standard deviations and median. Comparisons of categorical variables was performed using Fisher's exact test or Chi-squared test. The median values of continuous variables were taken as the cut-offs under the consideration of clinical practice. Events were defined as deaths that occurred due to disease progression or any other reasons. OS was defined from the time of surgery until death or the last follow-up visit. Survival analysis of OS was performed by Kaplan–Meier analysis and a log-rank test. Univariate and multivariate Cox proportional hazards models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) with regard to OS and to determine the independent prognostic factors. The significance level of all statistical tests was set as $p < 0.05$.

Results

Demographics and clinical findings

Demographics and clinical details of these patients were summarized in Table 1 (and Online Resource 1). A total

of 102 patients (56 males and 46 females) with ATG were enrolled, with a mean of 40 ± 14.4 years, and a median of 41 years (range 18–68 years). The median preoperative KPS (pre-KPS) of patients was 80, and median postoperative KPS (post-KPS) of one week after surgery was 60. The duration of symptoms was range from 0.1 to 196 months, with a median duration of 1 month. Of all patients, 62 (60.8%) patients had glioblastoma (GBM). According to tumor grade, 14 (15.9%) patients had low-grade glioma (LGG, referred to Grade II) and 88 (84.1%) patients had high-grade glioma (HGG, referred to Grade III and Grade IV).

Radiologic findings

All patients underwent brain MRI evaluation preoperatively (Table 1). The mean diameter of all tumors was 4.4 ± 1.5 cm, and median diameter was 4.0 cm. Preoperative hydrocephalus was found in 52 cases (51.0%). The tumor location in 40 (39.2%) patients was confined to lateral thalamus, whereas the tumors were beyond thalamus in the remaining 62 patients. Of these 62 patients, the range of extension included corpus callosum (15, 14.7%), internal capsule, basal ganglia (17, 16.7%), lateral or third ventricle (13, 12.7%) and brainstem (17, 16.7%). Most of the tumors in radiological features presented contrast-enhancement images, which were found in 87 (85.3%) patients.

Management of surgery and adjuvant therapy

Appropriate surgical approaches were designed for each patient individually (Table 2). The surgical approaches included precentral interhemispheric transcallosal interforniceal approach (30, 29.4%), temporal transventriclular approach (49, 48.0%), parieto-occipital transventriclular approach (15, 14.7%) and other approaches (8, 7.9%). The common surgical approaches were shown in illustrative cases (Fig. 1, Case 1 and Case 2). The number of patients receiving GTR/NTR was 46 (45.1%), STR was 50 (49.0%) and PR was 6 (5.9%). Among 30 patients operated with precentral interhemispheric transcallosal interforniceal approach, the

Table 1 Summary of demographics, clinical and radiological features of all patients

Characteristics	n
Age < 41 years	49 (48%)
Sex (male)	56 (54.9%)
Pre-KPS < 80	34 (33.3%)
Post-KPS < 60	32 (31.4%)
Duration of symptoms ≤ 1 month	59 (57.8%)
Hospital way (Emergency)	14 (15.9%)
Glioma type	
GBM	62 (60.8%)
Other types	40 (39.2%)
WHO grade	
LGG (Grade II)	14 (15.9%)
HGG (Grade III and IV)	88 (84.1%)
Side of tumors	
Left	57 (55.9%)
Right	41 (40.2%)
Bilateral	4 (3.9%)
Diameter < 4.0 cm	52 (51%)
Preoperative hydrocephalus	52 (51%)
Location of tumors	
Confined in thalamus	40 (39.2%)
Beyond the thalamus	62 (61.8%)
Range of extension	
Corpus callosum, lobes	15 (14.7%)
Internal capsule, basal ganglia	17 (16.7%)
Lateral or third ventricle	13 (12.7%)
Brainstem	17 (16.7%)
Cystic change	14 (13.7%)
Enhancement	87 (85.3%)

Table 2 Summary of surgical and adjuvant therapies of all patients

Variable	n
Surgical approaches	
Precentral interhemispheric transcallosal interforniceal approach	30 (29.4%)
Temporal transventriclular approach	49 (48%)
Parieto-occipital transventriclular approach	15 (14.7%)
Frontal transcortical approach and Others	8 (7.9%)
Extent of resection	
GTR/NTR	46 (45.1%)
STR	50 (49%)
PR	6 (5.9%)
Intraoperative third ventriculostomy	23 (76.7%)
Surgical complications[a]	7 (23.3%)
Postoperative paralysis or exacerbation	25 (24.5%)
Postoperative hydrocephalus	11 (10.8%)
Postoperative coma	6 (5.9%)
Postoperative hemorrhage	4 (3.9%)
Perioperative death	5 (4.9%)
Others	12 (11.8%)
Adjuvant therapies	
Radiotherapy and chemotherapy	23 (22.5%)
Only radiotherapy	25 (24.5%)
Only chemotherapy	19 (18.6%)
No	20 (19.7%)
NA	15 (14.7%)

NA not available

[a]Some patients had several complications simultaneously after surgery

third ventriculostomy also was performed intraoperatively in 23 (76.7%) patients. However, approximately a quarter of all patients had slight or severe complications associated with surgery within one week after surgery, including postoperative paralysis or exacerbation (25, 24.5%), postoperative hydrocephalus (11, 10.8%), postoperative coma (6, 5.9%), postoperative hemorrhage (4, 3.9%), postoperative death (5, 4.9%) and others (12, 11.8%). Even so, almost half of these patients gradually improve after postoperative management and rehabilitation training. Patients out of the hospital received radiotherapy and/or chemotherapy based on pathological diagnosis, extent of resection and patients' performance status. In this study, 23 (22.5%) patients received both radiotherapy and chemotherapy (chemoradiotherapy), 25 (24.5%) received only radiotherapy, 19 (18.6%) received only chemotherapy, and 20 (19.7%) received no any adjuvant therapy.

Molecular and pathological characteristics

All tissue samples were used for pathological and molecular examinations. Immunohistochemistry and genetic testing were performed in most of the samples. IDH1 detection was available in 68 patients, and there were IDH1 mutants in only 4 (5.9%) patients. P53 expression status was available in 64 patients, and 56 (87.5%) were mutant. ATRX was available in 41 patients, and only 7 (17.1%) patients had ATRX deleted. MGMT promoter (MGMTp) methylation status was available in 44 patients, and only 15 (34.1%) patients showed methylation. H3K27M detection was available only in 19 patients according to the revised 2016 World Health Organization (WHO) classification and 12 (63.2%) were mutant (Online Resource 2). Meanwhile, we analyzed the correlation between H3K27M with other molecular markers (Online Resource 3).

Survival analysis

All patients were followed up for 12 to 75 months. The OS ranged from 1 week to 75 months, and median OS was 13.6 months. The 1-year and 2-year survival rate were 62.7% and 24.5%, respectively. Survival analysis was performed to demonstrate the univariate and multivariate analyses of prognostic factors on OS (Table 3, Fig. 2). Univariate analysis revealed significant differences in OS between subgroups of several variables including preoperative KPS, postoperative KPS, duration of symptoms, hospital way, WHO grade, diameter of tumor, location of tumors, EOR, adjuvant therapies, and Ki-67 ($p < 0.05$). A multivariable COX regression analysis further showed that the patients with pre-KPS ≥ 80, duration of symptoms > 1 month, LGG and GTR/NTR had better OS than their counterparts, respectively (Fig. 2). Furthermore, pre-KPS (HR 0.416, 95% CI 0.176–0.981, $p = 0.045$), duration of symptoms (HR 0.466, 95% CI 0.241–0.905, $p = 0.024$), WHO grade (HR 14.580, 95% CI 2.271–78.120, $p = 0.002$), and EOR (HR 3.171, 95% CI 1.277–7.875, $p = 0.013$) were considered as independent prognostic factors in patients with ATG (Table 3).

Discussion

Thalamic gliomas are rare tumors, especially in adults [1–3]. To date, there were only a few studies reported on TGs. The prognostic outcomes of TG patients remained poor regardless of the types of treatment [1–3, 11, 16, 19–21] and no availability of clinical practice guidelines. Although surgical resection of TG is controversial, recent studies indicated that surgical resection of thalamic tumors may benefit the survival of patients, whereas these studies included a small sample size of thalamic gliomas [13, 16, 22]. Thus, it is urgent and important to investigate the application and efficacy of comprehensive treatments including surgery and adjuvant therapy and to determine the possible prognostic factors of ATGs. We herein reported the largest case series of ATG patients so far for evaluating the clinical outcomes of these patients. The findings of our study demonstrated that ATG patients receiving maximal surgical resection might have better survival outcomes than those who had biopsy or partial resection in the previous studies (median OS, 13.6 vs. ~ 12 months) [13, 15, 19, 23] and the median OS are approximate to survival time of the supratentorial lobar glioblastomas who received standard treatments (13.6 vs. 14.6 months) [24].

Although most of these rare tumors occur in children, these also occur across various age groups in adults (range 18–68 years). This study revealed that there may be two age peaks of this disease in adults, which are 20–29 and 40–49 age ranges, especially the latter. The number of males was more than females, with a male to female ratio of 1.2:1 (56:46). Univariate analysis revealed that age and sex were not prognostic factors of ATGs, and these results were consistent with the previous studies [23, 25].

Duration of symptoms, hospital way and KPS score might reflect the development process of these tumors and recent status of patients. Previous studies revealed that the duration of symptoms was correlated with survival in brain malignant tumors. Univariate analysis revealed that the patients with shorter duration (≤ 1 month)/emergency into hospital had poorer OS and multivariate COX regression analysis showed that the duration of symptoms was an independent prognostic factor. We speculated that the tumors within shorter duration of symptoms (often indicative of HGG) might have faster growth and progression, leading to worse outcomes. This result was similar to the previous reports regarding to bilateral thalamic gliomas, suggesting that patients with

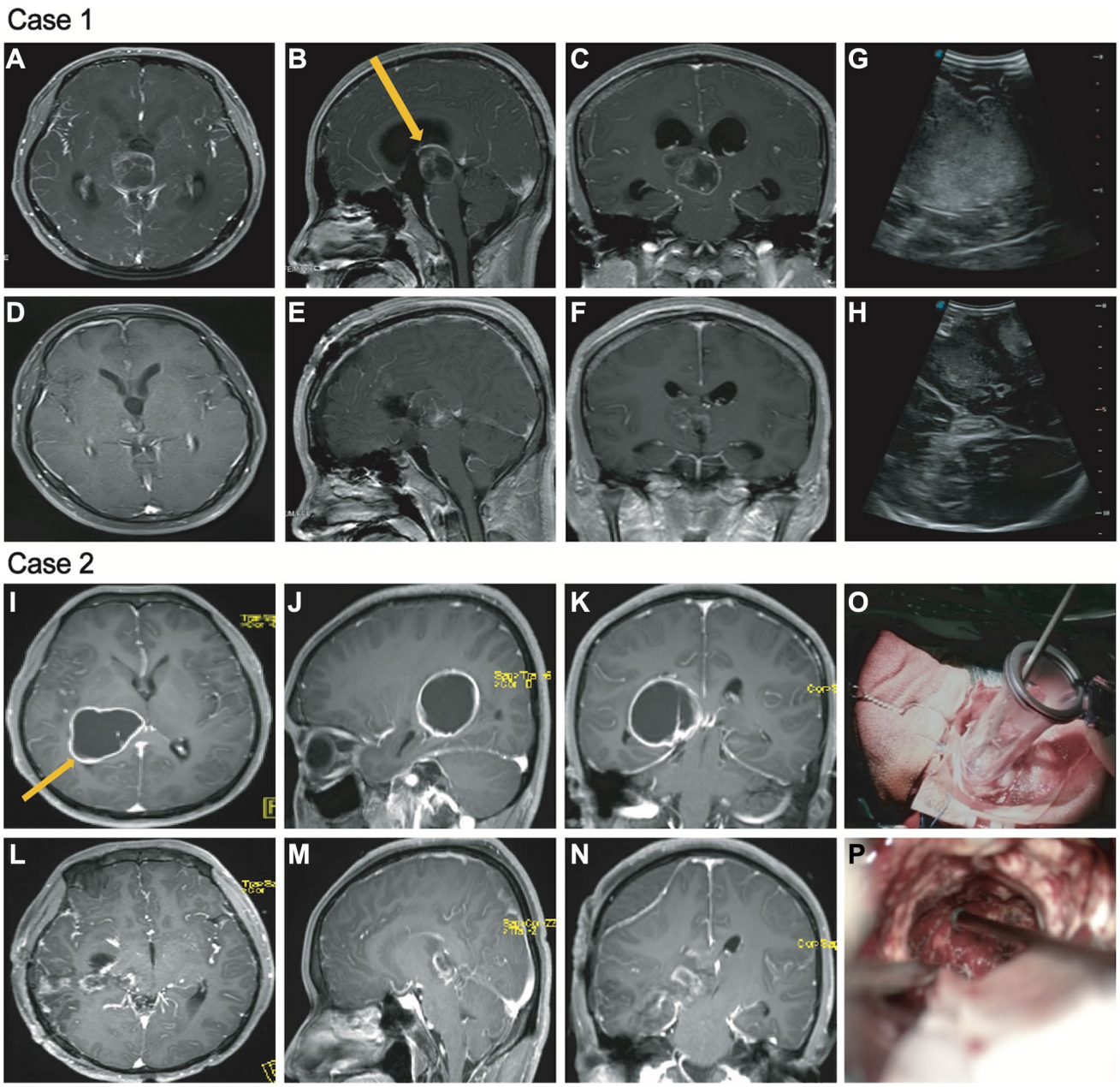


Fig. 1 Illustrative cases. Case 1: A 43-year-old male with the complaint of headache and insomnia for over 1 month was admitted to our hospital. Radiologic examination (Fig. 1a–h) revealed a lesion located in the right thalamus protruding toward the third ventricle (Fig. 1a–c). Surgical resection of the tumor was conducted through precentral interhemispheric transcallosal interforniceal approach (Fig. 1b, yellow arrow) with intraoperative ultrasound (Fig. 1g, h). The postoperative course was relatively stable. Postoperative MRI revealed GTR of the tumor (Fig. 1d–f) and pathology confirmed the diagnosis of glioblastoma (grade IV). Radiotherapy and chemotherapy were administrated to the patient postoperatively. He was still alive for 17 months after surgery. Case 2: A 36-year-old male with the complaint of left limb numbness for over 2 months and aggravated 1 week was admitted to our hospital. Neurologic examination revealed hypoesthesia of the left limb. Radiologic examination (Fig. 1i–n) revealed a space-occupying lesion located in the right thalamus and lateral ventricle with irregular ring-enhancement and cystic change (Fig. 1i–k). The patient underwent surgical resection through right temporal transventriclular approach (Fig. 1i, yellow arrow) assisted with intraoperative tubular retractor system (Fig. 1o) and subcortical electrical stimulation (Fig. 1p). Postoperative MRI revealed GTR of the tumor (Fig. 1l–n). Immunohistochemical examination showed P53, TERT250, H3K27M mutant, MGMTp methylation positive and Ki-67 index of 15–20%, but no IDH1 mutation and no ATRX loss. Finally, the patient was diagnosed as having diffuse midline glioma, H3K27M mutant (grade IV). Subsequently, the patient received radiotherapy and chemotherapy and had superior survival status. She was alive for 15.5 months after surgery

Table 3 Cox regression analysis for overall survival of adult thalamic glioma

Variable	n	Univariate analysis		Multivariable analysis		
		χ^2	p value	HR[a]	95% CI[b]	p value
Pre-KPS, < 80/ ≥ 80	34/68	5.820	**0.016**	0.416	0.176, 0.981	**0.045**
Post-KPS, < 60/ ≥ 60	34/68	11.222	**0.001**	0.541	0.273, 1.075	0.080
Duration of symptoms, ≤ 1 > 1 (month)	59/43	9.106	**0.003**	0.466	0.241, 0.905	**0.024**
Hospital way, emergency	14/88	6.784	**0.009**	1.018	0.351, 2.954	0.974
WHO grade, LGG/HGG	14/88	19.881	**< 0.001**	14.580	2.271, 78.120	**0.002**
Diameter, < 4.0/ ≥ 4.0 (cm)	52/50	5.073	**0.024**	0.594	0.233, 1.515	0.276
Location of tumors, confined/beyond in thalamus	40/62	13.191	**< 0.001**	2.079	0.871, 4.963	0.099
Extent of resection, (GTR,NTR)/(STR,PR)	46/56	19.863	**< 0.001**	3.171	1.277, 7.875	**0.013**
Adjuvant therapies, Radio + chemo/radio/chemo/no	23/25/19/20	14.014	**0.007**	1.238	0.974, 1.574	0.081
Ki-67, < 10/ ≥ 10 (%)	14/55	10.047	**0.002**	2.900	0.999, 8.422	0.050

The bold p value underlines the statistically significant outcome measure (HR)

[a]Hazard ratio

[b]95% confidence interval

the duration of symptoms ≥ 2 months had longer survival than their counterparts [16, 19]. Usually, the lower KPS of patients who were admitted through emergency had poorer outcome. Univariate analysis revealed that patients with pre-KPS ≥ 80 and post-KPS ≥ 60 had better survival outcome. Furthermore, multivariate analysis demonstrated that pre-KPS as an independent prognostic factor in patients with ATG. Several studies have showed that patients with high pre-KPS have better survival and might be an independent prognostic factor [16, 23, 25].

Most of the TGs have similar radiological features, which are often presented as space-occupying lesions located in the thalamus with/without the involvement of adjacent structures with hypointense T1 signal and hyperintense T2 and FLAIR signal, and contrast-enhancement in most of HGGs and cystic changes in few cases [1, 16]. Majority of the TGs were located in lateral thalamus, while only a few were bilaterally involved [1, 2, 19, 23]. In this study, only 4 (3.9%) tumors were involved in both sides of the thalamus among the included patients. Our previous study [19] and others [5] revealed that bilateral involvement of thalamus predicted poorer survival rate. Approximately half of these patients experienced preoperative hydrocephalus with varying degrees, which mainly resulted from extension to the third ventricle due to relatively small tumors or pushing and blocking the ventricle system from large tumors. Over half of the tumors had extended thalamic periphery into other adjacent structures, leading to an increase in the difficulty of surgical excision and postoperative severe complications. In addition, these patients always had poorer survival rate, which was consistent with those findings in the previous studies [13, 15, 17, 22].

Numerous studies have showed that GTR/NTR of tumor was correlated with longer survival in supratentorial gliomas, which mainly refers to the cerebral hemisphere gliomas [26, 27]. Most of TG patients reported by early studies received only biopsy or PR with or without postoperative radiotherapy for palliative care [8–10]. With the advancements in microsurgery and intraoperative assisted techniques [28, 29], surgical resection of deep-seated tumors can be performed carefully, which in turn can better protect the important brain structures and functions. This study is conducted exclusively on ATG patients, revealing that patients who received GTR/NTR had a favorable prognosis. Intraoperative assistive techniques, including navigation system, B-ultrasonic localization, tubular retractor, electrical stimulation, might be helpful in accurate positioning, safe and maximum resection of tumors, and improving survival outcomes [30–32]. Whereas, biopsy with auxiliary equipment was still a treatment choice for unresectable tumors [8, 33]. Based on our surgical experience of 4 bilateral TGs and literature reports [19], surgery for these bilateral tumors cannot bring a survival benefit and might lead to severe complications, and even death. Therefore, more aggressive surgical resection with intraoperative assisted techniques should be considered for these lateral tumors.

The role of adjuvant radiotherapy and chemotherapy for TGs, regardless of children or adults, still remained a controversy [4, 16, 23, 25]. The study conducted by Steinbok et al. [4] in 2016 showed that patients who received adjuvant therapy had a worse survival outcome. However, other studies reported the opposite prognostic outcomes with adjuvant therapy in TGs [16, 23, 25]. In our study, with the inclusion of the larger sample size, the results of postoperative adjuvant therapy, including radiotherapy and/or chemotherapy, was considered helpful for prolonging survival time, but was not considered as an independent prognostic factor. Furthermore, comprehensive analysis of resection and adjuvant therapy

demonstrated that patients receiving combined-modality therapy (CMT) regimen of GTR/NTR plus chemoradiotherapy had longer OS than those receiving other regimens. Similarly, CMT regimen is a better selection in other types of glioma, such as cerebral GBM or elderly GBM, as reported in the previous reports [24, 34]. Regrettably, less than 1/3 of all patients in this study had received CMT regimen of radiotherapy and chemotherapy after surgery. Based on the above outcomes, if more patients had received CMT regimen, they might have longer survival. Compared to the historic data of TGs with biopsy or PR, the patients in this study had better median OS and acceptable complications associated with surgery.

Although H3K27M-mutant gliomas occur primarily in children, they can also be encountered in adults [35–41]. Common midline locations included brainstem, thalamus, and spinal cord [36, 42–44]. Base on the revised 2016 World Health Organization (WHO) classification [45], "Diffuse midline glioma, H3 K27M-mutant" was recognized as a distinct entity and patients with H3K27M-mutant glioma had poorer survival outcomes [36, 39, 42, 46]. Although the results of survival analysis showed no significant difference between H3K27M mutant and OS in this study, patients with H3K27M mutant had poor survival outcome. Several earlier studies on TGs revealed similar outcomes after reviewing the published literatures [43, 47]. The study conducted by Wang et al. [43] in 2018 with a larger series of H3K27M-mutant DMG in different anatomical locations demonstrated that H3K27M mutation was mainly associated with a poorer prognosis in infratentorial gliomas when compared with the corresponding H3 wild-type gliomas, but not in supratentorial gliomas.

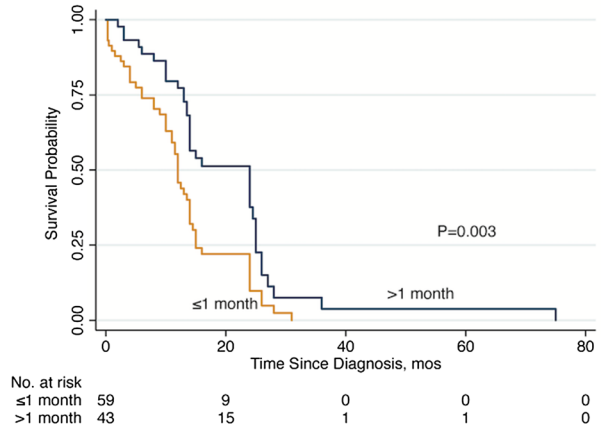
Limitations

Finally, there are some limitations that should be noted in this study. Long time span could lead to a lack of partial clinical data, such as long-term imaging and incomplete data of progression-free survival (PFS). Survival analysis of PFS and growth pattern analysis were not performed in many of the patients. Additionally, majority of the patients had poorer compliance with adjuvant therapy due to side effects, economic hardships, and other factors, which may influence the evaluation of authentic effect of adjuvant therapy. Moreover, postoperative quality of life was not evaluated in patients with TGs, and this requires further investigation in our future works.

Conclusion

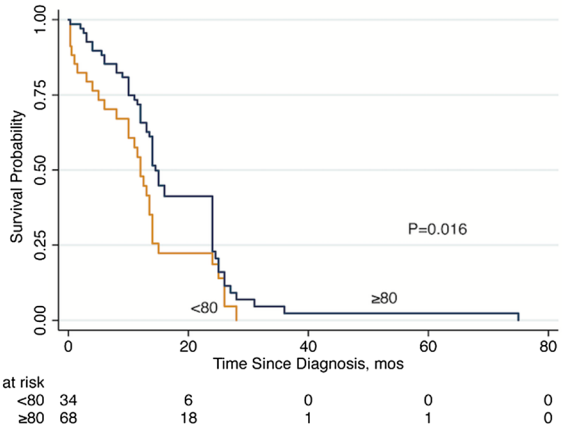
This study comprehensively summarized the characteristics, management and survival outcome of ATGs within the largest sample size till date. Maximum surgical resection can bring survival benefits. Combined-modality therapy regimen of GTR/NTR plus chemoradiotherapy may contribute to overall survival. This study might assist in deeply understanding the clinical characteristics and survival, and also provide a guideline for managing ATG patients.

A Duration of symptoms



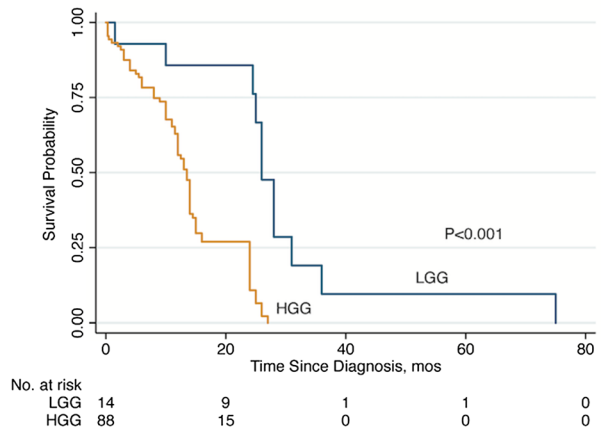
No. at risk					
≤1 month	59	9	0	0	0
>1 month	43	15	1	1	0

B Preoperative KPS



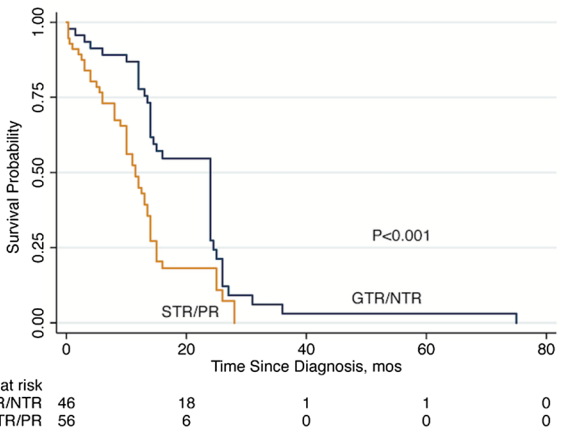
No. at risk					
<80	34	6	0	0	0
≥80	68	18	1	1	0

C WHO Grade



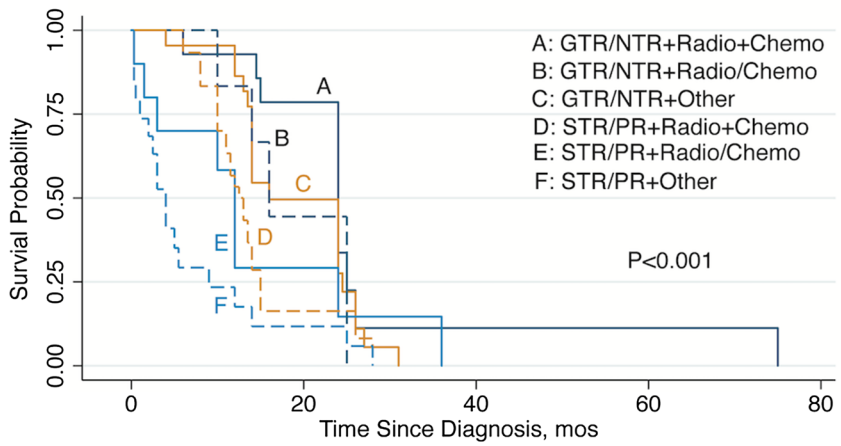
No. at risk					
LGG	14	9	1	1	0
HGG	88	15	0	0	0

D Extent of resection (EOR)



No. at risk					
GTR/NTR	46	18	1	1	0
STR/PR	56	6	0	0	0

E Treatment regimens



No. at risk					
Regimen A	14	7	1	1	0
Regimen B	22	9	0	0	0
Regimen C	10	2	0	0	0
Regimen D	7	2	0	0	0
Regimen E	30	2	0	0	0
Regimen F	19	2	0	0	0

◂**Fig. 2** Kaplan–Meier survival curve of prognostic factors of ATG. **a** Kaplan–Meier survival curve representing ATG patients stratified by the duration of symptoms ($p = 0.003$). **b** Representing ATG patients stratified by preoperative KPS ($p = 0.016$). **c** Representing ATG patients stratified by WHO grade ($p < 0.001$). **d** Representing ATG patients stratified by EOR ($p < 0.001$). **e** Representing ATG patients stratified by treatment regimens ($p < 0.001$)

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this manuscript.

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