Prognostic factors of gliosarcoma in the real world: a retrospective cohort study

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Abstract

Purpose: Gliosarcoma is a histopathological variant of glioblastoma, which is characterized by a biphasic growth pattern consisting of glial and sarcoma components. Owing to its scarcity, data regarding the impact of available treatments on the clinical outcomes of gliosarcoma are inadequate. The purpose of this retrospective cohort study was to analyze the prognostic factors of gliosarcoma.

Methods: By screening the clinical database of neurosurgical cases at a single center, patients with gliosarcoma diagnosed histologically from 2013 to 2021 were identified. Clinical, pathological and molecular data were gathered founded on medical records and follow-up interviews. Prognostic factors were derived using Cox proportional hazards model with backward stepwise regression analysis.

Results: Forty-five GSM patients were included. Median overall survival was 25.6 months (95%CI 8.0–43.1), and median relapse free survival was 15.2 months (95%CI 9.7–20.8). In multivariable analysis, total resection ($p=0.023$, HR=0.192, 95%CI 0.046–0.797) indicated an improved prognosis. And low expression of Ki-67 ($p=0.059$, HR=2.803, 95%CI 0.963–8.162) would be likely to show statistical significance. However, there might be no statistically significant survival benefit from radiotherapy with concurrent temozolomide ($n=33$, 73.3%, log-rank $p=0.99$) or adjuvant temozolomide ($n=32$, 71.1%, log-rank $p=0.74$).

Conclusion: This single centre retrospective study with a limited cohort size has demonstrated the treatment of gross total resection and low expression of Ki-67 are beneficial for patients with GSM, while radiotherapy or temozolomide is not.

Introduction

Gliosarcoma (GSM) is a rare malignant tumor of the central nervous system (CNS), and has been classified as glioblastoma (GBM) since the publication of 2016 World Health Organization Classification of Tumors of the Central Nervous System. It is considered as a histopathological variant of GBM, as well as epithelioid GBM and giant cell GBM, accounting for about 2–4% of all cases (Louis et al. 2016; Wen and Huse 2017). GSM presents unique histopathological manifestations characterized by a biphasic growth model of glial and sarcomatous elements. The glioma components often exhibit the typical characteristics of glioblastoma, and have different degrees of anaplasia and glial fibrillary acidic protein (GFAP) expression. Meanwhile, the sarcomatoid area appears microscopically show dense long-spindle cells arranged within a fishbone fibrosarcoma structure, and occasionally malignant fibrous histiocytomas. The key points of diagnosis are the reticular fibres in sarcoma and GFAP expression in glioma (Kiang et al. 2021). GSM has similar radiological and clinical representations to GBM but a comparatively poorer prognosis (Kozak et al. 2009; Frandsen et al. 2018; Yi et al. 2019; Louis et al. 2021). Several researches have reported the median overall survival (OS) of gliosarcoma ranging from 6.6 to 18.5 months (Singh et al. 2012; Walker et al. 2013; Adeberg et al. 2016; Ma et al. 2020). At present, special therapies for GSM are virgin, and treatments still cannot exceed the limits of GBM guidelines,

including maximum surgical resection, radiotherapy (RT) and temozolomide (TMZ) (Gittleman et al. 2018).

Data regarding the impact of excision extension and postoperative adjuvant therapy on GSM outcomes are insufficient. Although gross total resection (GTR) of GBM independent of adjuvant therapy has been associated with progression free survival (PFS) improvement, this has not yet been confirmed in GSM (Singh et al. 2012). Some studies have elucidated a potential a possible benefit of RT and TMZ for GSM (Walker et al. 2013; Huang et al. 2020). However, there is still considerable controversy due to the lack of forward-looking clinical evidence (Smith et al. 2018; Srivastava et al. 2018). Distinctive histopathological properties may be associated with the differential therapeutic susceptibility between GSM and GBM. In addition, age, tumor size (Chen et al. 2019) and the diagnosis of primary or secondary (Jin et al. 2020) have also been reported being associated with GSM prognosis. There are still questions: what type of patient features indicate a better prognosis, and what kind of treatments can benefit GSM patients.

Here we performed a retrospective cohort study of 45 GSM patients at single centre. The purposes of our study were to analyze the independent prognostic factors of GSM and to understand the efficacy of classical treatments on survival outcomes.

Materials And Methods

Patients

From November 2013 until May 2021, patients with pathologically authenticated GSM were scanned from the medical record database of our hospital. Below are other criteria for inclusion. Patients were treated with at least one surgical resection of GSM, including the primary operation and reoperation. In accordance with the safety principle, the focus and surrounding brain tissue should be removed as much as possible. Patients had undergone at least one postoperative cranial magnetic resonance (MR) or computerized tomography (CT) examination, which was compared with the preoperative imaging data to clarify the location and integrity of resection (Fig. 1A-B). The GSM was diagnosed according to the biphasic growth pattern of hematoxylin-eosin (HE) staining as well as GFAP staining demonstrating GFAP-positive glioma components and GFAP-negative sarcoma components containing tumor spindle cells (Fig. 1C-F). The pathological specimens before the release of 2016 World Health Organization Classification of Tumors of the Central Nervous System were reviewed and confirmed by the pathologist. Radiologic and pathologic findings were read and examined by specialists who did not know patient information following the principle of blindness.

During the course of clinical data collection, we found that data collected since 2013 was relatively intact due to our electoral medical record system. Patients were routinely follow-up every three months until April 2022. Meanwhile, there was no notable change in the treatment of GSM during this period. We excluded the patients with uncertain pathological diagnosis or severely incomplete clinical data.

Following the identification of the cohort, the clinical records of patients in the cohort were reviewed carefully, including disease-specific demographic, clinical and treatment characteristics.

Data Compilation

Clinical or treatment-related variables included age, sex, Karnofsky performance score (KPS), diagnosis of primary or secondary, single or multiple lesions, tumor location, preoperative size, epileptic seizure, intracranial hypertension, Ki-67 level, genetic mutation (e.g., IDH1, p53, PTEN, MGMT, 1p/19q codeletion, TERT, BRAF, PIK3CA, ATRX, EGFR), surgical resection extension, adjuvant therapies (RT, concurrent TMZ, adjuvant TMZ, targeted therapy). The conditions of postoperative complications were difficult to collect, and were not included in the analysis due to the high scarcity and the poor reliability. Tumor-specific characteristics were acquired from the initial MR or CT examinations. Typically, early imaging examinations provided a generalized diagnostic such as glioma instead of GSM. The final diagnosis was pathologically determined during subsequent surgical treatment.

Outcome

We defined the first diagnosis date as the day of the first neurosurgery for GSM confirmed by postoperative pathology, and the OS was calculated from this day as the starting point.

In 8 cases of secondary GSM, all of these patients had explicit primary and secondary pathological diagnosis. The primary diagnosis was GBM (WHO IV) in 5 cases and non-GBM (WHO II-III) in 3 cases. The location of the secondary GSM was identical to the primary tumor, and the time interval between two onset was no more than two years. According to 2016 World Health Organization Classification of Tumors of the Central Nervous System, these patients can be clearly defined as secondary GSM. Before the first diagnosis of GSM, all secondary GSM patients in this cohort had received neurosurgery and at least one adjuvant treatment. The diagnosis of primary and secondary is worth being included in Cox proportional hazards model.

Another survival analysis index was relapse free survival (RFS). For either primary or secondary GSM after tumor resection, relapse of the disease was defined as the date of radiographic recurrence necessitating either secondary surgical intervention or adjuvant therapy. RFS is defined from the date of the first resection of GSM lesions until the date of the first indication of tumor recurrence during the imaging examination. Clinical manifestations, multiple imaging examinations and secondary postoperative pathology identified and excluded the possibility of tumor pseudo-progression in recurrent patients.

Statistical Analysis

Cox regression model was used for univariable analysis, and the hazard ratio (HR) and its 95% confidence interval (95%CI) were estimated. Kaplan-Meier survival curves were plotted according to different prognostic factors and were analyzed using log-rank test. Then, multivariate analysis recruiting proper variables was performed by backward regression method to confirm the statistical significance of prognostic factors. Calculations and graphical representations were performed using the R software package (version 4.0.3, The R Foundation for Statistical Computing).

Results

Cohort Characteristics

A total of 45 patients with histopathologically confirmed GSM between 2013 and 2021 was included (Table 1). As of the last follow-up, 30 patients (66.7%) had relapsed from the first GSM resection operation. Among them, 24 patients (53.3%) had passed away. In 15 patients (33.3%), no tumor recurrence was observed during postoperative imaging reexamination. In the cohort, 26 cases were medial and young (age<60, 57.8%) and 32 cases were males (71.1%). Most patients were diagnosed with primary GSM (n = 37, 82.2%), with the remainder being secondary GSM transformed from other types of glioma (n = 8, 17.8%). Median preoperative KPS was 80 (range 20–100). Preoperatively, 5 patients (11.1%) had epileptic seizures, and 36 patients (80%) suffered from ventricular enlargement and intracranial hypertension caused by tumor compression. Almost all but one patient had a single lesion (n = 44, 97.8%), primarily in temporal (n = 19, 42.2%) and frontal (n = 12, 26.7%) lobes. Other tumor locations included parietal lobe (n = 5, 11.1%), basal ganglia (n = 4, 8.9%), callosum (n = 3, 6.7%), thalamus (n = 1, 2.2%) and brainstem (n = 1, 2.2%). In terms of laterality, the left side (n = 20, 44.4%) was a little more than the right side (n = 16, 35.6%), others were located deep in the brain (n = 9, 20.0%). Most tumors had a maximum diameter greater than 3 centimeters (n = 32, 71.1%).

The majority successfully underwent GTR (n = 41, 91.1%) and the remaining patients underwent subtotal resection (STR) and near total resection (NTR), based on the detailed surgical records and postoperative imaging data of each patient. Benefit from the progress of surgical technology and strictly observing surgical indications, the complete resection rate of malignant brain tumors increases gradually in our medical centre, and some deep brain tumors can also be totally removed.

Except for one perioperative death, all cases had received at least one adjuvant therapy within the specified time, mainly RT (n = 33, 73.3%), concurrent TMZ (n = 33, 73.3%), adjuvant TMZ (n = 32, 71.1%). This is the reliable information from clinical data. Some patients (n = 11) only accomplished adjuvant TMZ treatment because of terrible postoperative physical condition or poor tolerance to radiotherapy. Coincidentally, all patients receiving RT in this study took TMZ simultaneously, and part of them (n = 21) also received adjuvant TMZ. A few patients were also treated with nimustine (n = 4, 8.8%) and bevacizumab (n = 2, 4.4%). Some recidivist patients received reoperation (n = 12, 40%) or secondary radiotherapy (n = 7, 23.3%), and five of them received both of them.

In some patients, gene mutations were detected through next generation sequencing (NGS) and/ or immunohistochemistry (IHC). The results are listed in Table 1.

Table 1
Clinical characteristics of 45 GSM cases

Characteristics	Number of patients (n = 45)	Proportion(%)
Relapse	30	66.7
Death	24	53.3
Age		
Average age, years	53.2	
Median age, years	56	
<60	26	57.8
≥60	19	42.2
Sex		
Male	32	71.1
Female	13	28.9
KPS		
≤70	15	33.3
>70	30	66.7
Primary or Secondary		
Primary GSM	37	82.2
Secondary GSM	8	17.8
GBM-origined	5	11.1
Non-GBM-origined	3	6.6
Number of lesions		
Single	44	97.8
Multiple	1	2.2
Size, diameter		
≤3cm	13	28.9
>3cm	32	71.1
Location		
Temporal	19	42.2
Frontal	12	26.7

Characteristics	Number of patients (n = 45)	Proportion(%)
Parietal	5	11.1
Basal ganglia	4	8.9
Callosum	3	6.7
Thalamus	1	2.2
Brainstem	1	2.2
Laterality		
Left	20	44.4
Right	16	35.6
Profound	9	20.0
Epileptic seizure		
No	40	88.9
Yes	5	11.1
Intracranial hypertension		
No	9	20.0
Yes	36	80.0
Level of Ki-67		
≤15%	15	33.3
>15%	30	66.7
Resection range		
GTR	41	91.1
STR/NTR	4	8.9
Biopsy	0	0
Radiotherapy		
No	11	24.4
Yes	33	73.3
Missing	1	2.2
Dose, mean (SD)	57.97 (2.75)	
Concurrent TMZ		

Characteristics	Number of patients (n = 45)	Proportion(%)	
No	11	24.4	
Yes	33	73.3	
Missing	1	2.2	
Adjuvant TMZ			
No	12	26.7	
Yes	32	71.1	
Missing	1	2.2	
Gene locus	Wild-type (%)	Mutated (%)	Missing
IDH1	40 (100.0)	0 (0.0)	5
p53	14 (33.3)	28 (66.7)	3
PTEN	5 (55.6)	4 (44.4)	36
MGMT	11 (64.7)	6 (35.3)	28
1p/19q codeletion	10 (66.7)	5 (33.3)	30
TERT	5 (27.8)	13 (72.2)	27
BRAF	19 (90.5)	2 (9.5)	24
PIK3CA	9 (81.8)	2 (18.2)	34
ATRX	8 (21.6)	29 (78.4)	8
EGFR	8 (80.0)	2 (20.0)	35

Median Os And Rfs

After discharge, patients were systematically re-evaluated and re-examined every three months. Most patients were given a long-term follow-up of more than 2 years, and the minimum follow-up period was 4 quarters. Survival data for 45 patients was clarified by April 2022, the date of death and recurrence were precisely obtained. The median OS and the median RFS were calculated via the Kaplan-Meier curve. In this cohort, the median OS was 25.6 months (95%CI 8.0–43.1) (Fig. 2A), and the median RFS was 15.2 months (95%CI 9.7–20.8) (Fig. 2B).

Characteristics Associated With Os

Potential prognostic factors were analyzed using the Cox proportional hazards model (Table 2). In backward regression multivariable analysis excluding the variables of all gene mutations but p53 due to their incomplete data, total resection ($p = 0.023$, HR = 0.192, 95%CI 0.046–0.797) was significantly associated with longer OS, indicating a better prognosis of GSM patients. Moreover, expression level of Ki-67 ($p = 0.059$, HR = 2.803, 95%CI 0.963–8.162) would probably be statistically significant if the sample size increased (Table 2).

However, none of RT with concurrent TMZ ($p = 0.991$, HR = 0.995, 95%CI 0.389–2.546) and adjuvant TMZ ($p = 0.742$, HR = 0.860, 95%CI 0.351–2.110) indicated a statistical significance either in univariable and multivariable analysis (Table 2).

All patients with secondary GSM ($n = 8$) received post-operative RT or TMZ after the first operation. Of them, 4 patients received renewedly radiotherapy and concurrent TMZ after the second operation, and others also accepted adjuvant TMZ treatment. Compared with patients with primary GSM, there was no significant difference in patients with secondary GSM ($p = 0.749$, HR = 0.850, 95%CI 0.315–2.298), whether for GBM-originated ($p = 0.317$, HR = 1.742, 95%CI 0.588–5.166) or non-GBM-originated ($p = 0.507$, HR = 0.503, 95%CI 0.066–3.827) (Table 2).

Table 2
Univariable and multivariable analysis according to OS and RFS

Variable Name	Univariable Analysis, OS		Multivariable Analysis, OS	
	p value	HR (95% CI)	p value	HR (95% CI)
Age	0.732	1.151 (0.515–2.572)		
Sex	0.358	0.678 (0.296–1.553)		
Primary or Secondary	0.749	0.850 (0.315–2.298)		
Primary vs. GBM-originated	0.317	1.742 (0.588–5.166)		
Primary vs. Non-GBM-originated	0.507	0.503 (0.066–3.827)		
KPS	0.847	0.919 (0.392–2.157)		
Location	0.548			
Frontal vs. deep	0.195	0.452 (0.136–1.500)		
Parietal vs. deep	0.989	0.990 (0.244–4.024)		
Temporal vs. deep	0.364	0.624 (0.226–1.728)		
Size	0.334	0.657 (0.280–1.542)		
Number of lesions	0.036	0.095 (0.011–0.853)		
Epileptic seizure	0.684	0.739 (0.172–3.170)		
Intracranial hypertension	0.377	0.639 (0.237–1.725)		
Ki-67 level	0.132	2.039 (0.807–5.151)	0.059	2.803 (0.963–8.162)
Resection range	0.125	0.382 (0.111–1.306)	0.023	0.192 (0.046–0.797)
Radiotherapy	0.991	0.995 (0.389–2.546)		
Concurrent TMZ	0.991	0.995 (0.389–2.546)		
Adjuvant TMZ	0.742	0.860 (0.351–2.110)		
Gene mutation				
IDH1	-	-		
p53	0.807	0.893 (0.360–2.216)		
PTEN	0.809	1.221 (0.243–6.122)		
MGMT	0.953	0.950 (0.173–5.229)		
1p/19q codeletion	0.381	2.057 (0.410–10.318)		
TERT	0.209	47.014 (0.116–18994)		

Variable Name	Univariable Analysis, OS		Multivariable Analysis, OS	
	p value	HR (95% CI)	p value	HR (95% CI)
BRAF	0.288	2.436 (0.472–12.569)		
PIK3CA	0.483	2.262 (0.232–22.095)		
ATRX	0.165	0.483 (0.173–1.349)		
EGFR	0.975	0.966 (0.111–8.415)		
Variable Name	Univariable Analysis, RFS		Multivariable Analysis, RFS	
	p value	HR (95% CI)	p value	HR (95% CI)
Age	0.700	1.171 (0.524–2.616)		
Sex	0.568	0.784 (0.341–1.805)		
Primary or Secondary	0.715	1.202 (0.448–3.228)		
Primary vs. GBM-originated	0.417	1.566 (0.529–4.636)		
Primary vs. Non-GBM-originated	0.646	0.624 (0.083–4.684)		
KPS	0.800	0.896 (0.383–2.096)		
Location	0.708			
Frontal vs. deep	0.367	0.578 (0.176–1.900)		
Parietal vs. deep	0.995	1.004 (0.250–4.041)		
Temporal vs. deep	0.424	0.660 (0.238–1.831)		
Size	0.426	0.706 (0.300–1.663)		
Number of lesions	0.022	0.071 (0.007–0.679)		
Epileptic seizure	0.857	0.875 (0.205–3.731)		
Intracranial hypertension	0.513	0.714 (0.260–1.958)		
Ki-67 level	0.130	2.066 (0.809–5.278)	0.052	2.996 (0.992–9.053)
Resection range	0.137	0.395 (0.116–1.345)	0.022	0.181 (0.042–0.782)
Radiotherapy	0.861	0.919 (0.360–2.348)		
Concurrent TMZ	0.861	0.919 (0.360–2.348)		
Adjuvant TMZ	0.631	0.804 (0.330–1.959)		
Gene mutation				
IDH1	-	-		

Variable Name	Univariable Analysis, OS		Multivariable Analysis, OS	
	p value	HR (95% CI)	p value	HR (95% CI)
p53	0.995	0.997 (0.402–2.474)		
PTEN	0.745	1.307 (0.261–6.550)		
MGMT	0.992	1.009 (0.184–5.527)		
1p/19q codeletion	0.433	1.900 (0.382–9.440)		
TERT	0.202	49.123 (0.125–19370)		
BRAF	0.270	2.529 (0.487–13.134)		
PIK3CA	0.838	1.252 (0.145–10.817)		
ATRX	0.298	0.581 (0.209–1.617)		
EGFR	0.951	1.070 (0.124–9.249)		

Kaplan-Meier curves have been drawn respectively for interested factors respectively. None of them demonstrated a significant difference. Median OS was 29.7 months (95%CI 11.5–47.9) in the total resection group (n = 41, 91.1%) and 4.8 months (95%CI 0.0–18.1) in the non total resection group (n = 4, 8.9%), p = 0.11 (Fig. 2C). Median OS was 17.0 months (95%CI 8.0–43.1) in Ki-67 high expression group (Ki-67 > 15%, n = 30, 66.7%) and cannot be calculated in Ki-67 low expression group (Ki-67 ≤ 15%, n = 15, 33.3%) because the median OS is unreached, p = 0.12 (Fig. 2D). Median OS was 25.6 months (95%CI 9.2–42.0) in the RT with concurrent TMZ group (n = 33, 73.3%) and 41.0 months (95%CI 0.0–82.1) in the non RT with concurrent TMZ group (n = 11, 24.4%), p = 0.99 (Fig. 3A), 29.7 months (95%CI 4.1–55.3) in the adjuvant TMZ group (n = 32, 71.1%) and 25.6 months (95%CI 0.0–54.3) in the non adjuvant TMZ (n = 12, 26.7%), p = 0.74 (Fig. 3B).

Median OS was 25.6 months (95%CI 9.2–42.0) in the RT with concurrent TMZ group (n = 33, 73.3%) and 41.0 months (95%CI 0.0–82.1) in the non RT with concurrent TMZ group (n = 11, 24.4%), p = 0.99 (Fig. 3A), 29.7 months (95%CI 4.1–55.3) in the adjuvant TMZ group (n = 32, 71.1%) and 25.6 months (95%CI 0.0–54.3) in the non adjuvant TMZ (n = 12, 26.7%), p = 0.74 (Fig. 3B).

In addition, according to the results of NGS and/ or immunohistochemistry (IHC), the fact whether some gene loci were mutated was used as a prognostic factor for survival analysis, including p53 (negative, n = 14, 33.3% vs. positive, n = 28, 66.7%, log-rank p = 0.81), ATRX (negative, n = 8, 21.6% vs. positive, n = 29, 88.4%, log-rank p = 0.16), BRAF (negative, n = 19, 90.5% vs. positive, n = 2, 9.5%, log-rank p = 0.27), TERT (negative, n = 5, 27.8% vs. positive, n = 13, 72.2%, log-rank p = 0.025), MGMT methylated (negative, n = 11, 64.7% vs. positive, n = 6, 35.3%, log-rank p = 0.95), 1p/19q codeletion (negative, n = 10, 66.7% vs. positive, n = 5, 33.3%, log-rank p = 0.37), PIK3CA (negative, n = 9, 81.8% vs. positive, n = 2, 18.2%, log-rank p = 0.47), EGFR (negative, n = 8, 80.0% vs. positive, n = 2, 20.0%, log-rank p = 0.97), PTEN (negative, n = 5, 21.6% vs. positive, n = 4, 88.4%, log-rank p = 0.81).

Characteristics Associated With Rfs

We carried out multivariable analysis to calculate RFS using the same method and variables. Similar to OS benefits, the results showed that the variable of total resection ($p = 0.022$, HR = 0.181, 95%CI 0.042–0.782) and low expression of Ki-67 ($p = 0.052$, HR = 2.996, 95%CI 0.992–9.053) were helpful to improve RFS (Table 2).

Similarly, RT with concurrent TMZ ($p = 0.861$, HR = 0.919, 95%CI 0.360–2.348) and adjuvant TMZ ($p = 0.631$, HR = 0.804, 95%CI 0.330–1.959) did not demonstrate RFS benefits either in univariable and multivariable analysis (Table 2).

There was no distinct difference between the primary group and the secondary group ($p = 0.715$, HR = 1.202, 95%CI 0.448–3.228), whether for GBM-originated ($p = 0.417$, HR = 1.566, 95%CI 0.529–4.636) or non-GBM-originated ($p = 0.646$, HR = 0.624, 95%CI 0.083–4.684) (Table 2).

Kaplan-Meier curves were drawn respectively for interested factors, and none of them were considered significant that could affect RFS. Median RFS was 25.3 months (95%CI 9.5–41.1) in the total resection group ($n = 41$, 91.1%) and 2.3 months (95%CI 0.0–13.9) in the non total resection group ($n = 4$, 8.9%), $p = 0.12$ (Fig. 2E). Median RFS was 18.5 months (95%CI 6.0–31.0) in Ki-67 high expression group (Ki-67 > 15%, $n = 30$, 66.7%) and cannot be counted in Ki-67 low expression group (Ki-67 $\leq$ 15%, $n = 15$, 33.3%) because the death toll is less than half, $p = 0.12$ (Fig. 2F).

Median RFS was 25.3 months (95%CI 10.4–40.2) in the RT with concurrent TMZ group ($n = 33$, 73.3%) and 31.1 months (95%CI 0.0–64.1) in the non RT with concurrent TMZ group ($n = 11$, 24.4%), $p = 0.86$ (Fig. 3C), 25.3 months (95%CI 9.7–40.9) in the adjuvant TMZ group ($n = 32$, 71.1%) and 14.3 months (95%CI 0.0–35.2) in the non adjuvant TMZ ($n = 12$, 26.7%), $p = 0.63$ (Fig. 3D).

Discussion

As a histological variant of GBM, GSM has some different prognostic factors. Reviewing the clinical data of the cohort, the people with high incidence of GSM are concentrated around the age of 60 ($50 \leq \text{age} < 70$, $n = 29$, 64.4%), mainly male ($n = 32$, 71.1%) and showing a predilection for temporal lobe ($n = 19$, 42.2%). The situation is generally consistent with the previous research results (Galanis et al. 1998; Han et al. 2010; Han et al. 2010; Singh et al. 2015; Jin et al. 2020; Pierscianek et al. 2021). In our cohort, the proportion of patients with secondary GSM is 17.8%, which is still consistent with existing reports (Perry et al. 1995; Han et al. 2010).

The median OS in our study were 25.6 months and longer than those in most other studies, which range from 5.7 months to 24.7 months (Cachia et al. 2015; Dejonckheere et al. 2021). The results of our study suggested total resection of GSM was associated with prolonged OS and RFS. Although some retrospective studies have reached the opposite conclusions (Singh et al. 2012; Adeberg et al. 2016; Dejonckheere et al. 2021). The resection range is a well-accepted independent prognostic factor for

improved OS in GSM (Kozak et al. 2009; Brown et al. 2016; Zhang et al. 2016; Frandsen et al. 2018; Jin et al. 2020). Cachia et al. reported that patients of primary GSM undergoing GTR tended to have a greater OS (median 24.7 months) than those having subtotal resection (median 10.1 months) (Cachia et al. 2015). And with advances in medical technology, more thorough surgeries accepted by patients over the past six years. In our cohort, even if the lesions were deep in 9 patients, 41 patients had undergone GTR, and no patients received biopsy. Most patients were in relatively good physical condition at the beginning of treatment (median KPS was 80) and were more inclined to tolerate the treatments with large physiological burden.

Currently, almost GSM patients are guided to accept the Stupp protocol in clinical practice, RT and chemotherapy following surgery as same as GBM (Galanis et al. 1998). Radiotherapy has been suggested to improve the outcomes of patients, because it may increase OS by 2–4 months (Wang et al. 2020). TMZ has been proved as the most effective chemotherapeutic drug for high-grade gliomas (Adeberg et al. 2016; Nabors et al. 2017). But due to the lack of prospective studies or large-scale multicenter retrospective studies, the debate on the therapeutic value of RT and TMZ in GSM remains unresolved (Frandsen et al. 2018). The scholars from Stanford University Medical Center provided that a significantly improved PFS (median 32.97 months) and OS (median 56.73 months) occurred in patients receiving surgical resection followed by RT and concurrent TMZ (Jin et al. 2020). Different from their results, RT, concurrent TMZ and adjuvant TMZ did not show any survival benefits. Our study are inclined to support the view that RT or TMZ is ineffective for GSM patients. The histopathological differences between GSM and classical GBM cannot be overlooked. GSM is rich in sarcoma components, which were insensitive to RT and chemotherapy (Zhang et al. 2021), which is related to minimal statistical effectiveness. In addition, lots of patients in this cohort have not yet arrived at the terminal of the life train, which inevitably influences the judgment of the effect of RT and chemotherapy.

Lower Ki-67 expression is parallel to a lower rate of tumor cell division (Davey et al. 2021), which indicates a longer RFS. This inference has been supported in the study of GSM (Ahmed et al. 2019), and our results enhance the reliability.

In univariable analysis, no statistically significant parameters were found ($p \leq 0.05$) but lesion number. But there is only one case with multiple lesions. The enormous sample size between groups makes the results lack credibility and be unable to participate in multivariable analysis. Existing reports suggest that TERT (Oh et al. 2016) and PIK3CA (Knobbe and Reifemberger 2003) mutations are frequent in GSM, but there is still a lack of evidence of prognostic relevance. In our study, the p values of TERT are below 0.05 in the log-rank test. The small sample size determines that the univariable analysis of these transgenations has no practical reference value. The results are just listed.

A series of other favorable prognostic factors have been reported previously, including MGMT methylation (Frandsen et al. 2018; Smith et al. 2018), KPS (Dejonckheere et al. 2021; Pierscianek et al. 2021), tumor size (Feng et al. 2019; Pierscianek et al. 2021), temporal tumor location (Frandsen et al. 2019), younger age (Frandsen et al. 2018; Ahmed et al. 2019; Feng et al. 2019; Huang et al. 2020;

Pierscianek et al. 2021). These conditions are rarely repeated because of small sample size. No such association was seen in our study.

Compared to prospective studies or large multi-centre randomized controlled trials (RCTs), there are many limitations to the single-centre retrospective cohort studies for rare diseases. The limited cohort size limits the analysis of potential subset analysis and may hinder our ability to adequately adjust for confounding covariates. All patients had obtained postoperative pathological diagnosis when they were selected into the cohort, which might result in inevitable selection bias. We should be cautious about the conclusions of this study, but we are confident to persist in the clinical value of our results for further prospective study or RCTs.

Conclusion

This study is a retrospective cohort study with limited cohort size, our results demonstrate GTR and low expression of Ki-67 are of great significance to the prognosis of GSM, while the survival benefits of adjuvant therapies including RT or TMZ are limited.

Declarations

Authors contributions ZY and HX conceived the project. ZY and ZZ obtained the requisite data, conducted the statistical analysis, interpreted the data, drafted the manuscript, generated tables and figures, and received the final manuscript submission. MX, KS, JS, WZ and LW critically revised the manuscript draft.

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Data availability All deidentified data used in the current manuscript can be provided by the authors per the readers requests. No data spread sheet has been made publicly available due to patient confidentiality.

Conflict of interest The authors have no competing interest, financial or otherwise to disclose.

Ethical approval This study was completed with ethics committee approval and all patients provided informed consent to study participation and image publication.

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Figures

Figure 1

(A, B) Horizontal T1-weighted contrast-enhanced MRI imaging of GSM located in the temporal lobe. **(C-F)** Representative images of GSM stained using HE, and immunolabeled using antibodies to GFAP, IDH1 and Ki-67. Through HE staining **(C)** and GFAP **(D)** staining, it can be observed that the biphasic growth pattern of GFAP-positive glioma components and GFAP-negative sarcoma components containing tumor spindle cells. GSM does not typically express IDH1 **(E)**, but generally has a high level of Ki-67 expression **(F)**.

Figure 2

Kaplan-Meier curves for OS (**A**) and RFS(**B**) of all patients included in our cohort. (**C**) Kaplan-Meier curves and log-rank tests according to OS were used for analysis of prognostic factors. According to resection range, they were divided into total resection group and non total resection group. (**D**) According to the expression level of Ki-67, they were divided into high expression group and low expression group. (**E, F**) Kaplan-Meier curves and log-rank tests according to RFS were used for analysis of prognostic factors.

Figure 3

The results of Kaplan-Meier curves and log-rank tests showed that the effect of radiotherapy & concurrent TMZ (**A**) or adjuvant TMZ (**B**) on the OS benefits of GSM was not statistically significant. The results of Kaplan-Meier curves and log-rank tests according to RFS indicated that there was no statistically significant impact of radiotherapy & concurrent TMZ (**C**) or adjuvant TMZ (**D**).