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CLINICAL STUDY

Clinical outcome of gliosarcoma compared with glioblastoma multiforme: a clinical study in Chinese patients

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Abstract Gliosarcoma (GSM) is a rare biphasic neoplasms of the central nervous system composed of a glioblastoma multiforme (GBM) admixed with a sarcomatous component. In clinical practice GSM is generally managed similarly to GBM. However, there are conflicting reports regarding their clinical aggressiveness, cell line of origin and possible prognosis compared with those of GBM. The objective of this study was to compare clinicpathological features in GSM patients with the GBM patients during the same study period. 518 patients with GBM were treated at our hospital between 2008 and 2013, among them 51 were GSM. In this series the GSMs represented 9.8 % of all GBMs and included 58.8 % male with a median age of 44.7 years. The locations, all supratentorial, included temporal in 41.2 %, frontal in 25.5 %, parietal in 19.6 %, and occipital in 13.7 %. All patients underwent tumor resection followed by post-operative radiation and adjuvant chemotherapy. The O6-methylguanine-DNA methyltransferase promoter methylation studies were significantly more frequent in the GBMs than GSMs (80.1 % vs. 44.7 %, $P < 0.001$). The median progression free survival and overall survival for the patients with GSM were 8.0 and 13.0 months, respectively, as compared with 9.0 and 14.0 months in the GBM group (log rank test $P = 0.001$ and 0.004, respectively). The Cox proportional hazards regression model indicated that the extent of tumor resection (HR = 1.518, $P = 0.009$) and pathological types (HR = 0.608, $P = 0.002$) were the significant prognostic factors in our own series. With regard to clinical features and outcomes, GSM and GBM cannot be distinguished clinically. GSM in China may be managed similarly to GBM, with maximal safe surgical resection followed by chemo-radiotherapy. Our study adds further evidence to support GSM as a unique clinical entity with a likely worse prognosis than GBM.

Keywords Gliosarcoma · Glioblastoma multiforme · Prognosis

Introduction

Gliosarcoma (GSM) is a rare primary malignant brain tumor accounting for less than 0.5 % of all intracranial tumors [1], and 2–8 % of all glioblastoma multiforme (GBM) [2]. In 2000, GSM was classified by the World Health Organization (WHO) grading scheme as a variant of GBM [3]. The current accepted definition in the 2007 WHO classification of GSM is a well-circumscribed lesion with clearly identifiable gliomatous and metaplastic mesenchymal components [4]. The tumor contains a portion that satisfies the histologic criteria for GBM, and a mesenchymal component that may display a variety of morphologies with origins from fibroblastic, cartilaginous, osseous, smooth muscle, striated muscle, or adipose cell lineage [3].

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Clinically similar to GBMs, GSMs usually affect patients in the fifth to seventh decade of life with a male preponderance [5, 6]. The principles of treatments with GSMs are generally managed in accordance with the prevailing guidelines for GBM Treatment includes tumor resection, postoperative radiation therapy and sometimes chemotherapy [7]. However, unique features of GSM including its clinical propensity to undergo extra-cranial metastasis, distinct radiological features and possible worse prognosis in comparison to GBM suggest that this may be a distinct clinico-pathological entity [8]. An epidemiological study by Kozak and colleagues reported a worse prognosis in patients with GSM than in those with GBM, and pathological and genetic studies have shown unique genetic profiles in GSM tissue distinct from those found in GBM [5]. Due to the rarity of GSM, experience reported in the literature is limited. In this report, we reviewed the clinical and radiologic presentation, pathologic diagnosis, and treatment outcomes for a series of Chinese patients diagnosed with GSM, and compared them with an entire group of patients with GBM.

Materials and methods

Ethics statement

All patients provided informed consent form for the current study and the clinical study was approved by the Medical Ethics Committee of Capital Medical University.

Patients and tumor specimens

Patients with GSM and GBM were initially identified through the database of our department of Neurosurgery at Beijing Tiantan Hospital with dates of diagnosis from 2008 through 2013. The clinical history of the patients was gathered retrospectively by chart review. All GBM and GSM cases enrolled in our analysis were examined and graded independently by two neuropathologists (who were blind to tumor genotypes), according to the 2007 World Health Organization (WHO) Classification of Tumors of the Central Nervous System [4]. The histologic diagnosis of GSM was established using the 2007 WHO criteria, specifically by determining: (1) the presence of dual morphologies in the tumor on hematoxylin and eosin (H&E) staining (1 of glial morphology and another of spindle morphology); (2) whether the area of glial morphology stained positive using antibodies against glial markers (glial fibrillary acidic protein, GFAP); and (3) whether the area appearing sarcomatous on H&E was negative for glial markers, yet positive for mesenchymal markers (Smooth muscle actin, SMA) (Fig. 1).

All patients in this study were treated with radiotherapy and nitrosourea-based chemotherapy after surgical resection. When the tumor recurrence and metastasis, patients underwent reoperation if possible or palliative treatment if impossible. The external-beam radiation was delivered by conventional fractionation up to a total dose of 5000–6000 cGy. Chemotherapeutic agents included nimustine (ACNU) and temozolomide (TMZ). These agents were given every 5–7 weeks for periods varying from 6 months to 2 years in standard doses: 2 mg/kg for ACNU and every 4 weeks for periods varying from 9 months to 2 years in standard doses: 200 mg/m^2/d in 5 days for TMZ.

Anatomical sites and sizes of tumors were determined by computerized tomography (CT) scanning or magnetic resonance imaging (MRI). Clinical details, including the patient's age of onset, gender, preoperative karnofsky performance status (KPS) score, tumor localization, extent of resection, adjuvant chemo-radiotherapy, progression free survival (PFS) and overall survival (OS) were noted.

MGMT promoter methylation analysis

Genomic DNA was isolated from frozen tumor tissue by using Qiagen kit (Qiagen, Valencia, CA). O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was analyzed by methylation-specific PCR (MSP). Tumor DNA (2 μg) was treated with sodium bisulfite using the CpG genome DNA modification kit (Qiagen). The primer sequences for the unmethylated reaction were 5′-TTTGTGTTTTGATGTTTGTAGGTTTTTGT-3′ (forward) and 5′-AACTCCACACTCTTCCAAAAACAAAACA-3′ (reverse). For the methylated reaction, they were 5′-TTTCGACGTTCGTAGGTTTTCGC-3′ (forward) and 5′-GCACTCTTCCGAAAACGAAACG-3′ (reverse). The annealing temperature was 59 °C. The PCR products were separated on 4 % agarose gels. The investigators who selected and analyzed the samples were blinded to all clinical information. Pyrosequencing analysis was carried out by Gene Tech (Shanghai) Company Limited. The GBM and GSM samples (methylation values [5 %]) were considered as being methylated. Characteristics of patients with GBM and GSM in relation to MGMT promoter methylation were shown in Fig. 2.

Statistical analysis

All statistical analyses were carried out with SPSS 19.0 (SPSS for Windows, version 19.0 [SPSS Inc., Chicago, Illinois, USA]). The one way ANOVA was used to compare data acquired in each group for the patient's age and KPS. Pearson Chi square test was used to compare gender. Continuity Correction Chi Square test was used to compare

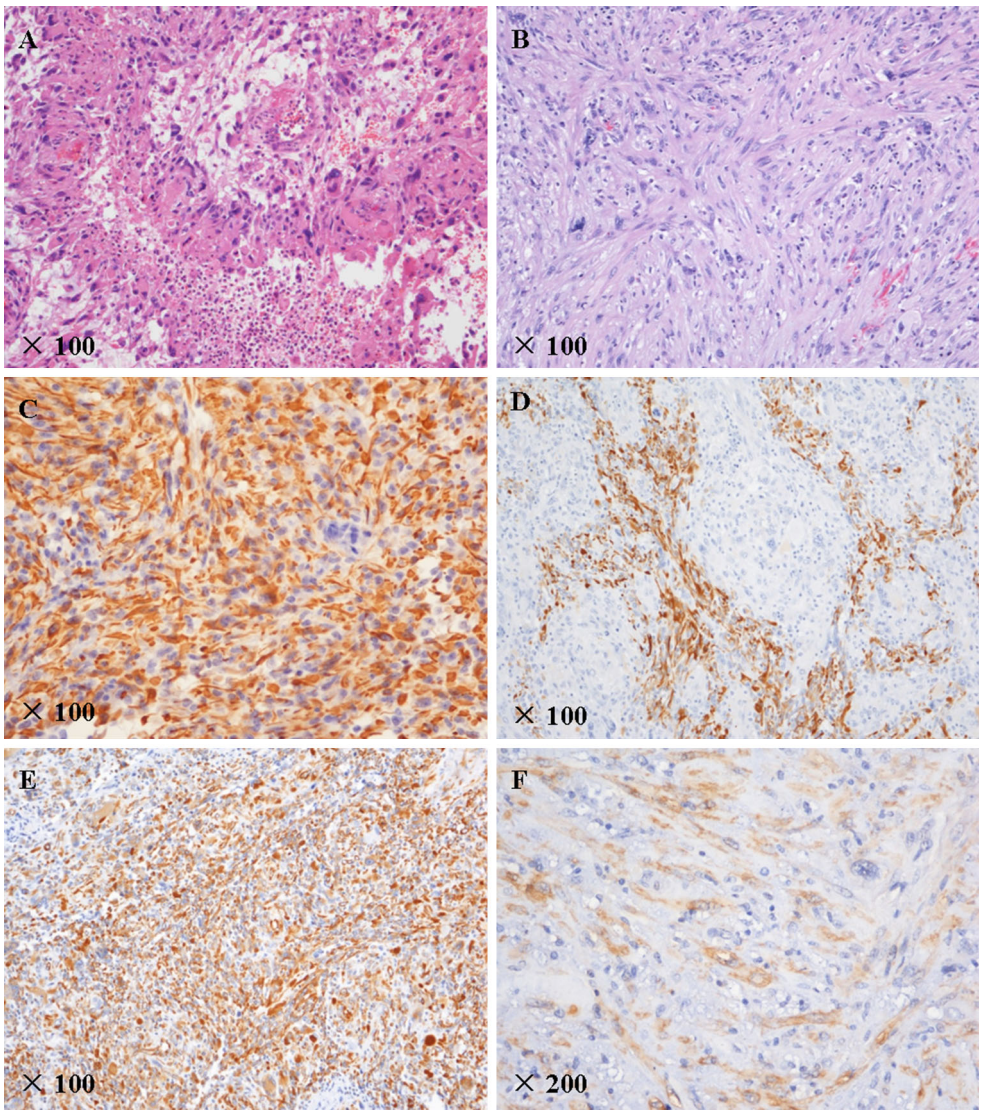

Fig. 1 Histology of glioblastoma multiforme and gliosarcoma are shown. **a** Hematoxylin and eosin (H&E) stain of the glioblastoma multiforme (×100) is shown. Glioma cells show polymorphic significantly, abundant cytoplasm and visible necrosis. **b** H&E stain demonstrates the biphasic pattern of the tumor of gliomatous cells and spindle cells consistent with gliosarcoma (×100). **c** Strong diffuse glial fibrillary acidic protein (GFAP) staining is evident in the glioblastoma multiforme (×100). **d** Focal GFAP staining is positive in the astrocytic portion of the gliosarcoma (×100). **e** Vimentin is strongly expressed in the gliosarcoma (×100). **f** Smooth muscle actin (SMA) is strongly expressed in the sarcomatous portion of the gliosarcoma (×200)

data acquired in each group for the tumor localization, extent of resection and incidences of MGMT promoter methylation. Mann–Whitney U test was used to compare extent of resection. Survival distributions were estimated by Kaplan–Meier analysis and compared among patient subsets using log-rank tests. Probability value was obtained from 2-sided tests, with a statistical significance of $P < 0.05$.

Results

Clinical characteristics

Between January 2008 and September 2013, 51 GSM patients and 467 GBM patients, who were treated in Neurosurgery Department of Beijing Tiantan Hospital were enrolled in our study. The incidence of GSM among the entire group of 518 patients was 9.8 %. Patient characteristics were described in Table 1. Of the 51 patients with GSM, the median age was 44.7 years (range 5–78 years) and 58.8 % were male. The median age of patients with GBM was 48.0 years (range 13–68 years) with a male predominance (63.0 % male). The patients presented with signs and symptoms consistent with an expanding intracranial mass, including headache, seizure, aphasia, hemiparesis, hemianopsia, and visual hallucination. The median pretreatment KPS score for GSM patients was 80 (range 40–100), and the median pretreatment KPS score for GBM patients was 80 (range, 40–90). As shown in Table 1, there were no significant differences in the median age (44.7 vs. 48.0, $P = 0.085$), the median KPS (82.2 vs. 79.3, $P = 0.174$) and gender (58.8 % vs. 63.0 %, $P = 0.563$) between GSM and GBM patients.

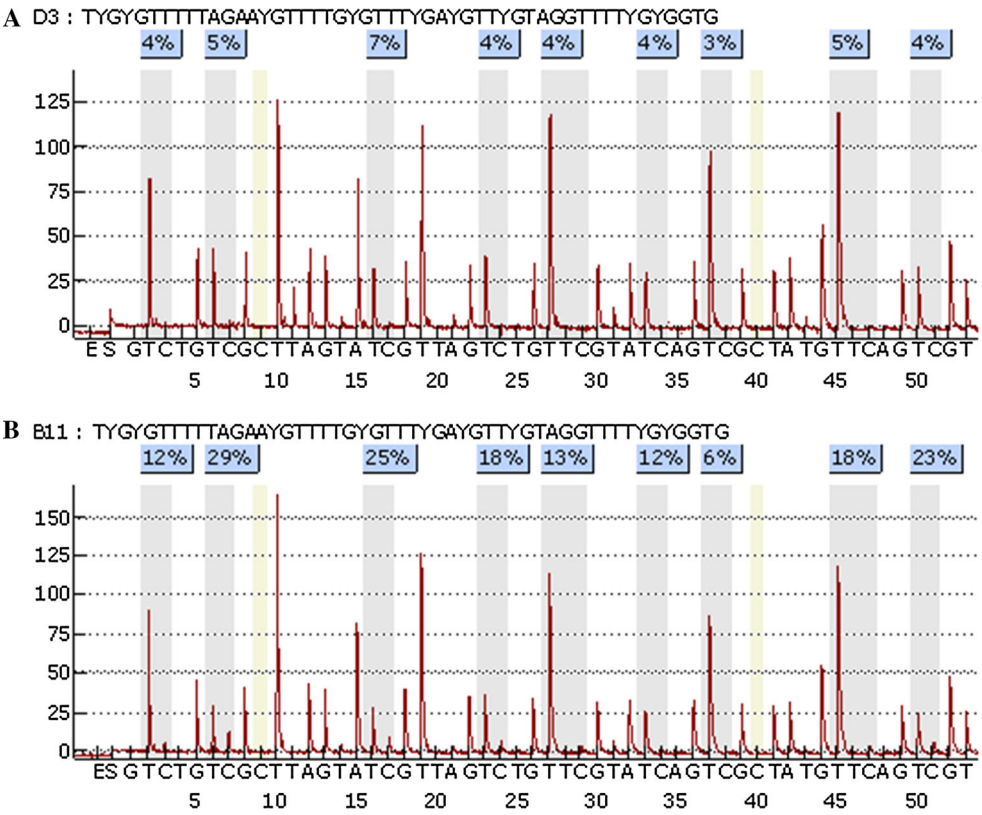

Fig. 2 Assay of MGMT promoter methylation in GBM and GSM samples. **a** Unmethylation of MGMT promoter in GBM and GSM patients. **b** Methylation of MGMT promoter in GBM and GSM patients

Table 1 Comparison of clinical characteristics between GBM and GSM

	GSM	GBM	*P* value
No. of cases	51	467	
Gender (male/female)	30/21	294/173	0.563
Median age at diagnosis (years)	44.7	48.0	0.085
KPS at diagnosis	80	80	0.174
Tumor location			
Frontal lobe (%)	25.5	50.3	0.001
Temporal lobe (%)	41.2	32.8	0.227
Parietal lobe (%)	19.6	12.2	0.135
Occipital lobe (%)	13.7	4.7	0.019
Extent of resection			0.716
Gross total resection (%)	72.5	70.0	
Subtotal resection (%)	23.5	25.9	
Partial resection (%)	4.0	4.1	
MGMT promoter methylation (%)	80.1	44.7	0.000
Radiotherapy (%)	100	100	1.0
Chemotherapy (%)	100	100	1.0

MGMT O6-methylguanine-DNA methyltransferase, *GSM* gliosarcoma, *GBM* glioblastoma multiforme, *KPS* karnofsky performance score

Radiological characteristics

Preoperative MRI studies were reviewed in all GSM and GBM patients. The majority of GSM were located in the temporal lobe (n = 21, 41.2 %). The remaining lesions were situated in the frontal lobe (n = 13, 25.5 %), parietal lobe (n = 10, 19.6 %) and occipital lobe (n = 7, 13.7 %) respectively. More than one half of the GBM (n = 235, 50.3 %) were found in the frontal lobe and the remainder were located in the temporal (n = 153, 32.8 %), parietal (n = 57, 12.2 %) and occipital lobes (n = 22, 4.7 %) respectively. Compare to GBM, GSM has an apparent proclivity for the temporal lobe (Table 1).

Surgical treatment

Tumor resections were divided into three levels by comparing the preoperative MRI with the postoperative one. Gross total resection (GTR): Tumors were total resection during operation, and postoperative MRI contrasting with no residue; Subtotal resection (STR): Tumors were resection as fully as possible during operation, but postoperative MRI contrasting with less than 5 % residue; Partial

resection (PR): Tumors were resection as possible during operation, and postoperative MRI contrasting with less than 20 % residue. All of the GSM patients underwent tumor resection which was classified as gross total in 37 patients, subtotal in 12 patients and partial in 2 patients. In the GBM patients, a GTR was achieved in 327 patients, STR of the tumor was performed in 121 patients and PR in 19 patients. There were no significant differences in the extent of tumor resection between the GSM and GBM patients ($P = 0.716$) (Table 1).

Methylation status of the MGMT promoter

MGMT promoter methylation studies were performed in 372 GBM cases and 38 GSM cases with sufficient DNA. MGMT promoter methylation was more common in GBM patients (298/372, 80.1 %) than in GSM patients (17/38, 44.7 %); and this difference was statistically significant ($P < 0.001$; Continuity Correction Chi Square test) (Table 1).

Metastasis

In GBM group, no distant metastasis was found in the follow-up. But, in the GSM group, extensive bone metastasis was found in a 55-year-old female patient with a temporal GSM. Intramedullary metastases were found in two cases, both of them were located in thoracic vertebra (Fig. 3).

Survival

No patient was lost to follow-up. All patients had died at the time of analysis in both the GSM group and the GBM group. The mean PFS for GSM patients was 8.9 months (median, 8 months; range, 3–18 months), as compared with 10.7 months (median, 9 months; range, 2–38 months) in the GBM group (log rank test, $P = 0.001$) (Fig. 4). The mean OS for GSM patients was 13.4 months (median, 13 months; range, 5–22 months), as compared with 15.8 months (median, 14 months; range, 3–51 months) in the GBM group (log rank test, $P = 0.004$) (Fig. 5). As the probability values indicated, the differences were statistically significant. The Cox proportional hazards regression model (Table 2) indicated that the extent of tumor

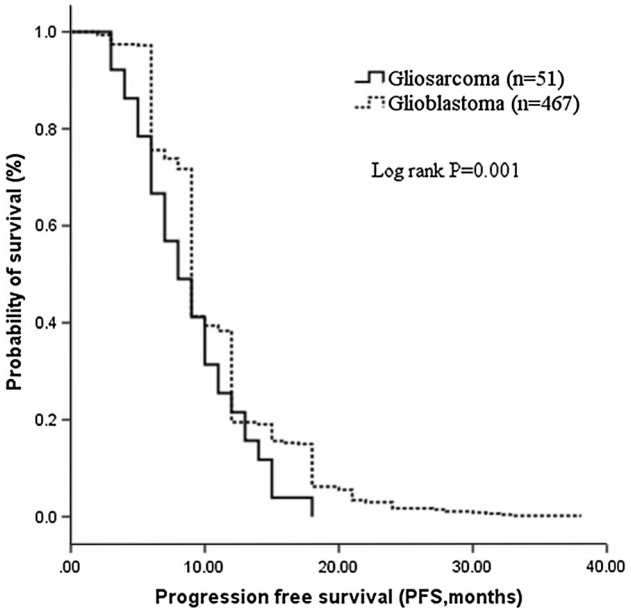

Fig. 4 Kaplan–Meier survival curve showing comparison of progression free survival of glioblastoma multiforme (GBM) versus gliosarcoma (GSM). The mean PFS for GSM patients was 8.9 months (median, 8 months; range, 3–18 months), as compared with 10.7 months (median, 9 months; range, 2–38 months) in the GBM group (log rank test, $P = 0.001$)

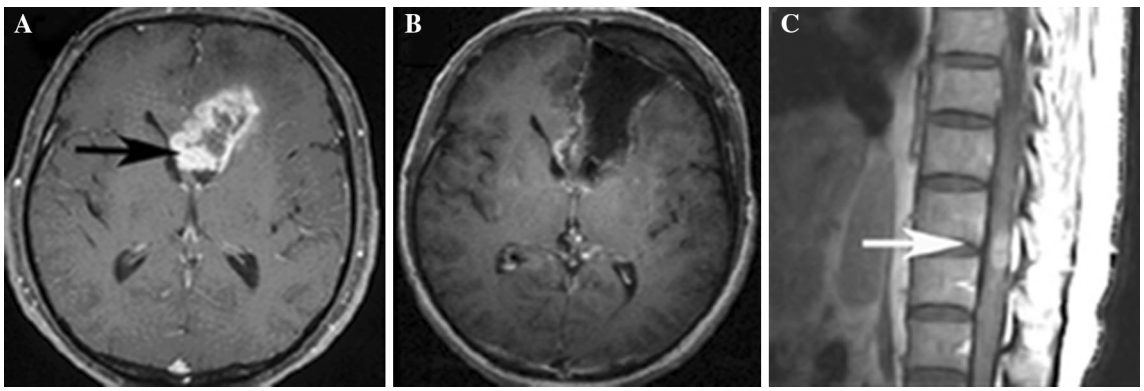

Fig. 3 Magnetic resonance imaging (MRI) manifestations of Gliosarcoma and intramedullary metastases. **a** A gadolinium-enhanced, T1-weighted axial image demonstrated a heterogeneously rim-enhancing left frontal gliosarcoma pre-operation. **b** Post-operative MRI showed a gross total resection (GTR) of the left frontal gliosarcoma. **c** Intramedullary metastasis was found in T10-12three months after operation (*Black arrow* shows the tumor, *white arrows* show the metastatic lesions)

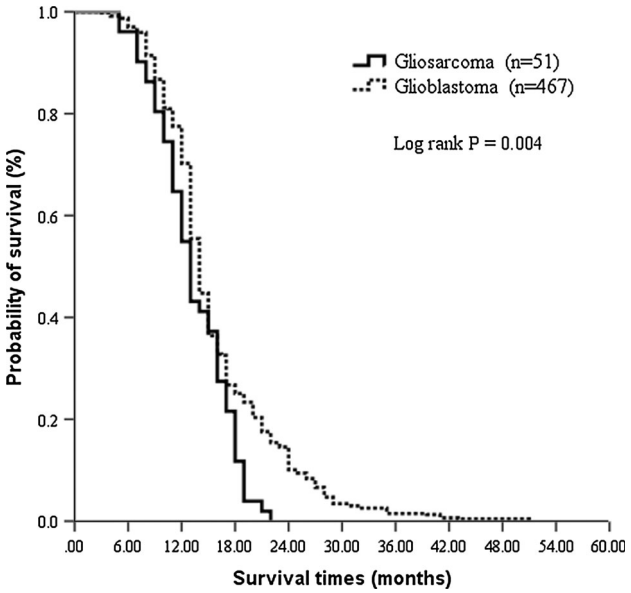

Fig. 5 Kaplan–Meier survival curve showing comparison of overall survival time of glioblastoma multiforme (GBM) versus gliosarcoma (GSM). All patients had died at the time of analysis in both the GSM group and the GBM group. The mean overall survival for GSM patients was 13.4 months (median, 13 months; range, 5–22 months), as compared with 15.8 months (median, 14 months; range, 3–51 months) in the GBM group (log rank test, $P = 0.004$)

resection (HR = 1.518, $P = 0.009$) and pathological types (HR = 0.608, $P = 0.002$) were the significant prognostic factors in our own series. Therefore, GSM patients showed worse outcomes than GBM patients; all the malignant gliomas, which underwent more tumor resection, showed better prognosis.

Discussion

GSM are clinically indistinguishable from GBM [9]. The reported incidence varies between 1.8 and 8 % of GBM patients, and in our study, the incidence of GSM is 9.8 %, slightly above the previous reports [2]. The tumor most commonly affects adults in the fourth to seventh decade of life [8], in our series, the median age is 44.7 years, which shows a trend of getting younger over the designated period of time. Some cases of infants and children have also been described [10, 11]. In our group, the youngest patient was 5 years old. Most studies report a high incidence of GSM either in the temporal or frontal lobe [1, 5]. Concordant with the literature, our series also showed a temporal lobe predilection, followed by frontal lobe tumor involvement. The median reported survival for untreated patients with primary GSM is 4 months [5], with radiation therapy delivering an improvement in median survival from 6.25 months to 10.6 months in one study [12]. A retrospective study based on the surveillance, epidemiology and end results (SEER) database indicated age, extent of resection and adjuvant radiotherapy as factors affecting overall survival, meanwhile, GSM had a slightly worse prognosis than GBM [5]. This finding of worse overall survival for GSM patients compared to GBM has also been reported in other retrospective studies without reaching statistical significance [6, 13]. In our series GSM patients, although they were managed similarly to GBM, with maximal safe surgical resection followed by chemo-radiotherapy as described by the Stupp protocol [8]. GSM still had an overall worse survival compared to the GBM group. The most important factors found to influence GSM overall survival are patients' age, extent of resection and use of adjuvant RT [5]. It was also reported that the patients with prevalence of sarcomatous component demonstrated prolonged survival compared to those with mainly gliomatous component [14]. Morantz et al. [15]. commented on the effect of chemotherapy on the outcome. They found a mild increase in survival in GSM patients with additional chemotherapy (36 weeks) compared with radiation therapy alone (33 weeks). Recent experimental studies reported that localized intracranial delivery of temozolomide can prolong the survival of experimental GSM animals and improve the treatment effect [16, 17]. Lee et al. reported that MGMT methylation and IDH1 mutation are rare events in GSMs (11.5 and 7.7 %, respectively), and only aggressive and repetitive local

Table 2 Cox proportional hazards regression model test for the OS values of all patients

	B	Wald	*P* value	Exp (B)	95% CI of exp(B)	
					Lower	Upper
Pathological types	−0.498	9.894	0.002	0.608	0.445	0.829
Age	−0.001	0.062	0.803	0.999	0.993	1.006
KPS at diagnosis	−0.001	0.104	0.747	0.999	0.993	1.005
Gender	0.043	0.068	0.795	1.044	0.757	1.439
Extent of resection	0.418	6.854	0.009	1.518	1.111	2.075
Tumor location	−0.192	3.473	0.062	0.825	0.674	1.010

KPS Karnofsky performance score

control seems to be effective in treatment of GSM [18]. Han et al. showed that the sarcomatous transformation seen in GBM could be associated with worse prognosis and alkylating chemotherapeutic agents may also be less effective when sarcomatous elements are present [8, 19]. In our study, the MGMT promoter methylations were significantly more frequent in the GBMs than GSMs (80.1 % vs. 44.7, $P < 0.001$), which might be helpful in clarifying the role of temozolomide in treating this unique clinical entity [19, 20].

Histologically, the GSM is characterized by a biphasic tissue pattern demonstrating areas of both glial and mesenchymal differentiation [3]. It is well known that irradiation of the central nervous system may cause eventual development of various types of malignant cerebral and meningeal tumors, predominantly secondary GSM [10, 21], but the exact pathogenesis of primary GSM is still controversial. At the beginning this neoplasm is thought to arise secondarily from the neoplastic transformation of stromal cells, which proliferate as a response of the host against the infiltration of malignant glioma cells [22]. Whereas morphological studies suggested that the sarcomatous component may evolve from microvascular proliferations within a highly malignant glial tumor. Numerous studies revealed the presence of identical p53 and PTEN mutations, similar chromosomal imbalances and cytogenetic alterations in both components of GSMs suggesting a monoclonal origin [2, 23–27]. In accordance with this finding, it is most likely that sarcomatous and gliomatous cells are derived from a common stem cell. Recent genetic studies of GSMs support this monoclonal hypothesis [28].

GSM is a very rare tumor entity in children. Michael Karremann et al. reported series of 23 pediatric GSM patients, which showed GSM was found in all pediatric age groups with a median age of 11 years. The median OS and PFS of the total cohort were 12.1 and 9.8 months with pediatric GSM, respectively [29]. In our study, there were 4 pediatric GSMs with the median age of 10 years and 5 pediatric GBMs with the median age of 13 years. The median OS and PFS were 13.8 and 10.2 months with pediatric GSM, respectively. The median OS and PFS were 12.2 and 9.5 months with pediatric GBM, respectively.

Unlike other central nervous system tumors including GBM, GSMs have the propensity of extracranial metastases [8]. Most extracranial metastases of GSM are located in the lung and liver, and there are reports of metastatic foci in cervical lymph nodes, spleen, adrenal glands, kidneys, oral mucosa, skin, bone marrow, skull, ribs, and spine [30–32]. In our group extensive bone metastases was found in a 55-year-old female patient with a temporal GSM. Intramedullary metastasis to the spine has also been reported in the literature [30]. In our group, intramedullary metastases were found in two cases, both of them were located in thoracic vertebra.

According to the majority of the authors GSMs and GBMs cannot be distinguished clinically, as both variants present with similar clinical features, patterns of relapse and overall survival [7, 13]. Recent study shows that the features unique to GSM compared to GBM include their temporal lobe predilection, potential to appear similar to a meningioma at surgery, infrequency of EGFR mutations and repeated reports of extracranial metastases [8].

Conclusion

The prognosis of primary GSM is still poor despite aggressive surgical resection and adjuvant multi-modality therapy is given. GSM in China may be managed similarly to GBM, with maximal safe surgical resection followed by chemo-radiotherapy. Adjuvant chemotherapy based on TMZ, currently one of the main treatment options for GBM, seems to have no definite survival benefit for GSM, which may be ascribed to rare MGMT methylation and IDH1 mutation in GSM. Our study adds further evidence to support GSM as a unique clinical entity with a likely worse prognosis than GBM. Further rigorous research into the clinical, genomic and molecular characteristics of GSM is required to better understand this malignant brain tumor.

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Compliance with ethical standards

Conflicts of Interest No potential conflicts of interest were disclosed.

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