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ORIGINAL ARTICLE

The clinical, radiological, and immunohistochemical characteristics and outcomes of primary intracranial gliosarcoma: a retrospective single-centre study

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Abstract

Primary intracranial gliosarcoma is a rare malignant brain tumour, and the most effective treatment for gliosarcoma remains unclear. This study aimed to identify risk factors for progression-free survival (PFS) and overall survival (OS) in these cases. This retrospective single-centre study evaluated 103 patients (median age, 51 years; 67 men [65%]) with primary intracranial gliosarcoma between 2006 and 2017. Treatments included surgery (GTR, 63 patients; STR, 39 patients; biopsy, 1 patient), radiotherapy (adjuvant, 76 patients; exclusive treatment, 1 patient), and chemotherapy (adjuvant temozolomide, 52 patients; adjuvant nimustine/teniposide, 19 patients; adjuvant bevacizumab, 1 patient; exclusive nimustine/teniposide treatment, 1 patient). The median OS was 13.3 months, and the median PFS was 9.1 months. In the multivariate analyses, the poor prognostic factors were ependymal lining enhancement of the lateral ventricle (PFS, HR 2.406, $p = 0.005$; OS, HR 2.946, $p = 0.009$) and enhancement in the motor functional cortex (PFS, HR 2.892, $p = 0.002$; OS, HR 2.639, $p = 0.009$). Good OS was predicted by adjuvant radiotherapy alone (HR 0.071, $p < 0.001$), adjuvant temozolomide-based chemotherapy alone (HR 0.063, $p = 0.005$), adjuvant temozolomide-based chemotherapy with concurrent radiotherapy (HR 0.056, $p < 0.001$), and salvage surgery at recurrence (HR 0.449, $p = 0.031$). The present study revealed that, in patients with primary intracranial gliosarcoma, enhancement in the functional motor cortex and ependymal lining enhancement of the lateral ventricle were both poor prognostic factors. Survival was optimized in cases treated using maximal safe resection followed by adjuvant temozolomide-based chemotherapy with concurrent radiotherapy. Furthermore, salvage surgery provided meaningful therapeutic benefits for recurrent gliosarcoma.

Keywords Immunohistology · Primary gliosarcoma · Radiotherapy · Temozolomide

Introduction

Primary gliosarcoma is a central nervous system neoplasm that consists of malignant glial and mesenchymal components and is generally regarded as a variant of glioblastoma multiforme (GBM) [1]. This tumour is rare and accounts for only 2–2.9% of glioblastomas [2–4]. The mesenchymal element generally resembles a fibrosarcoma [5], although other types of mesenchymal elements are occasionally observed. The prognosis of patients with primary gliosarcoma seems to be related to O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, isocitrate dehydrogenase 1 (IDH-1) mutation, TP53 mutation, phosphatase and tensin homologue (PTEN) mutation, and epidermal growth factor receptor (EGFR) amplification [6–8], which highlights the need for customized treatments. The similar genetic alterations in the glial and mesenchymal components suggest a monoclonal origin for the metaplastic mesenchymal differentiation of the glioma-genesis cell [8, 9].

Primary gliosarcoma is considered similar to glioblastoma, and the standard treatment is based on Stupp's protocol, generally including maximal safe resection followed by adjuvant chemoradiotherapy [10, 11]. Although several cases have

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been reported, the available data remain limited, and there is no clear consensus regarding effective treatment(s) for primary gliosarcoma. Therefore, this study aimed to verify the effectiveness of adjuvant chemoradiotherapy for primary gliosarcoma, based on its effects on overall survival (OS), as well as related risk factors.

Materials and methods

This retrospective study included patients with pathologically confirmed primary intracranial gliosarcoma at Beijing Tiantan Hospital, Capital Medical University, between 2006 and 2017. The retrospective protocol was approved by our institutional review board, and the requirement for informed consent was waived. Primary intracranial gliosarcoma was defined as de novo and newly diagnosed tumours. Clinical data were extracted from the patients' electronic medical records and included age, sex, preoperative and postoperative Karnofsky Performance Scale (KPS) scores, extent of surgical resection, radiological features, immunohistochemical findings (MGMT, p53, PTEN, and EGFR), treatment(s) after surgery, and treatment(s) at recurrence. Neuroradiological features were evaluated based on preoperative contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) findings. Data regarding radiotherapy (RT) and chemotherapy doses were not available and were omitted from the statistical analysis.

The extent of resection was classified as gross total resection (GTR), subtotal resection (STR), or biopsy. Resection of a gross tumour that removed ≥ 90% but < 100% of the tumour tissue was defined as STR. Anatomical characteristics included the tumour's texture, boundary, blood supply, and ventricular opening, which were judged by our chief neurosurgeon. Tumour texture was classified as soft, hard, or mixed, and tumour blood supply was categorized as either abundant or general, as described in a previous study [12]. All neuroradiological features were reviewed by two neuroradiologists, who were blinded to the diagnosis and judged the following features: tumour side, midline shift, cystic and solid patterns, tumour number, enhancement pattern, tumour location, signal intensity on contrast-enhanced T1-weighted images (T1WI) and T2-weighted images (T2WI), surrounding edema, and tumour size.

Statistical analysis

Overall survival (OS) was calculated as the period from the date of surgery to the date of death or last follow-up, and progression-free survival (PFS) was calculated as the date of surgery to the date of the first increase in tumour size on follow-up imaging. Differences in survival outcomes were evaluated using the Kaplan–Meier method and the log-rank test. Variables with p values of < 0.2 after the univariate analyses were included in the Cox proportional hazards model with forward elimination, and variables were removed from the model based on p values of > 0.1. Results were reported as the estimated hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed using the IBM SPSS software (version 23.0).

Results

Patients and treatment characteristics

The patients' characteristics are shown in Table 1. The 103 patients (67 men, 65%) had an average follow-up of 23.3 months, and 9 patients (8.7%) were lost to follow-up. The median age was 51 years (range, 19–78 years). The median OS was 13.3 months (range, 0.2–117.7 months), and the median PFS was 9.1 months (range, 0.2–114.0 months). The median preoperative and postoperative KPS scores were both 80%. At the time of the analysis, 1 patient had died because of intracranial infection, and all other deaths were related to cerebral tumour progression.

The therapeutic regimens are also shown in Table 1. Surgery was performed for all 103 patients, which was classified as GTR (63 patients), STR (39 patients), or biopsy (1 patient). Seventy-seven patients received RT, which included adjuvant external beam radiotherapy (EBRT) for 75 patients, adjuvant gamma knife radiosurgery for 1 patient and exclusive EBRT for 1 patient. Adjuvant chemotherapy was performed for 72 patients, which included temozolomide (TMZ) treatment for 52 patients, nimustine/teniposide (ACNU/VM26) treatment for 19 patients, and bevacizumab treatment for 1 patient. Exclusive ACNU/VM26-based chemotherapy was performed for 1 patient. Surgery was generally followed by adjuvant treatment, which involved TMZ-based chemotherapy with concurrent RT (49 patients, 47.6%), RT alone (9 patients, 8.7%), or TMZ-based chemotherapy alone (3 patients, 0.03%), although surgery alone was performed for 12 patients (11.7%). Twenty-one patients (20.4%) received other treatment regimens. Sixty-four patients (62.1%) experienced local recurrence, including 26 patients who received chemotherapy (TMZ, 15 patients; bevacizumab, 6 patients; and ACNU/VM26: 5 patients), 12 patients who received RT (EBRT, 10 patients; gamma knife radiosurgery, 2 patients), and 13 patients who underwent salvage surgery.

Neuroradiological features

The preoperative MRI or CT findings are described in Table 2. Five patients had multiple tumours, and all other patients had a single tumour. The tumour locations were left side (49 patients), right side (45 patients), or bilateral (4 patients). A midline shift was detected for 58 patients. Sixty-seven tumours were solitary lesions, and 31 tumours were cystic and

Table 1 Univariate analyses of patient and treatment characteristics

	$N = 103$	n^a (%)	p value for PFS	n^b (%)	p value for OS
Median age, years (range)	51 (19–78)		0.661		0.836
Sex			0.124		0.123
Male	67	70.0		88.5	
Female	36	64.7		70.6	
Postoperative KPS			0.310		0.040*
≥ 70%	81	68.9		79.7	
< 70%	22	65.0		90.5	
Extend of resection			0.816		0.552
Gross total resection	63	70.2		83.1	
Subtotal resection	39	66.7		80.0	
Biopsy	1	0.0		100.0	
Radiotherapy after surgery			0.096		< 0.001***
No	17	52.9		100.0	
Yes	77	71.1		77.6	
Unknown	9				
Chemotherapy after surgery			0.086		0.002**
No	21	61.9		95.2	
TMZ-based	52	64.7		68.6	
ACNU/VM26-based	20	80.0		100.0	
Bevacizumab-based	1	100.0		100.0	
Unknown	9				
Treatments after surgery			0.046*		< 0.001***
Adjuvant RT alone	9	77.8		88.9	
Adjuvant TMZ-based chemotherapy alone	3	66.7		100.0	
Adjuvant TMZ-based chemotherapy with concurrent RT	49	64.6		66.7	
Others	21	81.0		100.0	
None	12	50.0		100.0	
Unknown	9				
Salvage surgery for recurrence					0.006**
No	51			94.1	
Yes	13			83.3	
Unknown	9				
Radiotherapy for recurrence					0.118
No	52			96.1	
Yes	12			75.0	
Unknown	9				
Chemotherapy for recurrence					0.035*
No	38			97.2	
TMZ-based	15			80.0	
Bevacizumab-based	6			100.0	
ACNU/VM26-based	5			100.0	
Unknown	9				

PFS progression-free survival, *OS* overall survival, *KPS* Karnofsky Performance Scale, *TMZ* temozolomide, *ACNU* nimustine, *VM26* teniposide, *RT* radiotherapy

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Percentage of recurrence

[b] Percentage of deaths

Table 2 Univariate analyses of imaging-based neuroradiological features

	$N = 103$	n^a (%)	p value for PFS	n^b (%)	p value for OS
Side			0.877		0.647
Left	49	72.3		80.4	
Right	45	64.1		87.8	
Both	4	75.0		75.0	
Unknown	5				
Midline shift			0.391		0.406
Yes	58	66.7		81.1	
No	40	72.2		86.8	
Unknown	5				
Cystic and solid patterns			0.977		0.207
Yes	31	62.1		90.0	
No	67	72.1		80.3	
Unknown	5				
Number of tumours			0.987		0.979
Single	93	68.6		82.6	
Multiple	5	75.0		100.0	
Unknown	5				
Enhancement pattern			0.505		0.906
Regular peripheral enhancement	14	75.0		92.3	
Irregular ring-like enhancement	65	72.1		85.2	
Homogeneous solid enhancement	19	50.0		68.8	
Unknown	5				
Location			0.263		0.174
Frontal lobe	18	66.7		72.2	
Parietal lobe	6	100.0		80.0	
Temporal lobe	29	65.4		80.0	
Thalamus	2	0.0		100.0	
Spinal cord	1	100.0		100.0	
Ventricle	1	100.0		100.0	
Brainstem	1	0.0		0.0	
Multiple	40	70.3		92.1	
Unknown	5				
Enhancement in thalamus functional region			0.619		0.137
Yes	35	62.9		85.7	
No	56	71.4		78.6	
Unknown	12				
Hyperintense T2WI foci in thalamus functional region			0.556		0.263
Yes	69	66.7		82.6	
No	22	72.7		77.3	
Unknown	12				
Enhancement in the brainstem			0.597		0.887
Yes	4	50.0		75.0	
No	87	69.0		81.6	
Unknown	12				
Hyperintense T2WI foci in the brainstem			0.043*		0.143
Yes	16	81.3		93.8	
No	75	65.3		78.7	
Unknown	12				
Enhancement in motor functional cortex			0.004**		0.022*

Table 2 (continued)

	$N = 103$	n^a (%)	p value for PFS	n^b (%)	p value for OS
Yes	15	86.7		100.0	
No	76	64.5		77.6	
Unknown	12				
Hyperintense T2WI foci in motor functional cortex			0.013*		0.274
Yes	32	87.5		90.6	
No	59	57.6		76.3	
Unknown	12				
Enhancement in sensory functional cortex			0.301		0.243
Yes	13	76.9		92.3	
No	78	66.7		79.5	
Unknown	12				
Hyperintense T2WI foci in sensory functional cortex			0.105		0.535
Yes	27	85.2		88.9	
No	64	60.9		78.1	
Unknown	12				
Ependymal lining enhancement of the lateral ventricle			0.021*		0.001**
Yes	22	71.4		95.2	
No	76	68.1		80.0	
Unknown	5				
Median diameter of oedema on T2WI, mm	7.90 (3.55–12.88)		0.447		0.327
Median diameter of tumour on contrast T1WI, mm	4.84 (1.58–8.73)		0.571		0.645

PFS progression-free survival, *OS* overall survival, *T1WI* T1-weighted imaging, *T2WI* T2-weighted imaging

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Percentage of recurrence

[b] Percentage of deaths

solid lesions. The tumours involved the frontal lobe (18 patients), parietal lobe (6 patients), temporal lobe (29 patients), or multiple lobes (40 patients). Five patients had tumours that involved the thalamus, ventricle, brainstem, or spinal cord.

Hyperintense foci on T2-weighted images were detected in the thalamus functional region (69 patients), brainstem (16 patients), functional motor cortex (32 patients), and functional sensory cortex (27 patients). The enhancement was marked in all tumours, with most lesions exhibiting a pattern of enhancement in the thalamus functional region (35 patients), brainstem (4 patients), motor functional cortex (15 patients, Fig. 1), sensory functional cortex (13 patients), and the

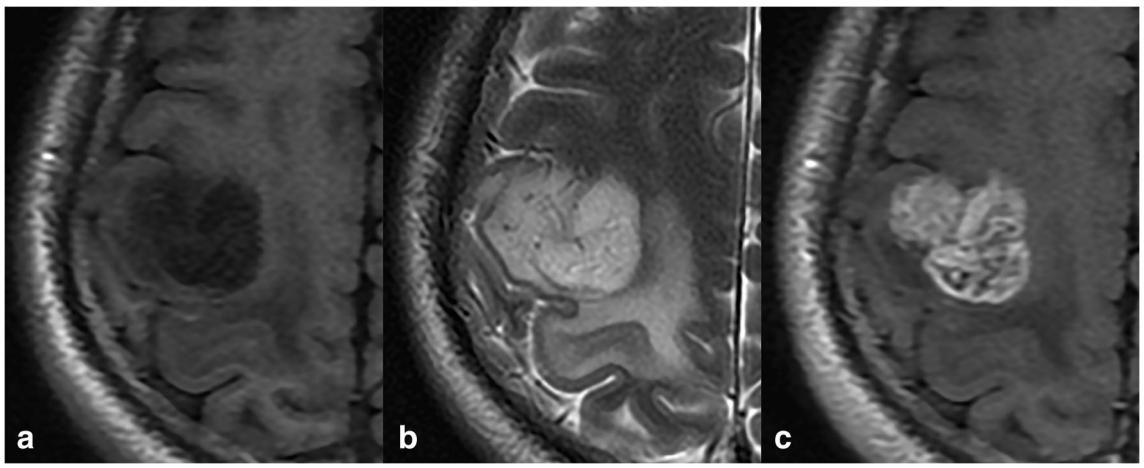

Fig. 1 Brain magnetic resonance imaging revealed a lesion in the right motor functional cortex with a low-intensity signal during T1-weighted imaging (**a**), a high-intensity signal during T2-weighted imaging (**b**), and a heterogeneous signal during enhancement (**c**)

ependyma of the lateral ventricle (22 patients, Fig. 2). The enhancement patterns were regular peripheral enhancement (14 patients), irregular ring-like enhancement (65 patients), or more homogeneous substantial enhancement (19 patients). The median diameters of edema on T2WI were 7.90 cm (range, 3.55–12.88 cm), and the median tumour diameter on contrast-enhanced T1WI was 4.84 cm (range, 1.58–8.73 cm).

Anatomic characteristics

The anatomic characteristics are described in Table 3. Twenty-two tumours were soft, 41 tumours were hard, and 39 tumours were both soft and hard (mixed). The blood supply was considered abundant for 77 tumours and general for 24 tumours. Sixteen tumours exhibited a clear demarcation from the brain parenchyma, while 85 tumours did not. Coincidentally, 16 tumours adhered to the dura mater, while 85 tumours did not. The ventricles were opened in 38 patients and closed in the remaining 64 patients.

Immunohistochemistry findings

Because of financial constraints, immunohistochemistry was only performed for a small proportion of patients (Table 4). Where available, the immunostained slides were evaluated based on the extent and intensity of staining for MGMT, p53, PTEN, and EGFR. The extent of positive staining was estimated first, and then staining intensity was scored semi-quantitatively from 0 to 3+. Nuclear staining for the MGMT protein was judged to be 0 for 1 tumour, ± or 1+ for 11 tumours, and 2+ or 3+ for 11 tumours. The staining for p53 protein was judged to be 0 for 2 tumours, ± or 1+ for 12 tumours, and 2+ or 3+ for 9 tumours. The staining for PTEN protein was judged to be 0 for 3 tumours, ± or 1+ for 9 tumours, and 2+ or 3+ for 10 tumours. The membranous staining for EGFR protein was judged to be 0 for 5 tumours, ± or 1+ staining for 7 tumours, and 2+ or 3+ for 11 tumours. Immunostaining for EFGR tended to be lower following tumour recurrence (Fig. 3).

Survival analyses

In the univariate analyses, PFS was improved in patients who underwent surgery followed by adjuvant TMZ chemotherapy with concurrent RT, relative to patients who underwent surgery alone (15.3 months vs. 5.3 months; $p = 0.02$). However, PFS was not increased in patients who underwent adjuvant TMZ chemotherapy with concurrent RT, relative to patients who received adjuvant TMZ chemotherapy alone (15.3 months vs. 19.4 months; $p = 0.917$) or who received adjuvant RT alone (15.3 months vs. 16.7 months; $p = 0.733$). Relative to the reference groups, poor PFS was significantly associated with hyperintense foci in the brainstem on T2WI (6.1 months vs. 15.9 months; $p = 0.043$), enhancement in the motor functional cortex (7.2 months vs. 15.3 months; $p = 0.004$), hyperintense foci in the motor functional cortex on T2WI (10.1 months vs. 15.9 months; $p = 0.013$), and ependymal lining enhancement of the lateral ventricle (5.5 months vs. 13.6 months; $p = 0.021$). In the multivariate analyses (Table 5), poor PFS was independently associated with ependymal lining enhancement of the lateral ventricle (HR, 2.406; 95% CI, 1.304–4.439; $p = 0.005$) and enhancement in the motor functional cortex (HR, 2.892; 95% CI, 1.485–5.630; $p = 0.002$) (Fig. 4).

In the univariate analyses, good OS was associated with high postoperative KPS scores (16.5 months vs. 7.5 months; $p = 0.04$) but not significantly associated with high preoperative KPS scores (12.6 months vs. 4.4 months; $p = 0.136$). Significantly improved OS was associated with adjuvant RT use (16.5 months vs. 5.7 months; $p < 0.001$), and OS was greatest for adjuvant

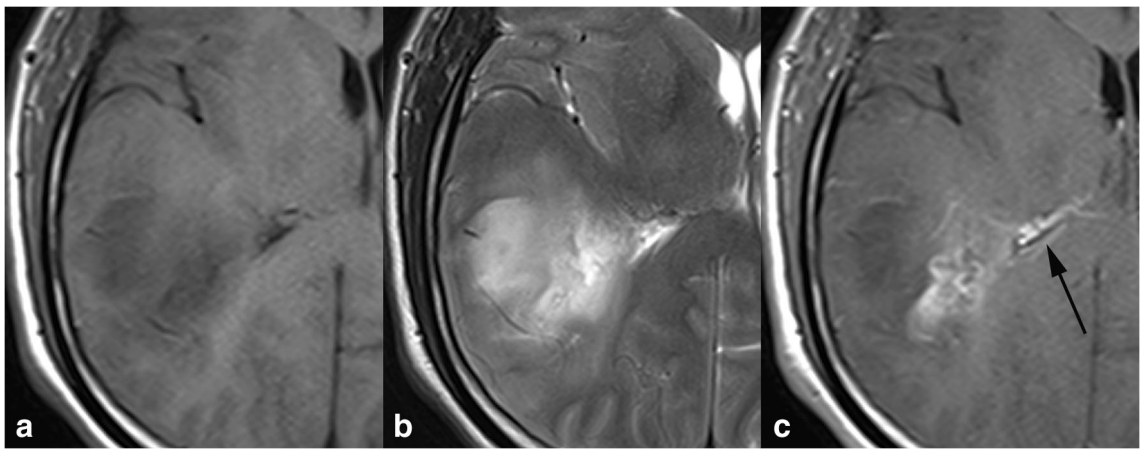

Fig. 2 Brain magnetic resonance imaging revealed a primary gliosarcoma extending from the right temporal lobe to the lateral ventricle, with a heterogeneous but predominantly hypointense signal during T1-weighted imaging (**a**) and hyperintensity during T2-weighted imaging (**b**). The enhancement reaches the vicinity of the ventricular system, making it possible to identify ependymal lining enhancement (**c**, arrow)

Table 3 Univariate analyses of features based on the surgical records

	$N = 103$	n^a (%)	p value for PFS	n^b (%)	p value for OS
Colour			0.239		0.904
Red	79	72.2		84.9	
White	15	46.2		76.9	
Yellow	6	50.0		66.7	
Multiple	2	00.0		100.0	
Unknown	1				
Blood supply			0.239		0.124
Abundant	77	67.9		80.7	
General	24	61.9		81.8	
Unknown	2				
Texture			0.491		0.403
Soft	22	64.7		76.5	
Hard	41	60.5		79.5	
Mixed	39	76.3		89.5	
Unknown	1				
Clear demarcation from the brain parenchyma			0.197		0.095
Yes	16	64.3		64.3	
No	85	69.2		86.1	
Unknown	2				
Tumour adhered to the dura mater			0.494		0.681
Yes	16	62.5		81.3	
No	85	69.7		83.1	
Unknown	2				
Ventricular opening			0.459		0.060
Yes	38	63.9		91.9	
No	64	70.2		77.2	
Unknown	1				

PFS progression-free survival, *OS* overall survival

[a] Percentage of recurrence

[b] Percentage of deaths

TMZ-based chemotherapy relative to other adjuvant chemotherapy or no adjuvant chemotherapy (18.3 months vs. 11.9 months vs. 8.8 months; $p = 0.002$). Besides, OS was significantly increased among patients who underwent surgery followed by adjuvant TMZ-based chemotherapy with concurrent RT, relative patients who underwent surgery alone (18.3 months vs. 4.1 months; $p < 0.001$), although this improvement was not observed when adjuvant TMZ chemotherapy with concurrent RT was compared to adjuvant TMZ chemotherapy alone (18.3 months vs. 21.4 months; $p = 0.312$) or adjuvant RT alone (18.3 months vs. 21.8 months; $p = 0.623$). Salvage surgery at recurrence provided improved OS (31.8 months vs. 13.3 months; $p = 0.006$), although the use of salvage RT did not significantly increase OS (17.3 months vs. 13.3 months; $p = 0.118$). Besides, there were no significant differences in OS when we compared patients who received TMZ-based chemotherapy to patients who received no chemotherapy (18.3 months vs. 11.9 months; $p = 0.063$), patients who received bevacizumab (18.3 months vs. 12.3 months; $p = 0.057$), or patients who received other drugs (18.3 months vs. 36.9 months; $p = 0.659$). Poor OS was significantly associated with an enhancement in the motor functional cortex (12.8 months vs. 15.9 months; $p = 0.022$) and the ependymal lining enhancement of the lateral ventricle (7.6 months vs. 16.5 months; $p = 0.001$), although good OS was associated with EGFR expression (Fig. 3). In the multivariate analyses (Table 5), poor OS was independently associated with ependymal lining enhancement of the lateral ventricle (HR, 2.946; 95% CI, 1.305–6.650; $p = 0.009$), enhancement in the motor functional cortex (HR, 2.639; 95% CI, 1.280–5.439; $p = 0.009$). However, favourable OS was independently associated with adjuvant treatment ($p = 0.004$) and salvage surgery at recurrence ($p = 0.031$) (Fig. 4).

Table 4 Univariate analyses of the immunohistochemistry results

	Number	n^a (%)	Hazard ratio (95% CI)	p value for PFS	Number	n^b (%)	Hazard ratio (95% CI)	p value for OS
MGMT				0.275				0.181
0	1	100.0	Reference		1	100.0	Reference	
± or 1+	11	81.8	1.844 (0.227–14.978)		11	81.8	1.383 (0.172–11.152)	
2+ or 3+	11	72.7	0.786 (0.093–6.664)		11	50.0	0.478 (0.054–4.237)	
P53				0.478				0.896
0	2	50.0	Reference		2	50.0	Reference	
± or 1+	12	100.0	0.981 (0.123–7.854)		12	83.3	0.624 (0.073–5.361)	
2+ or 3+	9	55.6	0.506 (0.056–4.599)		9	77.8	0.590 (0.065–5.385)	
PTEN				0.063				0.301
0	3	100.0	Reference		3	100.0	Reference	
± or 1+	9	88.9	1.413 (0.358–5.579)		9	77.8	1.299 (0.328–5.148)	
2+ or 3+	10	60.0	0.319 (0.071–1.431)		10	70.0	0.506 (0.120–2.142)	
EGFR				0.003**				0.029*
0	5	100.0	Reference		5	100.0	Reference	
± or 1+	7	85.7	0.148 (0.035–0.633)		7	71.4	0.192 (0.046–0.798)	
2+ or 3+	11	63.6	0.071 (0.015–0.325)		11	72.7	0.169 (0.043–0.666)	

PFS progression-free survival, *OS* overall survival, *CI* confidence interval, *MGMT* O6-methylguanine-DNA methyltransferase, *PTEN* phosphatase and tensin homologue, *EGFR* epidermal growth factor receptor

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Percentage of recurrence

[b] Percentage of deaths

Discussion

Primary gliosarcoma is a rare clinicopathological variant of glioblastoma that is traditionally associated with a poor prognosis [8]. However, our understanding of the optimal treatment is limited by the fact that most research has involved retrospective studies. Nevertheless, to the best of our knowledge, this is the largest single-centre study to address the clinical features and outcomes of primary gliosarcoma, which revealed that survival was significantly related to MRI features, adjuvant treatment, and salvage surgery at recurrence. For example, a poor prognosis was associated with an enhancement in the functional motor cortex or ependymal lining enhancement of the lateral ventricle. Relative to surgery alone, OS was improved when patients underwent maximal safe resection plus adjuvant RT alone, adjuvant TMZ-based chemotherapy alone, or adjuvant TMZ-based chemotherapy with concurrent RT.

Gliosarcoma represents approximately 1.8% of primary tumours in the central nervous system [13], and a previous study at our centre revealed that the incidence of gliosarcoma was 9.8% among 518 patients with gliosarcoma and glioblastoma [14]. Most gliosarcoma cases involve patients who are approximately 50 years old [2, 15–21], and the present study confirmed that the median age was 51 years (range, 19–78 years) with a large proportion of male patients ($n = 67$, 65.0%). Among our patients with primary gliosarcoma, the median OS was 13.3 months (range, 0.2–117.7 months), and the median PFS was 9.1 months (range, 0.2–114.0 months), which are similar to other results in adult primary gliosarcoma, with reported median OS values of 7.3–18.5 months and median PFS values of 3.0–8.3 months [2–4, 6, 8, 9, 13, 15, 16, 19–24]. One retrospective study revealed a median OS of 18.5 months [11], although that might be attributed to younger patient ages and standardized treatment (maximally safe surgical resection followed by uniform adjuvant therapy based on Stupp's protocol). Another study revealed a median OS of 7.3 months [15], which is likely related to the poor postoperative KPS scores, a lower rate of GTR, and inability to complete postoperative RT. Interestingly, most patients (78.6%) excellent postoperative KPS scores of ≥ 70%, which was associated with prolonged survival (Table 1).

Primary gliosarcoma is generally managed based on the current guidelines for glioblastoma multiforme, which involves maximal safe resection followed by adjuvant therapy based on Stupp's protocol [11, 14]. A greater extent of resection may help improve outcomes [4, 8, 10, 24], although we found that the extent of resection was not associated with PFS ($p = 0.816$) or OS ($p = 0.552$), which agrees with findings from other studies [2, 11, 14, 15, 20, 21, 23]. Most patients receive RT in conventional fractions with a total dose of 40–60 Gy [2, 4, 8, 15, 23, 25], and some studies have indicated that RT might not improve survival [2, 15, 25], while other studies have suggested that higher total RT doses (≥ 53.6 Gy)

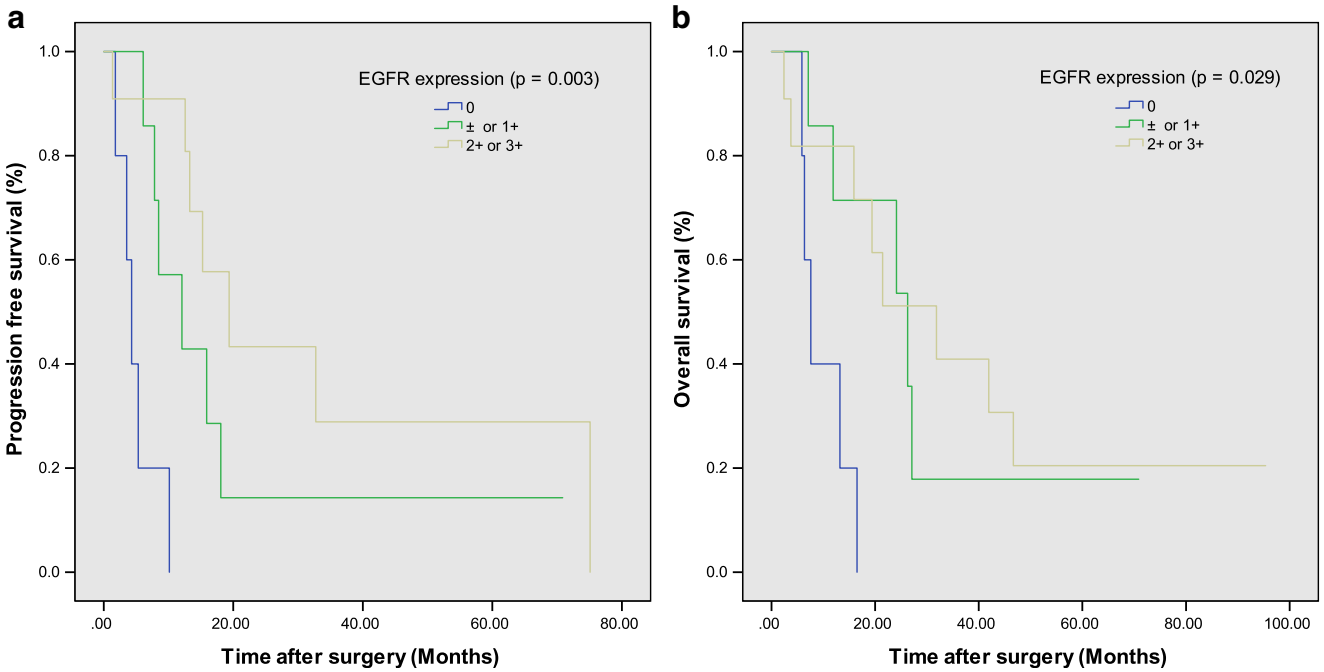

Fig. 3 Relationships between epidermal growth factor receptor (EGFR) expression and progression-free survival (**a**) and overall survival (**b**)

may improve survival [2, 8, 23]. The present study revealed that RT provided a benefit in terms of OS but not PFS, and adjuvant TMZ-based chemotherapy also provided a benefit in terms of OS but not PFS (Table 1). Moreover, adjuvant TMZ-

Table 5 Factors independently related to progression-free survival and overall survival

	PFS			OS		
	HR	95% CI	*p*	HR	95% CI	*p*
Ependymal lining enhancement of the lateral ventricle			0.005**			0.009**
No	Reference	Reference		Reference	Reference	
Yes	2.406	1.304–4.439		2.946	1.305–6.650	
Enhancement in motor functional cortex			0.002**			0.009**
No	Reference	Reference		Reference	Reference	
Yes	2.892	1.485–5.630		2.639	1.280–5.439	
Treatment after surgery						0.004**
None				Reference	Reference	
Adjuvant RT alone				0.071	0.016–0.312	
Adjuvant TMZ-based chemotherapy alone				0.063	0.009–0.429	
Adjuvant TMZ-based chemotherapy with concurrent RT				0.056	0.015–0.212	
Others				0.059	0.016–0.218	
Salvage surgery at recurrence						0.031*
No				Reference	Reference	
Yes				0.449	0.216–0.931	

PFS: progression-free survival, OS: overall survival, HR: hazard ratio, CI: confidence interval, RT: radiotherapy, TMZ: temozolomide

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

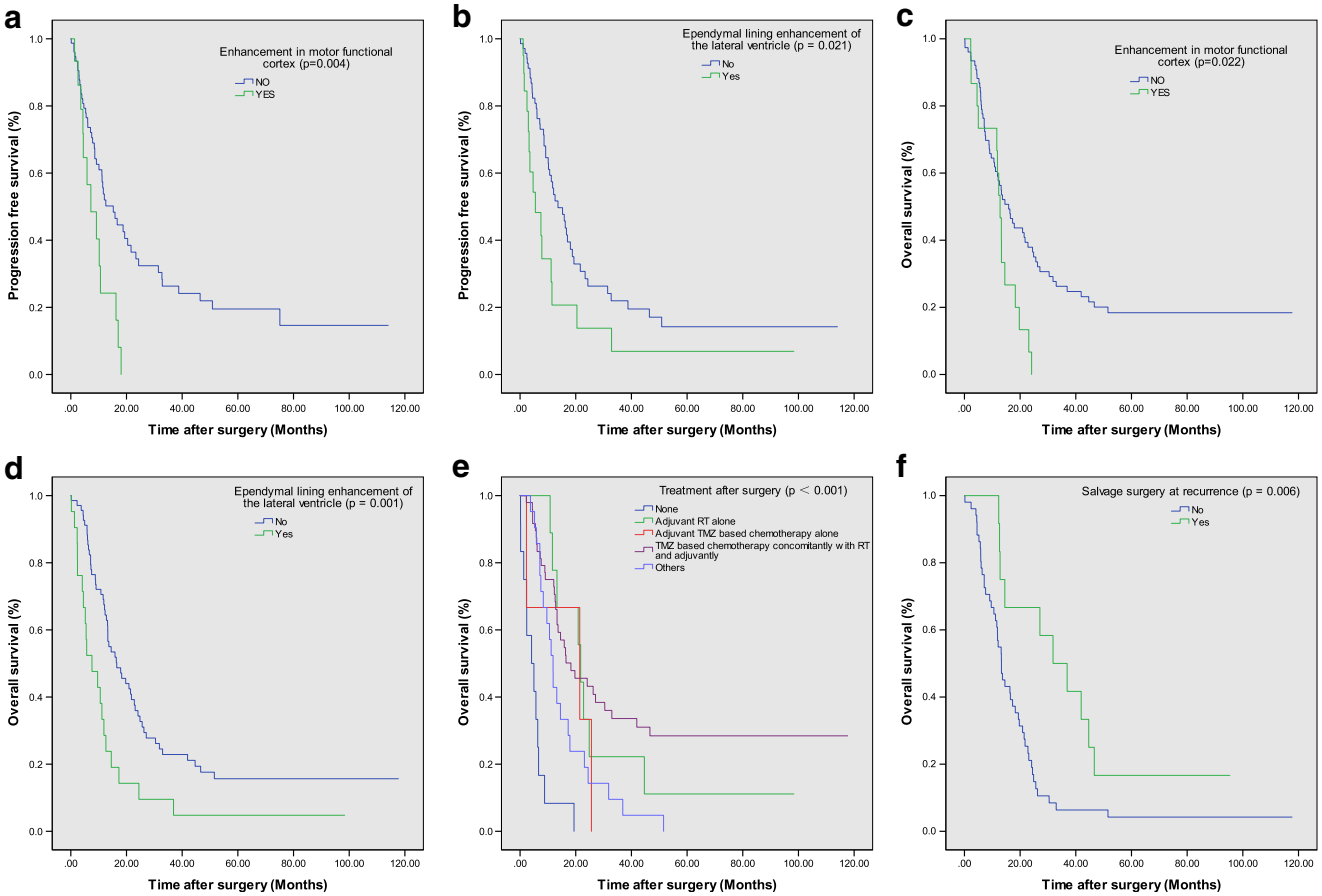

Fig. 4 Relationships of progression-free survival with ependymal lining enhancement of the lateral ventricle (**a**) and enhancement in the motor functional cortex (**b**). Relationships of overall survival with ependymal lining enhancement of the lateral ventricle (**c**), enhancement in the motor functional cortex (**d**), treatment after surgery (**e**), and salvage surgery at recurrence (**f**)

based chemotherapy was independently associated with OS (Table 5), which is consistent with the results reported by Adeberg et al. [26]. There is conflicting evidence regarding the optimal chemotherapy in this setting, with some reports suggesting that TMZ-based chemotherapy provided significant therapeutic benefits [8, 20, 25]. However, an earlier study found that TMZ-based chemotherapy was not associated with favourable OS [2], and current studies have also suggested that TMZ-based chemotherapy was superior to RT alone in terms of the effect on OS [19, 23]. These findings raise questions regarding the efficacy of TMZ treatment for primary gliosarcoma, although surgery followed by adjuvant TMZ-based chemotherapy and concurrent RT is considered the optimal management strategy. Frandsen et al. recently performed a nationwide study of patients in American hospitals, and suggested that combining adjuvant chemotherapy with concurrent RT improved survival [24], although they did not specifically evaluate concurrent chemoradiotherapy using TMZ treatment. In our patients, adjuvant TMZ-based chemotherapy with concurrent RT provided better survival than surgery alone, although there was no benefit when we compared this strategy to adjuvant RT alone (18.3 months vs. 21.8 months; $p = 0.623$) or adjuvant TMZ-based chemotherapy alone (18.3 months vs. 21.4 months; $p = 0.312$).

To the best of our knowledge, few therapies have been evaluated for recurrence of primary gliosarcoma, although one previous study revealed that increased OS was associated with salvage surgery, chemotherapy, or chemoradiotherapy at recurrence (HR, 0.38; $p < 0.001$). Relative to patients who received no salvage treatment in the present study, improved median OS was associated with salvage surgery (31.8 months vs. 13.3 months; $p = 0.006$) and salvage adjuvant RT (17.3 months vs. 13.3 months; $p = 0.118$) (Table 1), although it is important to note that the improvement for RT was not significant and we did not have data regarding the extent of resection and RT doses. Moreover, we failed to detect a significant benefit for salvage bevacizumab treatment (14.5 months vs. 11.9 months; $p = 0.695$). However, the 51 patients with recurrence were identified only based on radiological evidence (not surgery or biopsy), which we believe suggests that salvage treatment using surgery, RT, or chemotherapy may be beneficial for these patients.

A few recent case series have attempted to describe the detailed imaging features of primary gliosarcoma [9, 18, 27,

28], which were suggested to be the same as the features of glioblastoma multiforme. Most tumours involved multiple lobes, with a temporal lobe predominance, as primary gliosarcoma are often large at the diagnosis (median diameter, 4.85 cm). Most primary gliosarcomas were single lesions, and only 5 cases involved multiple lesions. Previous investigators have described gliosarcoma as a supratentorial tumour with solid and cystic components, as well as moderate or marked irregular peritumoral edema. The relatively solid sarcomatous component with dense cellularity and a fibrous nature is indicated by areas with hypointensity to white matter on T1WI, hyperintensity on T2WI, and homogeneous or inhomogeneous intensified peripheral enhancement. In contrast, the gliomatous component with associated necrotic or cystic changes is indicated by the central hyperintensity on T2WI.

Furthermore, the thick walls and rim or ring-like enhancement are likely caused by the peripheral displacement of the vessels as the tumour grows [27, 28]. However, only a few studies have mentioned relatively high-intensity areas in DWI, which correspond to cellular components, and hypointense areas that correspond to the tumour's necrotic-cystic components [9, 28]. Moreover, it is unclear whether the imaging features of primary gliosarcoma are related to survival. Our univariate and multivariate analyses revealed that poor OS and PFS were associated with an enhancement in the functional motor cortex or ependymal lining enhancement of the lateral ventricle. Sampaio et al. were the first to describe ependymal enhancement in primary gliosarcoma and suggest that it might develop when the tumour reaches the vicinity of the ventricular system and becomes able to infiltrate via contiguous spreading [9]. Thus, the poor prognosis of patients with ependymal enhancement would be related to the failure of total resection, although we did not detect a significant relationship between ependymal enhancement and extent of resection ($p = 0.942$). Nevertheless, there was a significant difference in ependymal enhancement according to ventricular opening status ($p = 0.001$), and we observed that ventricular opening was marginally associated with more reduced survival (16.5 months vs. 9.1 months, $p = 0.06$; Table 3).

Few studies have analysed the molecular or genetic markers of gliosarcoma, such as MGMT, P53, PTEN, and EGFR. However, MGMT promoter methylation is related to increased survival in patients with malignant gliomas treated using alkylating agents [6]. Other studies have also confirmed that a significant fraction of primary gliosarcomas exhibited MGMT promoter methylation and protein expression, which was associated with a good prognosis [6, 24]. However, the differences in OS and PFS according to MGMT protein expression were not statistically significant, and we also failed to detect significant differences according to MGMT protein expression (Table 4). Nevertheless, a recent study revealed that MGMT protein expression was associated with a poor prognosis in patients with gliosarcoma [29]. Other investigators have suggested that the MGMT protein could be expressed in gliosarcoma, despite methylation of the MGMT promoter [6], which would imply that MGMT protein expression may not be a reliable biomarker for diagnosis and prognostication. Another study revealed that somatic mutations in the TP53 gene were associated with poor survival and played a role in treatment resistance ($p = 0.019$), although there was no significant difference in OS according to PTEN mutation status ($p = 0.819$) [25]. In the present study, expressions of p53 and PTEN were not associated with OS (Table 4). The intracellular tyrosine kinase of the EGFR activates signalling cascades that lead to cell proliferation, angiogenesis, and inhibition of apoptosis [29]. However, studies have indicated that primary gliosarcoma has relatively low frequencies of EGFR amplification, EGFR VIII mutation, and EGFR protein expression [8, 30–32]. Only one clinical study has indicated that EGFR protein expression was related to a poor prognosis [29], while our findings suggest that EGFR protein overexpression was associated with a good prognosis in the univariate analysis. These conflicting findings may be related to the complexities of the EGFR signalling pathways and the small sample size, although we cannot explain the differences in prognosis based on EGFR expression.

Although various studies have retrospectively demonstrated that the clinical features (gender, age, KPS at diagnosis, extent of resection, tumour location, PFS and OS) of gliosarcoma were similar to those of GBM [3, 8, 14, 15, 24], there are still conflicting reports regarding its clinical outcome compared with that of GBM all the time. In an early study in our centre, compared with glioblastoma patients, gliosarcoma patients had a worse PFS (8 months gliosarcoma vs. 9 months GBM, $p = 0.001$) and OS (13 months gliosarcoma vs. 14 months GBM, $p = 0.004$), MGMT promoter methylation was less common in gliosarcoma patients (44.7% gliosarcoma vs. 80.1% GBM, $p < 0.001$) [14]. However, using the National Cancer Database, Frandsen et al. provides that there was no difference in survival (10.7 months gliosarcoma vs. 11.9 months GBM, $p = 0.068$) and MGMT promoter methylation (2.2% gliosarcoma vs. 1.8% GBM, $p = 0.093$, over 90% of gliosarcoma patients and GBM patients were respectively unknown about MGMT promoter methylation) between gliosarcoma patients and glioblastoma patients [24]. Furthermore, another study showed that gliosarcoma demonstrated worse OS on subset analysis of patients who had received TMZ-based chemoradiotherapy (11.0 months gliosarcoma vs. 17.3 months GBM, $p = 0.006$). They also showed a lower MGMT promoter methylation (12.5%, $n = 8$) in primary gliosarcoma patients, which might regard as a poor prognostic factor [8]. Accordingly, there may be a difference in MGMT promoter methylation between gliosarcoma and GBM, but the role of MGMT promoter methylation in the prognosis of patients with gliosarcoma is unclear. Furthermore, it is still uncertain whether there are differences in patterns of relapse and overall survival between gliosarcoma and GBM.

Study limitations

The main limitations of the present study were the retrospective design and the small sample size, which limited the statistical power. Besides, we did not have available data to investigate variables that might influence survival, such as RT dose and metastasis. Furthermore, we did not consider the number of adjuvant treatment cycles that were completed, and, probably, many patients did not complete their adjuvant therapy because of comorbidities, poor performance status, or economic considerations [10]. Moreover, only a small proportion of patients had available immunohistochemistry data, which suggests that our findings were subject to selection bias and do not support the conclusive characterization of the molecular features of primary gliosarcoma. Because of the retrospective nature of our study, we have tried our best to collect various data at the beginning of our study; however, at the early period before 2016, only immunohistochemistry was performed to make a definite diagnosis (only enough for diagnosis and differentiate diagnosis), which is indeed a limitation of our study. Our present series included the patients with MGMT data reported in the previous study [14], but the results of MGMT methylation examination were not open-access and were inaccessible for us. We had realized this shortage and routinely examined MGMT and other markers for gliomas since 2016, and we would summarize and analyse these results in future studies with enough sample size. Immunostaining for the molecular or genetic markers may not be suitable or sufficient to provide a comprehensive view of the genomic alterations. Whole-exome sequencing (WES), copy number alteration (CNA) analysis, and genome-wide DNA methylation might be needed to portend the prognosis of gliosarcoma patients.

Conclusions

This retrospective single-centre study revealed that primary gliosarcoma patients experienced a survival benefit when maximal safe resection was combined with adjuvant TMZ-based chemotherapy and concurrent RT. Besides, salvage surgery appeared to provide a meaningful therapeutic benefit for recurrent gliosarcoma. Poor outcomes were associated with an enhancement in the functional motor cortex and ependymal lining enhancement of the lateral ventricle, while MGMT promoter methylation was associated with increased survival after TMZ-based chemotherapy. However, larger prospective studies are needed to confirm our findings and evaluate new treatment regimens.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Institution Review Board of the Beijing Tiantan Hospital, affiliated with the Capital Medical University.

Informed consent No image or video from which the patient can be identified is included in the manuscript. For this type of study, formal consent is not required.

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