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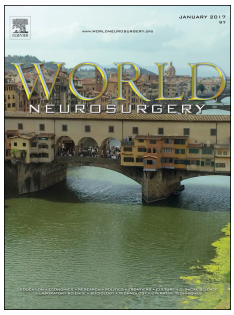

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Informed consent: Informed consent was obtained from all individual participants included in the study.

Abstract

Objective We aim to elucidate the clinical characteristics of patients with primary spinal cord glioblastoma (PSC GBM) and prognostic factors for their outcomes.

Methods A cohort of 11 patients with pathologically diagnosed PSC GBM from our center was retrospectively reviewed. The clinical, radiological, operative and molecular information were recorded, and univariate analysis was performed to identify prognostic factors.

Results The patient cohort included 5 males (45.5%) and 6 females (54.5%) with a median age of 26 years (range 9-69 years). The median duration of the preoperative symptoms was 4.0 months (range 0.5-120 months). Subtotal resection (STR) was achieved in 8 patients (72.7%) and partial resection (PR) in 3 (27.3%). Two patients (18.2%) underwent postoperative adjuvant chemo-radiotherapy, three patients underwent (27.3%) chemotherapy only, and six patients (54.5%) neither. Two patients underwent additional therapy with bevacizumab. After a mean follow-up of 12.4 months (range 1-33 months), Kaplan-Meier plot showed that the median progression-free survival (PFS) and overall survival (OS) was 6.0 (range 0.5-12.0) months and 12.0 (range 1.0-33.0) months, respectively, and one-year survival was 31.8%. Age at diagnosis and duration of the preoperative symptoms were confirmed as prognostic factors of PFS and OS in univariate analysis ($P<0.05$).

Conclusions Despite aggressive treatment, PSC GBM still have a dismal prognosis and lead to severe neurological deficit. Age at diagnosis and duration of the preoperative symptoms were confirmed as prognostic factors, yet the role of adjuvant radio-chemotherapy and extent of resection (EOR) are still unclear, necessitating further research.

Key words Primary spinal cord glioblastoma, Prognosis, Surgery, Chemotherapy, Radiotherapy

Introduction

Spinal cord tumors are rare compared to intracranial tumors, account for less than 10% of all central nervous system neoplasms[1]. Nevertheless, primary spinal cord glioblastoma (PSC GBM) is extremely rare, only representing 1.5% of all spinal cord tumors[2]. In spite of the progression of surgical techniques and postoperative adjuvant therapy such as chemo-radiotherapy, PSC GBM still shows a gloomy prognosis. The overall survival (OS) of PSC GBM patients is approximately 10-14 months[3, 4], and often lead to severe neurological deficit, reduced the quality of life.

To the best of our knowledge, to date the largest single-center study involving 15 PSC GBM patients was reported by Yi S et al. in 2019[5]. However, for the reason of its rarity, most previous studies are merely case reports[4, 6-22] or several small sample series[23-30]. Owing to limited studies, the clinical features, optimal therapeutic regimen and prognosis factors of PSC GBM remain controversial[29]. Herein, we present a consecutive cohort of eleven patients with histologically proven PSC GBM in our center and analyze their clinical, radiological, operative, molecular information based on our own experience and literature review. Moreover, we found that the duration of the preoperative symptoms was confirmed as a prognostic factor in PSC GBM, which has not been previously reported. We hope the present study may provide some new clinical evidence to this extremely rare malignant disease.

Materials and Methods

Patients from our center

Between May 2015 and July 2019, a cohort of 14 patients who underwent tumor removal in the neurosurgical department of Beijing Tsinghua Changgung Hospital were pathologically diagnosed with spinal cord GBM according to the 2016 WHO classification of the central neural system tumors. Eleven (78.6%) patients with PSC GBM were finally included for analysis because one patient was lost to follow-up after discharge and two patients had undergone prior resection of spinal cord low-grade diffuse astrocytoma. This study was approved by our institutional review board. Brain and total spinal cord magnetic resonance imaging (MRI) were performed for all patients before surgery in the aim of excluding spinal cord metastatic lesion arise from primary brain GBM, and the whole central nervous system MRI were also performed after the surgical treatment. All the patients underwent maximal safe surgical resection with intraoperative neurophysiological monitoring. Subtotal resection (STR) was defined as surgical removal of at least 80% of the tumor on MRI, while partial resection (PR) was defined as <80% tumor resection. Neurological examination was assessed in all patients. Modified McCormick classification applied to assess neurological status, American Spine Injury Association (ASIA) grading system applied to assess the degree of spinal cord injury and Karnofsky Performance Status (KPS) scale applied to assess functional status. The assessment was performed before surgery, at one week after surgery, at three months after surgery, at one year after surgery, and semi-annually thereafter. Post-operative adjuvant therapies included radiotherapy (RT), chemotherapy (CMT) and bevacizumab. The clinical, radiological, operative and pathological information of all patients were recorded.

Molecular information

The expression of isocitrate dehydrogenase 1 (IDH1), Ki-67, P53 and H3 K27M were detected by immunohistochemistry staining (IHC) as reported previously[31-33]. The Ki-67 index was graded as either high (＞40%) or low (≤40%) for analysis, based on the percentage of IHC-positive cells.

Follow‑ up and statistical analysis

Patients were regularly followed by outpatient consultation or telephone follow-up survey every 3 months, or 1 month if necessary. The PFS was defined as the duration between the surgery and the date of recurrence as demonstrated by MRI. The OS was defined as the duration between the surgery and the death or last known follow-up. All data were analyzed using IBM SPSS Statistics (Version 25.0; IBM Corp., New York, USA) and R software (version3.5.0; R Foundation for Statistical Computing, Vienna, Austria). PFS, OS and survival as a function of time were calculated using the Kaplan–Meier method. Moreover, Kaplan-Meier (log-rank test) analysis was used to evaluate different survival results of PFS and OS according to various clinical variables. The maximally selected log-rank statistic was used to dichotomize Ki-67 index for both PFS and OS, and a minimum P value approach was used to perform a cutoff point analysis. The maximally selected log-rank statistic was calculated using the "maxstat (version 0.7−25)" package in R software. A two-sided P value <0.05 was considered statistically significant.

Literature research

This study retrieved recent published literature with the following keywords such as "spinal cord glioblastoma multiforme," "spinal cord glioblastoma" and "spinal cord malignant glioma" in the PubMed database. All 49 articles published during the recent 5 years (from 2015 to 2020) were carefully reviewed by two authors (Kaiyuan Yang and Weitao Man), the source and date of each patient reported in literature were also checked to exclude duplicates. The inclusion criteria were as follows: (1) patients with PSC GBM confirmed by surgery and pathological information; (2) patients with post-operative follow-up more than 3 months unless reached the endpoint; and (3) cases reported in the

English literature. The exclusion criteria were as follows: (1) PSC GBM concurrent with other malignant or benign tumors and (2) patients with secondary spinal cord GBM who had undergone prior resection of spinal cord low-grade glioma or a diagnosis with evidence of secondary metastases from primary brain GBM. Finally, a total of 26 studies (involving a total of 57 patients) had outcome data met our requirements and were included in the analysis.

Results

Demographics and clinical features

In the present retrospective study, 11 patients met the inclusion criteria of primary spinal cord glioblastoma in our institution. There were 5 male (45.5%) and 6 female (54.5%) patients. Their median age at diagnosis was 26 years (range 9–69 years). Median preoperative KPS score was 40 (range, 20–90). The median duration of the preoperative symptoms was 4.0 months (range 0.5–120 months). The most frequent preoperative presentations included back pain (seven cases, 63.6%), motor deficits (ten cases, 90.9%), sensory disturbance (eleven cases, 100%) and sphincter dysfunction (six cases, 54.5%). The preoperative neurological examination showed that 4 patients were at Grade II of the modified McCormick classification, followed by 2 at Grade III and 5 at Grade IV. The preoperative ASIA grading system assessment showed 2 patients presented with an ASIA B examination below the involved spinal cord level, followed by 3 patients presented with ASIA C and 6 patients presented with ASIA D. The clinical data of the 11 patients are listed in **Table 1**.

Radiological features

Tumor locations included the cervical region (5 cases, 45.5%), the cervicothoracic region (3 cases, 27.3%), the thoracic region (1 case, 9.1%), and the thoracolumbar region (2 cases, 18.2%). According to the T1-weighted MRI, the tumor had isointensity signal in 5 cases, hypointensity signal in 4 cases and iso-hypo-signal intensity in 2 cases. The T2-weighted MRI demonstrated hyperintensity in all cases. Contrast-enhanced T1-weighted MRI showed 9 cases with heterogeneous enhancement, and 2 cases with homogeneous enhancement. MRI of the spine also revealed that the presence of peritumoral spinal cord edema in all cases and cystic changes in 4 cases, however, syringomyelia were rarely present and was found in only 1 case. Moreover, MRI demonstrated the presence of intramedullary lesion with exophytic growth in 2 cases. An illustrative example of a case is shown in **Fig. 1**.

Treatment and pathological findings

All the patients underwent microsurgical exploration through the posterior approach. Six of the patients underwent a laminectomy and the other five patients underwent a laminoplasty. STR of the tumor was achieved in 8 patients (72.7%) and PR was performed in the other 3 patients (27.3%). Two patients accepted postoperative temozolomide (TMZ) chemotherapy combined with fractionated intensity modulated radiotherapy with a total dose of 45 Gy in 25 fractions to the involved spinal cord. Three patients received only TMZ chemotherapy, and six patients had neither for various reasons. Besides, two patients underwent additional bevacizumab therapy after tumor recurrence as the salvage treatment.

Histopathological analysis revealed all tumors showed typical histological indications of glioblastoma. Immunohistochemical analysis of IDH1, Ki-67, P53 and H3 K27M were available for 6 (54.5%), 11 (100%), 11(100%) and 5 (45.5%) patients, respectively. Notably, in all detected cases no patient harbored IDH1 mutation. P53 mutation was observed in 7 patients (54.5%), and the H3 K27M mutation was found in 2 patients (18.2%). In our patient cohort, the median Ki-67 index was 30% (range: 10% to 60%), and a high Ki-67 index (＞40%) was found in 4 (36.4%) patients. These findings

are summarized in **Table 1** and **Table 2**.

Patient outcomes and univariate analysis of survival

As for neurological status, eight patients (72.7%) had a stable or improved Modified McCormick score post-operatively. Six patients (54.5%) maintained a stable examination at 3 months follow-up, however, only one patient (9.1%) maintained a stable examination at the 1 year follow-up assessment. With regard to the degree of spinal cord injury, it revealed that six patients (54.5%) had a stable or improved postoperative ASIA score. At 3 months follow-up, three patients (27.3%) had a decrement in their ASIA score and only one patient (9.1%) maintained a stable examination at the 1 year follow-up assessment. Besides, the KPS score was used to assess functional status of the patients. Six patients (54.5%) had a stable or improved postoperative KPS score, four patients (36.4%) had a stable KPS at 3 months follow-up and only one patient (9.1%) maintained a stable KPS in the subsequent year. However, the worsening of postoperative Modified McCormick score, ASIA score or KPS score were found no statistically significant (0.05) correlation with a shorter PFS or OS.

In our patient cohort, the follow-up period ranged from 1 to 33 months (mean 12.4 months). Ten patients underwent recurrence of the tumor, one patient died during perioperative period, and in 6 patients (54.5%) the tumor had disseminated to the different location in central nervous system. Nine patients died and two patients still alive at the last follow-up. The median PFS of 11 patients was 6 months (95% CI, 1.58-10.42 months), the median OS was 12 months (95% CI, 8.33-15.67 months), and one-year survival was 31.8%. Patient age at initial diagnosis and duration of preoperative symptoms were considered as prognostic factors in univariate analysis ($P<0.05$). Briefly, younger age (<30 years) patient group showed poor prognosis in both PFS and OS (median PFS, 1.0 vs. 8.5 months, p=0.049; median OS, 5.0 vs. 31.0 months, p=0.045), and we also found that the survival time in the long duration of symptoms group ($\geqslant 6$ months) were significantly longer (median PFS, 8.5 vs. 3.0 months, p=0.005; median OS, 31.0 vs. 8.0 months, p=0.007). Notably, high Ki-67 index ($>40\%$) indicated dismal prognosis in both PFS and OS (median PFS, 1 vs. 8 months, p=0.064; median OS, 3 vs. 31 months, p=0.058), moreover, tumor protein P53 mutation also indicated a shorter OS (median OS, 8 vs. 33 months, p=0.064), though the P value didn't achieve statistically significant (0.05). However, EOR and postoperative adjuvant therapy were found to confer no survival benefit. Univariate analysis results and the Kaplan-Meier estimates of PFS and OS stratified by prognostic factors are shown in **Table 2** and **Figure 2**, respectively.

Literature review

The relevant clinical features and outcomes of 57 patients found in 26 articles which met our requirements[4, 6-28, 30, 34] were summarized in **Table 3**. The mean age of the 57 patients reviewed was 31.3 years and most (n=30, 52.6%) were male. The mean duration of the illness was 3.8 months. The majority of the tumors located in the cervical region (n=18, 31.6%) and the thoracic region (n=19, 33.3%). The most common surgery type was biopsy, which was performed in 22 (38.6%) cases. Cerebrospinal fluid dissemination was found in 13 (22.8%) patients. 29 (50.9%) patients received postoperative radiotherapy combined with chemotherapy. The mean follow-up period was 13.3 months and 50.2% of patients had survived 1 year later.

Discussion

In this study, we found that patient age at diagnosis and duration of the preoperative symptoms were confirmed as prognostic factors in univariate analysis. PSC GBM can occur at any age from children to elderly people, but mainly affects younger patients[35]. In the present study, the youngest patient was 9

years old, while the oldest patient was 69 years old. Their median age at diagnosis was 26 years, which is consistent with the previous studies[23, 30, 35]. Moreover, we also found that the median PFS and OS was better in older age (＞30 years) patient group compared to the younger age (＜30 years) patient group. These results are similar to the findings of Moinuddin et al.[35] and Konar et al.[36], they both found that older patient group (18 to 65 years) had better OS than younger patient (< 18 years) group. However, Cheng et al. [30]reported that patients older than 40 years had shorter PFS and OS compared with younger patients with PSC GBM. Duration of the preoperative symptoms is another prognostic factor found in our study. In our patient cohort, patients with long presenting history (≥6 months) had better PFS and OS. The median duration of the preoperative symptoms was 4.0 months, much shorter than other common spinal tumors, which revealed the highly aggressive growth pattern and malignant feature of PSC GBM[26, 37].

Nowadays, molecular biomarkers such as Ki-67, P53, IDH and H3 K27M may be more influential than histopathology alone. Ki-67 represent the proliferation capacity of tumor cells, which could be used to predict the early dissemination of GBM[38]. The higher expression of Ki-67 in tumor cells means more capable of proliferation and invasion, which associated with a malignant feature and dismal prognosis[39]. In our patient cohort, high Ki-67 index (＞40%) was found in 4 (36.4%) of 11 patients, which lead to a shorter PFS and OS (p=0.064 and p=0.058, respectively). P53 mutation is also considered an early event in malignant astrocytic tumors[40]. Different from gliomas in brain, spinal cord gliomas commonly exhibit tumor protein P53 mutation without IDH1/2 mutation[41]. In our patient cohort, all detected cases no patient harbored IDH1 mutation, however, P53 mutation was observed in 7 of 11 patients (54.5%), which also indicated a shorter OS (p=0.064). These results match well with the findings of previous studies[39, 41]. Nevertheless, the survival time influenced by Ki-67 index and P53 mutation didn't reach statistically significant (0.05), which may because of the lack of adequate cases.

The prognostic implication of H3 K27M mutation in diffuse midline glioma (DMG) has been widely explored in previous studies, most have indicated that DMG with H3 K27M mutation lead to a dismal clinical outcome[18, 42, 43]. However, owing to limited studies, the prognostic significance of H3 K27M mutation in PSC GBM remains unclear and controversial. In the analysis by Yi S et al.[5], PSC GBM patients with H3 K27M mutation showed longer OS and disease-free survival (DFS) than H3 K27M wildtype patients. Moreover, they also found that in all 25 patients with primary spinal cord grade IV glioma (glioblastoma and DMG with H3 K27M-mutation), H3 K27M mutation patients group still showed longer OS and DFS than negative K27M mutation patients, which means unlike in brain glioma, H3 K27M mutation in PSC GBM and DMG is not a major gloomy prognostic factor probably. In contrast, some other studies indicated H3 K27M-mutation in spinal cord malignant gliomas represents poor clinical outcome. A retrospectively study by Karremann M et al.[42] revealed that H3 K27M-mutant DMG significantly associated with a worse survival outcome across all midline locations including spinal cord, and Uppar A et al.[18] reported a H3 K27M-mutation PSC GBM patient with extremely dismal outcome died on postoperative day 23. It is worth noting that we found H3 K27M mutation in 2 patients (18.2%) and they showed the shortest and longest survival time (1 month vs. 33 months) in our patient cohort.

Despite aggressive treatment, PSC GBM patients in our cohort reflected a disappointing clinical outcome with a median OS of 12 months, which is similar with the previous studies[29, 30, 44]. In the univariate analysis of our study, both PFS and OS didn't benefit from the extent of resection (EOR) and postoperative adjuvant treatment (including radiotherapy, chemotherapy and bevacizumab).

GTR (gross total resection) can significantly improve survival outcome in brain GBM[45], however,

the role of aggressive surgical intervention in PSC GBM is still unclear. Several studies have found GTR did not benefit PSC GBM patients, even could worsened postoperative neurological and functional status[23, 29, 30, 35, 44]. These results are consistent with our findings. Thus, in the surgical treatment of PSC GBM, maybe we don't need to pursue GTR. With the advantages of surgical techniques such as intraoperative neurophysiological monitoring and 5-ALA fluorescence-guided resection, etc., we could perform a maximal safe resection to obtain a histopathological diagnosis and to decompress the spinal cord, do our best to avoid causing new and permanent neurological deterioration.

Equally, the effectiveness of postoperative radiotherapy (RT) in spinal cord GBM has been questioned in the previous studies. A study involving 14 PSC GBM patients by Cheng et al.[30] showed a beneficial effect of postoperative radiotherapy as an important prognostic factor affecting the survival outcome. Liu et al.[46] also found that postoperative radiotherapy could prolong the OS in spinal cord high-grade glioma patients. However, some studies have failed to demonstrate its benefit in spinal cord GBM, even showed a negative effect on survival outcome[29, 35]. On the other hand, for the risk of spinal cord toxicity and secondary tumors associated with postoperative RT, radiation therapy in children may requires more careful consideration[47].

Thus far, there are no clinical trials have evaluated the advantage of temozolomide (TMZ) in the chemotherapy of PSC GBM. Some previous studies found that TMZ did not demonstrate a significantly improved survival outcomes of PSC GBM[35, 37, 44]. However, the combination of postoperative RT and temozolomide CMT could contribute to a better survival outcome in PSC GBM[27, 30, 36]. Moreover, bevacizumab in the treatment of PSC GBM should also be considered because the value of decrease peritumoral edema, bring transient symptom relief and steroid-sparing effects[48]. Chamberlain MC et al.[49] and Thomas J. Kaley et al.[48] found that bevacizumab as a salvage therapy could demonstrated some responses which correlated with clinical improvement in recurrent spinal cord GBM and spinal cord high-grade glioma patients. In our patient cohort, though survival outcome didn't significantly benefit from postoperative adjuvant treatment, an increase of PFS and OS was observed. Therefore, an adjuvant multimodal therapy of PSC GBM may be necessary.

This study has several limitations. First, because of the rarity of PSC GBM, this is a small retrospective single-center study included only 11 patients. Thus, our statistical data did not have enough power to perform multivariate analysis. Second, molecular biomarkers were absent in some patients due to limited tumor tissue sample. Third, we should continue this present study until the last patient in our cohort reached the endpoint, because 2 patients still alive at the current stage.

Conclusion

The present study indicates that PSC GBM is an extremely rare malignant tumor. Due to absence of effective therapeutic regimen, PSC GBM have a gloomy prognosis and lead to severe neurological deficit. According to our study, age at diagnosis and duration of the preoperative symptoms were confirmed as prognostic factors. However, the role of adjuvant radio-chemotherapy and extent of resection are still unclear and requires further investigation of the multimodal treatment in a larger sample sizes prospective cohort.

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Figure legends

Fig.1 Illustration of case 2. Preoperative magnetic resonance imaging (MRI) (a–c) showed an intramedullary lesion at the T11-L1 level with exophytic growth. The mass showed mild hyperintensity on sagittal (a) T2-weighted images (WI) and irregularly heterogeneous enhancement on gadolinium-enhanced sagittal (b) and axial (c) T1 WI. Postoperative MRI (d) revealed subtotal resection of the tumor. Follow-up MRI (e, f) obtained 6 months after surgery demonstrated stable disease. However, 1 year after surgery, gadolinium-enhanced sagittal (g) T1 WI confirmed tumor local recurrence. The patient refused any adjuvant treatment or reoperation. After that the patient showed progressive deterioration of neurological and functional status, and folllow-up MRI (h-j) obtained 27 months after surgery revealed widespread spinal and intracranial metastasis. Unfortunately, the patient died 31 months after her surgery.

Fig.2 Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) rates stratified by covariates in our patient cohort. (a, b) Comparison of PFS and OS based on patient age at initial diagnosis (**<** 30 and **>** 30 years) in our patient cohort. (c, d) Comparison of PFS and OS between long preoperative duration of the symptoms (DOS) (≥6 months) group and short DOS (**<** 6 months) group in our patient cohort. (e, f) Comparison of PFS and OS between high Ki-67 index (**>** 40%) group and low Ki-67 index (≤40%) group in our patient cohort. (g) Comparison of OS between P53 mutation positive (+) group and negative (-) group in our patient cohort. (h) Comparison of OS between patients underwent postoperative adjuvant treatment (radiotherapy [RT]/temozolomide [TMZ]/ bevacizumab

[BEV]) or not.

Table 1 Clinical characteristics of 11 operated cases of primary spinal cord glioblastoma from our center

Case	Age (years), sex	Duration of pre-op symptoms	Location	Presentations	Pre-op status of KPS/ASIA/ McC	MRI features (T1/T2/ +GA)	EOR	Molecular Features	Post-op Treatment	PFS (mos)	Salvage treatment	OS (mos)	Status at the last follow-up
1	10, F	1 month	C2-7, IM	Neck pain, paresthesia, paraplegia, fever, urinary and fecal incontinence	40/C/IV	Iso-Hypo-/ Hyper-/ Hetero-	STR	P53 (+)	None	0.5	None	3	Death with rec. and RF
2	38, F	2 years	T11-L1, IM+ IDEM	Bil legs pain, weakness, hypoesthesia; urinary retention, constipation	40/B/IV	Iso-/Mild Hyper-/ Hetero-	STR	P53 (+)	None	12	None	31	Death with rec./diss.
3	34, M	3 months	T11-12, IM	Right leg weakness and hypoesthesia; right hip pain	80/D/II	Iso-/Mild Hyper-/ Homo-	STR	P53 (+)	None	6	None	12	Death with rec.
4	15, M	2 months	C2-T1, IM	Neck pain, bli upper limbs weakness and paresthesia	40/D/III	Iso-/Mild Hyper-/ Hetero-	PR	P53 (-)	None	4	None	10	Death with rec.
5	26, F	0.5 month	C2-6, IM	Right upper limb weakness, pain and numbness;	60/D/II	Hypo-/Hyper-/ Hetero-	STR	IDH1(-), P53 (+)	TMZ	1	None	5	Death with rec./diss.

				back pain								
6	32, F	1 year	C4-7, IM	Left hand weakness, limbs hypoesthesia, shoulder pain; right hand numbness	90/D/II	Iso-/Hyper-/ Hetero-	PR	IDH1(-), H3K27M (+), P53 (-)	TMZ+ bevacizumab	9	TMZ+ bevacizumab	33	Death with rec.
7	9, M	3 months	C6-T9, IM	Neck pain, bli upper limbs itching, bli legs weakness and hypoesthesia; urinary and fecal incontinence	40/C/IV	Iso-Hypo-/ Hyper-/ Hetero-	PR	IDH1(-), H3K27M (-), P53 (+)	None	1	None	12	Death with rec. and hydrocephalus
8	10, M	4 months	C4-T7, IM, with CNS multiple diss.	Respiratory failure, paraplegia, bil legs hypoesthesia; urinary retention, constipation	20/C/IV	Hypo-/Hyper-/ Hetero-	STR	IDH1(-), H3K27M (+), P53 (+)	None	1	None	1	Perioperative death with RF and hydrocephalus
9	44, M	5 months	Medulla-C 3, IM	Bli limbs weakness, right limbs paresthesia and back numbness; gait abnormality; dysphagia	60/D/II	Hypo-/Hyper-/ Hetero-	STR	IDH1(-), H3K27M (-), P53 (+)	RT (45Gy) +TMZ	3	None	8	Death with rec./diss.

10	69, F	10 years	C1-4, IM	Neck and back pain, bli limbs weakness, bli upper limbs numbness; urinary retention, constipation	50/D/III	Iso-/Hyper- / Homo-	STR	IDH1(-), H3K27M (-), P53 (-)	TMZ	8.5	Bevacizumab	12.5	Alive with rec./diss.
11	12, F	6 months	T11-S2, IM+ IDEM	Lumbar pain; progressive bil legs pain, weakness and hypoesthesia; urinary retention, constipation	40/B/IV	Hypo-/Hyper-/ Hetero-	STR	P53 (-)	RT (45 Gy) +TMZ	8	None	9	Alive with rec./diss.

M, male; F, female; Bil, bilateral; IM, intramedullary; IDEM, intradural and extramedullary; T1, T1-weighted image; T2, T2-weighted image; +GA, gadolinium administration; Iso-, isointensity;
Hyper-, hyperintensity; Hypo-, hypointensity; Hetero-, heterogeneous; Homo-, homogeneous; Pre-op, pre-operation; Post-op, post-operation; EOR, extent of resection; PR, partial resection; STR, subtotal resection; Rec., recurrence; Diss., dissemination; RF, respiratory failure; ASIA, American Spine Injury Association score; KPS, Karnofsky Performance Status; McC, Modified McCormick classification grade; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide.

Table 2 Univariate analysis of survival (log-rank test)

Clinical factors	PFS			OS		
	Median PFS (95% CI)	Mean PFS (95% CI)	P value	Median OS (95% CI)	Mean OS (95% CI)	P value
Age (years)			0.049*			0.045*
＜30 (n=6)	1.00 (0.00-3.40)	3.42 (0.63-6.20)		5.00 (0.00-11.72)	7.00 (3.20-10.80)	
＞30 (n=5)	8.50 (3.13-13.87)	7.70 (4.73-10.67)		31.00 (1.36-60.64)	23.20 (12.18-34.23)	
Sex			0.168			0.132
Male (n=5)	4.00 (1.51-6.49)	3.67 (1.79-5.54)		10.00 (5.71-14.29)	8.60 (4.60-12.60)	
Female (n=6)	8.00 (0.00-17.00)	6.50 (2.76-10.24)		31.00 (0.00-69.92)	22.67 (10.41-34.92)	
Duration of symptoms (months)			0.005*			0.007*
＜6 (n=7)	3.00 (0.00-7.10)	2.83 (1.17-4.50)		8.00 (0.30-15.70)	7.29 (4.04-10.54)	
⩾6 (n=4)	8.50 (7.52-9.48)	9.38 (7.61-11.14)		31.00	32.00 (30.04-33.96)	
Pre-operative KPS			0.888			0.374
＜50 (n=6)	4.00 (0.00-9.88)	5.58 (1.47-9.70)		10.00 (0.00-23.72)	12.44 (2.07-22.82)	
⩾50 (n=5)	6.00 (0.00-12.44)	5.50 (2.46-8.54)		12.00 (3.41-20.59)	18.20 (5.76-30.64)	
Extent of resection			0.868			0.410
STR (n=8)	6.00 (0.00-13.38)	5.81 (2.77-8.85)		8.00 (0.00-16.32)	14.46 (4.83-24.09)	
PR (n=3)	4.00 (0.00-8.80)	4.67 (0.09-9.24)		12.00 (8.80-15.20)	18.33 (3.92-32.75)	
Adjuvant treatment			0.976			0.224
RT/TMZ/BEV	8.00 (0.00-18.74)	5.90 (2.70-9.10)		33.00	22.40 (8.43-36.37)	
None	4.00 (0.00-9.88)	5.14 (1.15-9.13)		10.00 (2.80-17.20)	11.50 (2.99-20.01)	
P53 mutation			0.519			0.064
Positive (+) (n=7)	3.00 (0.00-7.10)	4.36 (0.73-7.99)		8.00 (0.30-15.70)	10.29 (2.83-17.74)	
Negative (-) (n=4)	8.00 (3.59-12.41)	7.38 (5.13-9.62)		33.00	25.33 (7.98-42.69)	
Ki-67 index			0.064			0.058
Low (⩽40%) (n=7)	8.00 (2.87-13.13)	6.79 (4.00-9.57)		31.00 (9.35-52.65)	21.14 (10.85-31.43)	
High (＞40%) (n=4)	1.00 (0.00-3.29)	2.38 (0.41-4.34)		3.00 (0.00-11.82)	6.50 (1.28-11.72)	

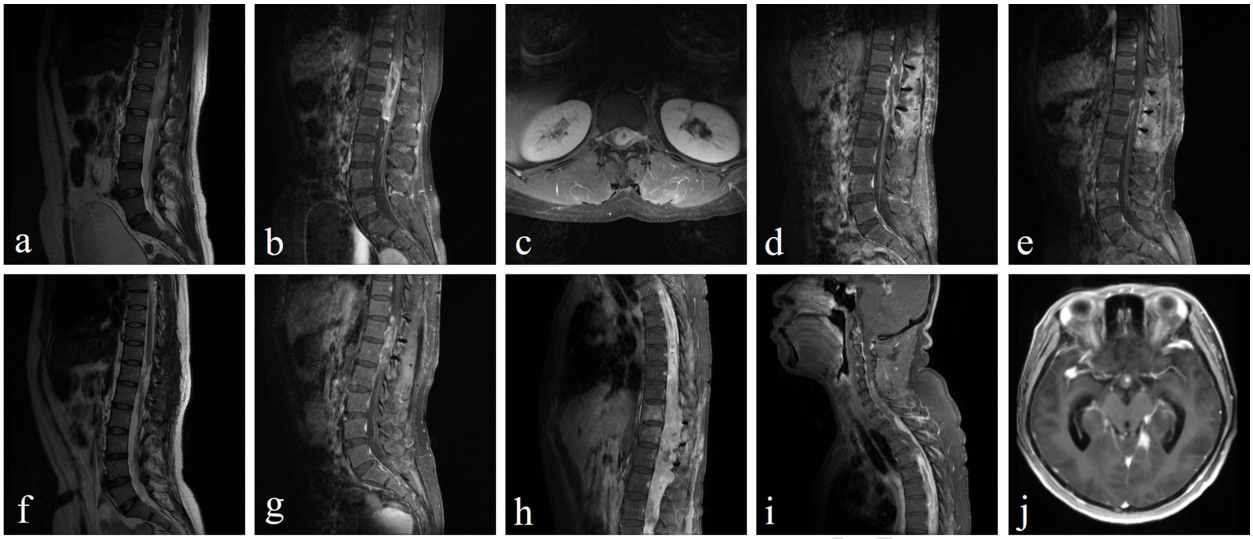
PFS, progression-free survival; OS, overall survival; 95% CI, 95% confidence interval; KPS, Karnofsky Performance Scale; PR, partial resection; STR, subtotal resection; RT, radiotherapy; TMZ, temozolomide; BEV, bevacizumab.

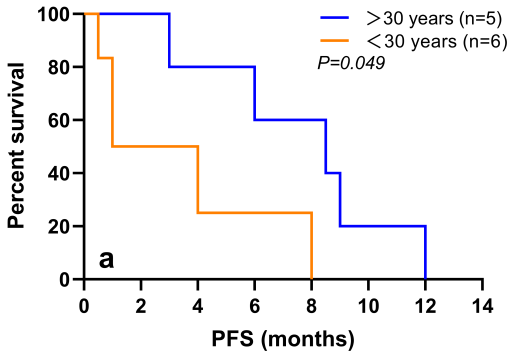
* $p < 0.05$ that indicates statistical significance.

Table 3 Characteristics and outcomes of 57 patients with primary spinal GBM described in 26 recent literature [4,6-28,30,34]

Variable	Value	Information Available for Analysis (n=57)
Mean age, years (range)	31.3 (4-76)	100%
Sex		100%
Male	30 (52.6%)	
Female	27 (47.4%)	
Mean duration of symptoms, months (range)	3.8 (0.3-36)	27/57
Tumor location		100%
Cervical	18 (31.6%)	
Cervicothoracic	6 (10.5%)	
Thoracic	19 (33.3%)	
Thoracolumbar	8 (14.0%)	
Lumbar	3 (5.3%)	
Conus medullaris	3 (5.3%)	
Surgery type		100%
Gross total resection	9 (15.8%)	
Subtotal resection	10 (17.5%)	
Partial resection	11 (19.3%)	
Biopsy	22 (38.6%)	
NOS	5 (8.8%)	
Adjuvant therapy		49/57
RT + CMT	29 (50.9%)	
RT alone	4 (7.0%)	
CMT alone	4 (7.0%)	
None	12 (21.1%)	
CSF dissemination	13 (22.8%)	31/57
Mean follow-up, months (range)	13.3 (0.1-52)	100%
1-year survival (%)	50.2	100%

NOS, not otherwise specified; RT, radiotherapy; CMT, chemotherapy; CSF, cerebrospinal fluid.

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>30 years (n=5)
<30 years (n=6)
P=0.049
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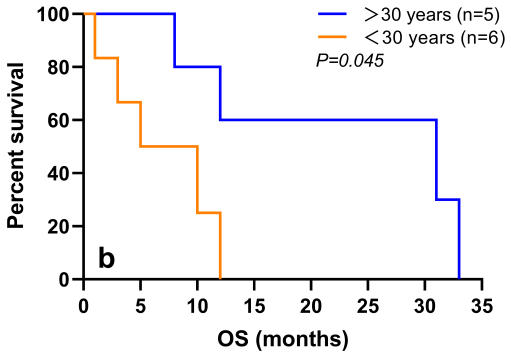
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OS (months)
>30 years (n=5)
<30 years (n=6)
P=0.045
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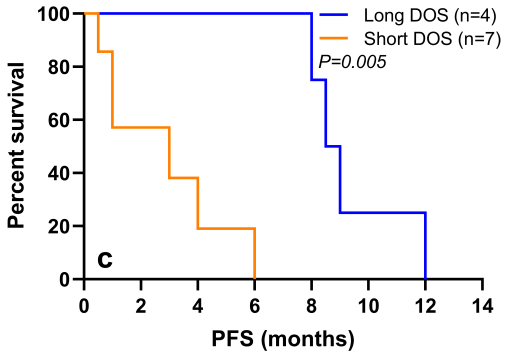
Percent survival
PFS (months)
Long DOS (n=4)
Short DOS (n=7)
P=0.005
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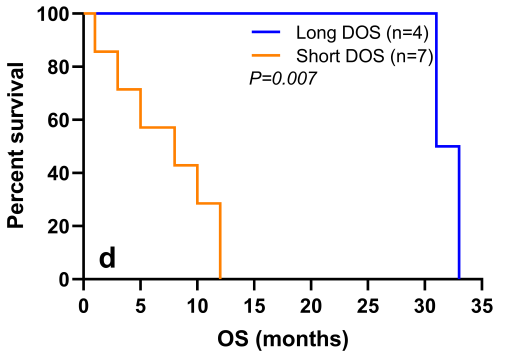
Percent survival
OS (months)
Long DOS (n=4)
Short DOS (n=7)
P=0.007
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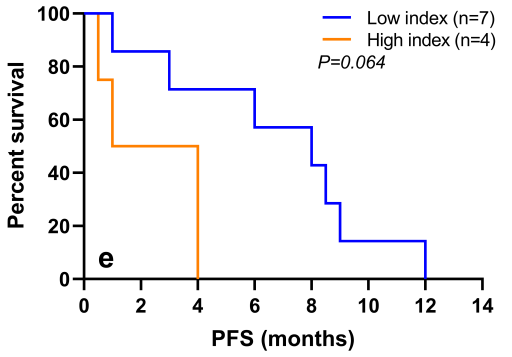
Percent survival
PFS (months)
Low index (n=7)
High index (n=4)
P=0.064
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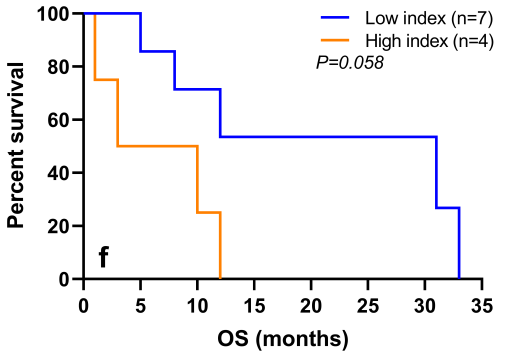
Percent survival
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Low index (n=7)
High index (n=4)
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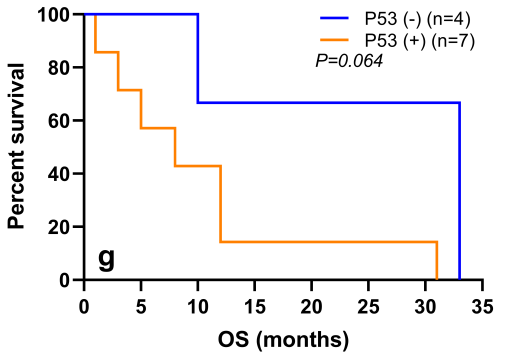
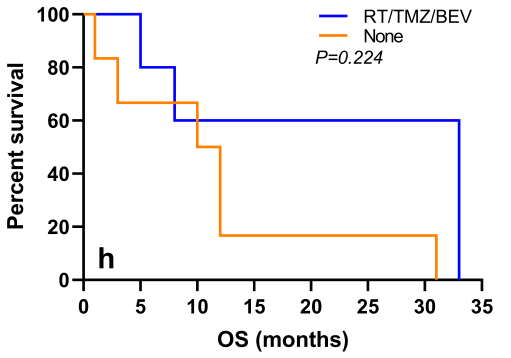

Percent survival
OS (months)
P53 (-) (n=4)
P53 (+) (n=7)
P=0.064
g


Percent survival
OS (months)
RT/TMZ/BEV
None
P=0.224
h

Abbreviations and Acronyms

ASIA: American Spine Injury Association
CMT: Chemotherapy
DFS: Disease-free survival
DMG: Diffuse midline glioma
EOR: Extent of resection
GTR: Gross total resection
IDH: Isocitrate dehydrogenase
IHC: Immunohistochemistry staining
KPS: Karnofsky Performance Status
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival
PR: Partial resection
PSC GBM: Primary spinal cord glioblastoma
RT: Radiotherapy
STR: Subtotal resection
TMZ: Temozolomide

Conflict of interest statement:

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.