Clinical Features and Outcomes of Primary Spinal Cord Glioblastoma: A Single-Center Experience and Literature Review

Kaiyuan Yang[1,2], Weitao Man[1,2], Linkai Jing[1,2], Zhenxing Sun[1,2], Ping Liang[1,2], James Wang[1,2], Guihuai Wang[1,2]

■ 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 were retrospectively reviewed. The clinical, radiologic, 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 was achieved in 8 patients (72.7%) and partial resection in 3 (27.3%). Two patients (18.2%) underwent postoperative adjuvant chemoradiotherapy, 2 patients underwent (27.3%) chemotherapy only, and 6 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 and overall survival were 6.0 (range, 0.5–12.0) months and 12.0 (range, 1.0–33.0) months, respectively, and 1-year survival was 31.8%. Age at diagnosis and duration of the preoperative symptoms were confirmed as prognostic factors of progression-free survival and overall survival in univariate analysis ($P < 0.05$).**

■ CONCLUSIONS: **Despite aggressive treatment, PSC GBM still has a dismal prognosis and leads to severe neurologic deficit. Age at diagnosis and duration of the preoperative symptoms were confirmed as prognostic factors, yet the role of adjuvant radiochemotherapy and extent of resection are still unclear, necessitating further research.**

INTRODUCTION

Spinal cord tumors are rare compared with intracranial tumors, accounting for <10% of all central nervous system neoplasms.[1] Nevertheless, primary spinal cord glioblastoma (PSC GBM) is extremely rare, representing only 1.5% of all spinal cord tumors.[2] Despite the progression of surgical techniques and postoperative adjuvant therapy such as chemoradiotherapy, PSC GBM still shows a gloomy prognosis. The overall survival (OS) of patients with PSC GBM is approximately 10–14 months,[3,4] and the disease often leads to severe neurologic deficit, reducing the quality of life.

To the best of our knowledge, the largest single-center study to date involving 15 patients with PSC GBM was reported by Yi et al. in 2019.[5] However, because of its rarity, most previous studies are merely case reports[4,6-22] or several small sample series.[23-30] Because there are limited studies, the clinical features, optimal therapeutic regimen, and prognosis factors of PSC GBM remain controversial.[29] Herein, we present a consecutive cohort of 11 patients with histologically proven PSC GBM in our center and

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

Abbreviations and Acronyms
ASIA: American Spine Injury Association
DMG: Diffuse midline glioma
GTR: Gross total resection
IDH-1: Isocitrate dehydrogenase 1
KPS: Karnofsky Performance Status
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival
PSC GBM: Primary spinal cord glioblastoma
RT: Radiotherapy
TMZ: Temozolomide

From the [1]School of Clinical Medicine, Tsinghua University, Beijing; and [2]Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

To whom correspondence should be addressed: Guihuai Wang, M.D., Ph.D. [E-mail: guihuai_wang@163.com]

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analyze their clinical, radiologic, operative, and 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 that the present study may provide some new clinical evidence for this extremely rare malignant disease.

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 World Health Organization classification of the central neural system tumors. Eleven patients (78.6%) with PSC GBM were included for analysis because 1 patient was lost to follow-up after discharge and 2 patients had undergone previous 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 arising from primary brain GBM, and MRI of the whole central nervous system was also performed after surgical treatment. All patients underwent maximal safe surgical resection with intraoperative neurophysiologic monitoring. Subtotal resection was defined as surgical removal of $\geq$80% of the tumor on MRI, whereas partial resection was defined as <80% tumor resection. Neurologic examination was assessed in all patients. The modified McCormick classification was used to assess neurologic status, the American Spine Injury Association (ASIA) grading system was used to assess the degree of spinal cord injury, and Karnofsky Performance Status (KPS) scale was used to assess functional status. The assessment was performed before surgery, at 1 week after surgery, at 3 months after surgery, at 1 year after surgery, and semiannually thereafter. Postoperative adjuvant therapies included radiotherapy (RT), chemotherapy, and bevacizumab. The clinical, radiologic, operative, and pathologic information of all patients was recorded.

Molecular Information

The expression of isocitrate dehydrogenase 1 (IDH-1), Ki-67, P53, and H3K27M was detected by immunohistochemistry staining as reported previously.[28,31,32] The Ki-67 index was graded as either high (>40%) or low ($\leq$40%) for analysis, based on the percentage of immunohistochemistry staining–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 progression-free survival (PFS) was defined as the duration between the surgery and the date of recurrence as shown by MRI. The OS was defined as the duration between surgery and death or last known follow-up. All data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, New York, USA) and R software version 3.5.0 (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 the 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 2-sided P value <0.05 was considered statistically significant.

Literature Research

This study retrieved recent literature in the PubMed database with keywords such as "spinal cord GBM multiforme," "spinal cord glioblastoma," and "spinal cord malignant glioma." All 49 articles published during the 5 years from 2015 to 2020 were carefully reviewed by 2 authors (K.Y. and W.M.); the source and date of each patient reported in the literature were also checked to exclude duplicates. The inclusion criteria were as follows: 1) patients with PSC GBM confirmed by surgery and pathologic information; 2) patients with postoperative follow-up >3 months unless they reached the end point; 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 previous resection of spinal cord low-grade glioma or a diagnosis with evidence of secondary metastases from primary brain GBM. A total of 26 studies (involving a total of 57 patients) had outcome data that 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 PSC GBM 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 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 (7 patients, 63.6%), motor deficits (10 patients, 90.9%), sensory disturbance (11 patients, 100%), and sphincter dysfunction (6 patients, 54.5%). The preoperative neurologic examination showed that 4 patients had grade II according to the modified McCormick classification, followed by 2 with grade III and 5 with grade IV. The preoperative ASIA grading system assessment showed that 2 patients presented with an ASIA grade B below the involved spinal cord level, followed by 3 patients with ASIA grade C and 6 patients with ASIA grade D. The clinical data of the 11 patients are listed in **Table 1**.

Radiologic Features

Tumor locations included the cervical region (5 patients, 45.5%), the cervicothoracic region (3 patients, 27.3%), the thoracic region (1 patient, 9.1%), and the thoracolumbar region (2 patients, 18.2%). According to T1-weighted MRI, the tumor signal was isointensity in 5 patients, hypointense in 4 patients, and isohypointense in 2 patients. T2-weighted MRI showed hyperintensity in all patients. Contrast-enhanced T1-weighted MRI showed 9 patients with heterogeneous enhancement and 2

Table 1. Clinical Characteristics of 11 Operated Cases of Primary Spinal Cord Glioblastoma from Our Center

Case	Age (years), Sex	Duration of Preoperative Symptoms	Location	Presentations	Preoperative Status of KPS/ASIA/McC	MRI Features (T1/T2/+GA)	Extent of Resection	Molecular Features	Postoperative Treatment	PFS (months)	Salvage Treatment	Overall Survival (months)	Status at Last Follow-Up
1	10, F	1 month	C2-7, IM	Neck pain, paresthesia, paraplegia, fever, urinary and fecal incontinence	40/C/IV	Isohypo-/hyper-/hetero-	STR	P53 (+)	None	0.5	None	3	Death with recurrence 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 recurrence/dissemination
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 recurrence
4	15, M	2 months	C2-T1, IM	Neck pain, bilateral upper limbs weakness and paresthesia	40/D/III	Iso-/mild hyper-/hetero-	PR	P53 (—)	None	4	None	10	Death with recurrence
5	26, F	0.5 month	C2-6, IM	Right upper limb weakness, pain and numbness; back pain	60/D/II	Hypo-/hyper-/hetero-	STR	IDH-1 (—), P53 (+)	TMZ	1	None	5	Death with recurrence/dissemination
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	IDH-1 (—), H3K27M (+), P53 (—)	TMZ+bevacizumab	9	TMZ+bevacizumab	33	Death with recurrence
7	9, M	3 months	C6-T9, IM	Neck pain, bilateral upper limbs itching, bilateral legs weakness and hypoesthesia; urinary and fecal incontinence	40/C/IV	Iso-hypo-/hyper-/hetero-	PR	IDH-1 (—), H3K27M (—), P53 (+)	None	1	None	12	Death with recurrence and hydrocephalus
8	10, M	4 months	C4-T7, IM, with central nervous system multiple diss	Respiratory failure, paraplegia, bilateral legs hypoesthesia; urinary retention, constipation	20/C/IV	Hypo-/hyper-/hetero-	STR	IDH-1 (—), H3K27M (+), P53 (+)	None	1	None	1	Perioperative death with RF and hydrocephalus
9	44, M	5 months	Medulla-C3, IM	Bil limbs weakness, right limbs paresthesia and back numbness; gait abnormality; dysphagia	60/D/II	Hypo-/hyper-/hetero-	STR	IDH-1 (—), H3K27M (—), P53 (+)	RT (45 Gy)+ TMZ	3	None	8	Death with recurrence/dissemination
10	69, F	10 years	C1-4, IM	Neck and back pain, bilateral limbs weakness, bilateral upper limbs numbness; urinary retention, constipation	50/D/III	Iso-/hyper-/homo-	STR	IDH-1 (—), H3K27M (—), P53 (—)	TMZ	8.5	Bevacizumab	12.5	Alive with recurrence/dissemination
11	12, F	6 months	T11-S2, IM+IDEM	Lumbar pain; progressive bilateral 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 recurrence/dissemination

KPS, Karnofsky Performance Status; ASIA, American Spine Injury Association; McC, McCormick classification; MRI, magnetic resonance imaging; GA, gadolinium administration; PFS, progression-free survival; F, female; IM, intramedullary; Iso-, isointensity; Hypo-, hypointensity; Hyper-, hyperintensity; Hetero-, heterogeneous; Homo-, homogeneous; STR, subtotal resection; RF, respiratory failure; IDEM, intradural and extramedullary; M, male; PR, partial resection; IDH-1, isocitrate dehydrogenase 1; TMZ, temozolomide; RT, radiotherapy.

patients with homogeneous enhancement. MRI of the spine also showed the presence of peritumoral spinal cord edema in all patients and cystic changes in 4 patients; however, syringomyelia was rarely present and was found in only 1 patient. Moreover, MRI showed the presence of intramedullary lesion with exophytic growth in 2 patients. An example is shown in Figure 1.

Treatment and Pathologic Findings

All patients underwent microsurgical exploration through the posterior approach. Six of the patients underwent a laminectomy and the other 5 patients underwent a laminoplasty. STR of the tumor was achieved in 8 patients (72.7%) and partial resection was performed in the other 3 patients (27.3%). Two patients accepted postoperative temozolomide (TMZ) chemotherapy combined with fractionated intensity modulated RT with a total dose of 45 Gy in 25 fractions to the involved spinal cord. Three patients received only TMZ chemotherapy, and 6 patients had neither for various reasons. In addition, 2 patients underwent additional bevacizumab therapy after tumor recurrence as the salvage treatment.

Histopathologic analysis showed that all tumors had typical histologic indications of glioblastoma. Immunohistochemical analysis of IDH-1, Ki-67, P53, and H3K27M were available for 6 (54.5%), 11 (100%), 11 (100%), and 5 (45.5%) patients, respectively. In all detected cases, no patient harbored IDH-1 mutation. P53 mutation was observed in 7 patients (54.5%), and the H3K27M mutation was found in 2 patients (18.2%). In our patient cohort, the median Ki-67 index was 30% (range, 10%–60%), and a high Ki-67 index (>40%) was found in 4 patients (36.4%). These findings are summarized in Tables 1 and 2.

Patient Outcomes and Univariate Analysis of Survival

Concerning neurologic status, 8 patients (72.7%) had a stable or improved modified McCormick score postoperatively. Six patients (54.5%) maintained stable examination results at 3 months follow-up; however, only 1 patient (9.1%) maintained a stable examination at 1 year follow-up assessment. Regarding the degree of spinal cord injury, 6 patients (54.5%) had a stable or improved postoperative ASIA score. At 3 months follow-up, 3 patients (27.3%) had a decrease in their ASIA score and only 1 patient (9.1%) maintained a stable examination result at 1 year follow-up assessment. In addition, KPS was used to assess functional status of the patients. Six patients (54.5%) had a stable or improved postoperative KPS, 4 patients (36.4%) had a stable KPS at 3 months follow-up, and only 1 patient (9.1%) maintained a stable KPS in the subsequent year. However, the worsening of postoperative modified McCormick score, ASIA score, or KPS showed no statistically significant (0.05) correlation with shorter PFS or OS.

In our patient cohort, the follow-up period ranged from 1 to 33 months (mean, 12.4 months).Ten patients experienced recurrence of the tumor, 1 patient died during the perioperative period, and in 6 patients (54.5%) the tumor had disseminated to the different location in central nervous system. Nine patients died and 2 patients were still alive at the last follow-up. The median PFS of 11 patients was 6 months (95% confidence interval, 1.58–10.42

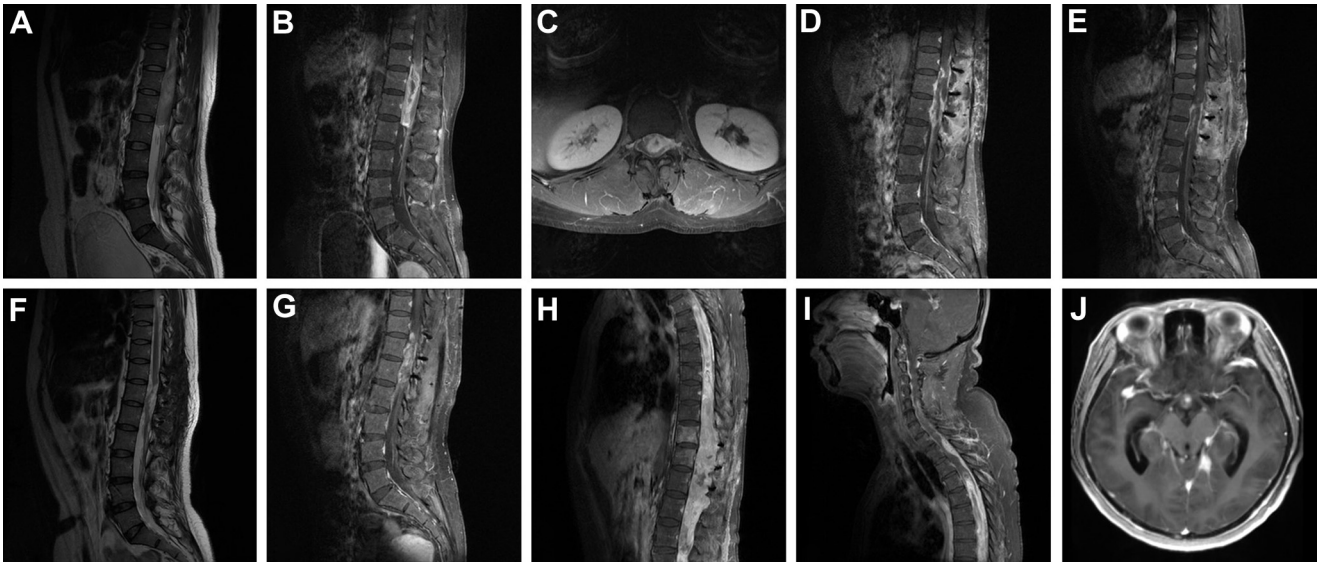

Figure 1. Case 2. Preoperative magnetic resonance imaging (MRI) (**A**–**C**) showing an intramedullary lesion at the T11-L1 level with exophytic growth. The mass showed mild hyperintensity on sagittal (**A**) T2-weighted images (WI) and irregularly heterogeneous enhancement on gadolinium-enhanced sagittal (**B**) and axial (**C**) T1 WI. Postoperative MRI (**D**) showing subtotal resection of the tumor. Follow-up MRI (**E** and **F**) obtained 6 months after surgery showing 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 neurologic and functional status, and follow-up MRI (**H**–**J**) obtained 27 months after surgery showed widespread spinal and intracranial metastasis. The patient died 31 months after her surgery.

Table 2. Univariate Analysis of Survival (Log-Rank Test)

	PFS			OS		
Clinical Factors	**PFS, Median (95% CI)**	**PFS, Mean (95% CI)**	***P* Value**	**OS, Median (95% CI)**	**OS, Mean (95% CI)**	***P* Value**
Age			0.049*			0.045*
<30 years (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 years (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			0.005*			0.007*
<6 months (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 months (n = 4)	8.50 (7.52–9.48)	9.38 (7.61–11.14)		31.00	32.00 (30.04–33.96)	
Preoperative Karnofsky Performance Status			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
Subtotal resection (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)	
Partial resection (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
Radiotherapy/temozolomide/bevacizumab	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; CI, confidence interval; OS, overall survival.
*$P < 0.05$, which indicates statistical significance.

months), the median OS was 12 months (95% confidence interval, 8.33–15.67 months), and 1-year survival was 31.8%. Patient age at initial diagnosis and duration of preoperative symptoms were considered as prognostic factors in univariate analysis ($P < 0.05$). A younger (<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 in the long duration of symptoms group (≥6 months) was significantly longer (median PFS, 8.5 vs. 3.0 months, $P = 0.005$; median OS, 31.0 vs. 8.0 months, $P = 0.007$). 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, $P = 0.064$), although the P value did not achieve statistical significance (0.05). However, extent of resection 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 that met our requirements[4,6-28,30,33] are 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 illness was 3.8 months. Most of the tumors were 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 patients (38.6%). Cerebrospinal fluid dissemination was found in 13 patients (22.8%). Twenty-nine

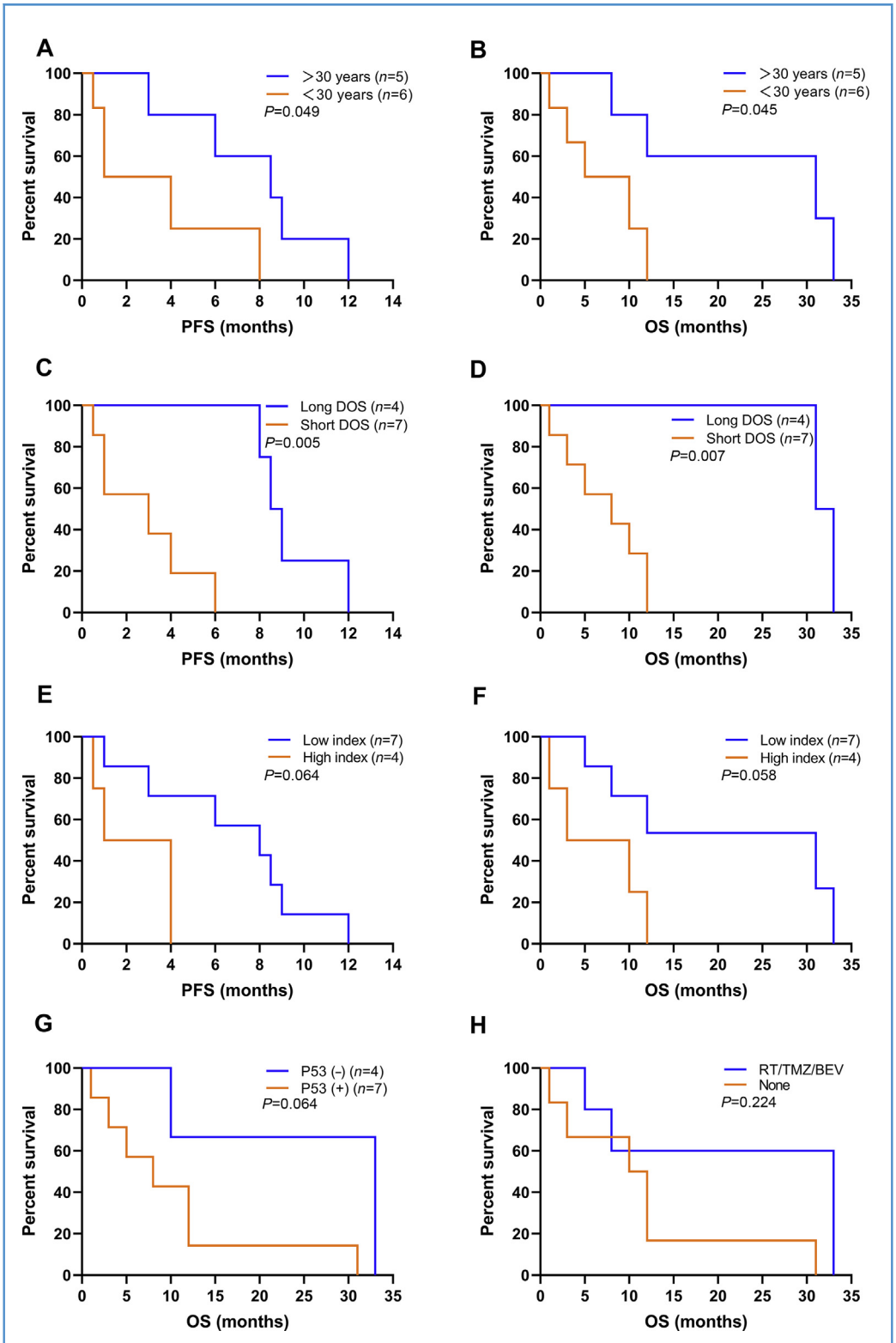

Figure 2. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) rates stratified by covariates in our patient cohort. (**A** and **B**) Comparison of PFS and OS based on patient age at initial diagnosis (<30 and >30 years) in our patient cohort. (**C** and **D**) Comparison 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** and **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 who underwent postoperative adjuvant treatment (radiotherapy [RT]/temozolomide [TMZ]/bevacizumab [BEV]) or not.

Table 3. Characteristics and Outcomes of 57 Patients With Primary Spinal Glioblastoma Described in 26 Recent Reports[6-28,30,34]

Variable	Value	Information Available for Analysis (n = 57) (%)
Age (years), mean (range)	31.3 (4–76)	100
Sex		100
Male	30 (52.6)	
Female	27 (47.4)	
Duration of symptoms (months), mean (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)	
Not otherwise specified	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)	
Cerebrospinal fluid dissemination	13 (22.8)	31/57
Follow-up (months), mean (range)	13.3 (0.1–52)	100
1-year survival (%)	50.2	100

Values are number (%) except where indicated otherwise.
RT, radiotherapy; CMT, chemotherapy.

patients (50.9%) received postoperative RT 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 preoperative symptoms were confirmed as prognostic factors in univariate analysis. PSC GBM can occur at any age from childhood to old age but mainly affects younger patients.[34] In the present study, the youngest patient was 9 years old, whereas the oldest patient was 69 years old. Their median age at diagnosis was 26 years, which is consistent with previous studies.[23,30,34] Moreover, we also found that the median PFS and OS was longer in the older (>30 years) patient group compared with the younger (<30 years) patient group. These results are similar to the findings of Moinuddin et al.[34] and Konar et al.,[35] who both found that older patients (18–65 years) had better OS than did younger patients (<18 years). 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 a long presenting history (≥6 months) had better PFS and OS. The median duration of the preoperative symptoms was 4.0 months, shorter than in other common spinal tumors, which shows the highly aggressive growth pattern and malignant feature of PSC GBM.[26,36]

Molecular biomarkers such as Ki-67, P53, IDH, and H3K27M may be more influential than histopathology alone. Ki-67 represents the proliferation capacity of tumor cells, which could be used to predict the early dissemination of GBM.[37] The higher expression of Ki-67 in tumor cells means that they are more capable of proliferation and invasion, which is associated with a malignant feature and dismal prognosis.[38] In our patient cohort, high Ki-67 index (>40%) was found in 4 of 11 patients (36.4%), which led 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.[39] Different from gliomas in brain, spinal cord gliomas commonly show tumor protein P53 mutation without IDH-1/2 mutation.[40] In our patient cohort of detected cases, no patient harbored IDH-1 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.[38,40] Nevertheless, the survival influenced by Ki-67 index and P53 mutation did not reach statistical significance (0.05), which may be because of the lack of adequate cases.

The prognostic implication of H3K27M mutation in diffuse midline glioma (DMG) has been widely explored in previous studies, most of which have indicated that DMG with H3K27M mutation leads to a dismal clinical outcome.[18,41,42] However, because studies are limited, the prognostic significance of H3K27M mutation in PSC GBM remains unclear and controversial. In the analysis by Yi et al.,[5] patients with PSC GBM with H3K27M mutation showed longer OS and disease-free survival than did patients with H3K27M wildtype. Moreover, these investigators also found that in all 25 patients with PSC grade IV glioma (glioblastoma and DMG with H3K27M-mutation), H3K27M mutation patients still showed longer OS and disease-free survival than did patients with negative K27M mutation, which means that unlike in brain glioma, H3K27M mutation in PSC GBM and DMG is probably not a major gloomy prognostic factor. In contrast, some other studies indicated H3K27M mutation in spinal cord malignant gliomas represents a poor clinical outcome. A retrospectively study by Karremann et al.[41] showed that H3K27M-mutant DMG was significantly associated with a

worse survival across all midline locations including spinal cord, and Uppar et al.[18] reported that a patient with H3K27M-mutation PSC GBM with extremely dismal outcome died on postoperative day 23. We found H3K27M mutation in 2 patients (18.2%) and they showed the shortest and longest survival (1 month vs. 33 months) in our patient cohort.

Despite aggressive treatment, patients with PSC GBM in our cohort reflected a disappointing clinical outcome, with a median OS of 12 months, which is similar to previous studies.[29,30,43] In the univariate analysis of our study, both PFS and OS did not benefit from the extent of resection and postoperative adjuvant treatment (including RT, chemotherapy, and bevacizumab).

Gross total resection (GTR) can significantly improve survival in brain GBM[44]; however, the role of aggressive surgical intervention in PSC GBM is still unclear. Several studies have found that GTR did not benefit patients with PSC GBM and could even worsen postoperative neurologic and functional status.[23,29,30,34,43] These results are consistent with our findings. Thus, in the surgical treatment of PSC GBM, perhaps it is not necessary to pursue GTR. With the advantages of surgical techniques (e.g., intraoperative neurophysiologic monitoring and 5-aminolevulinic acid fluorescence-guided resection), we can perform a maximal safe resection to obtain a histopathologic diagnosis and to decompress the spinal cord, doing our best to avoid causing new and permanent neurologic deterioration.

Similarly, the effectiveness of postoperative RT in spinal cord GBM has been questioned in previous studies. A study involving 14 patients with PSC GBM by Cheng et al.[30] showed a beneficial effect of postoperative RT as an important prognostic factor affecting survival. Liu et al.[45] also found that postoperative RT could prolong the OS in patients with spinal cord high-grade glioma. However, some studies have failed to show its benefit in spinal cord GBM, even showing a negative effect on survival.[29,34] On the other hand, for the risk of spinal cord toxicity and secondary tumors associated with postoperative RT, RT in children may require more careful consideration.[46]

No clinical trials have evaluated the advantage of TMZ in the chemotherapy of PSC GBM. Some previous studies have found that TMZ did not show significantly improved survival in PSC GBM.[34,36,43] However, the combination of postoperative RT and TMZ chemotherapy could contribute to a better survival in PSC GBM.[27,30,35] Moreover, bevacizumab in the treatment of PSC GBM should also be considered because of the value of decreasing peritumoral edema, which brings transient symptom relief and steroid-sparing effects.[47] Chamberlain et al.[48] and Kaley et al.[47] found that bevacizumab as a salvage therapy showed some responses that correlated with clinical improvement in patients with recurrent spinal cord GBM and spinal cord high-grade glioma. In our patient cohort, although survival did not significantly benefit from postoperative adjuvant treatment, an increase of PFS and OS was observed. Therefore, 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 that included only 11 patients. Thus, our statistical data did not have enough power for multivariate analysis to be performed. Second, molecular biomarkers were absent in some patients because of the limited tumor tissue sample. Third, we should continue this present study until the last patient in our cohort reaches the end point, because 2 patients are still alive.

CONCLUSIONS

The present study indicates that PSC GBM is an extremely rare malignant tumor. Because of the absence of an effective therapeutic regimen, PSC GBM has a gloomy prognosis and leads to severe neurologic deficit. According to our study, age at diagnosis and duration of preoperative symptoms were confirmed as prognostic factors. However, the role of adjuvant radiochemotherapy and extent of resection is still unclear and requires further investigation of the multimodal treatment in prospective cohort with a larger sample size.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Kaiyuan Yang: Methodology, Investigation, Software, Formal analysis, Writing - original draft. **Weitao Man:** Investigation, Validation, Data curation, Writing - review & editing. **Linkai Jing:** Formal analysis, Writing - review & editing. **Zhenxing Sun:** Visualization, Validation. **Ping Liang:** Data curation, Software. **James Wang:** Resources, Supervision. **Guihuai Wang:** Conceptualization, Resources, Supervision, Project administration.

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