A systematic review of overall survival in pediatric primary glioblastoma multiforme of the spinal cord

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OBJECTIVE The incidence of primary spinal cord glioblastoma multiforme (GBM) in the pediatric age group is very rare. Only a few case series and case reports have been published in the literature; therefore, overall survival (OS) outcome and the as-yet poorly defined management options are not discussed in detail. The authors performed a cumulative survival analysis of all reported cases of pediatric spinal cord GBM to identify the predictive factors related to final survival outcome.

METHODS A comprehensive search for relevant articles was performed on PubMed's electronic database MEDLINE for the period from 1950 to 2015 using the search words "malignant spinal cord tumor" and "spinal glioblastoma multiforme." This study was limited to patients younger than 18 years of age. Survival rates for children with various tumor locations and treatments were collected from the published articles and analyzed.

RESULTS After an extensive literature search, 29 articles met the study inclusion criteria. From the detailed information in these articles, the authors found 53 children eligible for the survival analysis. The majority (45%) of the children were more than 12 years old. Thirty-four percent of the cases were between 7 and 12 years of age, and 21% were younger than 7 years. In the Kaplan-Meier survival analysis, children younger than 7 years of age had better survival (13 months) than the children older than 7 years (7–12 years: 10 months, > 12 years: 9 months; $p = 0.01$, log-rank test). Fifty-five percent of the children were female and 45% were male. A cervical tumor location (32%) was the most common, followed by thoracic (28.3%). Cervicothoracic (18.9%) and conus (18.8%) tumor locations shared the same percentage of cases. Cervical tumors had a worse outcome than tumors in other locations ($p = 0.003$, log-rank test). The most common presenting symptom was limb weakness (53%), followed by sensory disturbances (25%). Median OS was 10 months. The addition of adjuvant therapy (radiotherapy [RT] and/or chemotherapy [CT]) after surgery significantly improved OS ($p = 0.01$, log-rank test). Children who underwent gross-total resection and RT had better outcomes than those who underwent subtotal resection and RT ($p = 0.04$, log-rank test). Cerebrospinal fluid spread, hydrocephalus, brain metastasis, and spinal metastasis were not correlated with OS in primary spinal GBM.

CONCLUSIONS Adjuvant therapy after surgery had a beneficial effect on overall outcome of spinal GBM in the pediatric age group. Gross-total resection followed by RT produced a better outcome than subtotal resection with RT. Further large-scale prospective study is required to establish the genetic and molecular factors related to OS in primary GBM of the spinal cord in pediatric patients.

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KEY WORDS children; spinal glioblastoma; survival outcome; spine; oncology

AMONG all pediatric tumors in the central nervous system, the incidence of intramedullary spinal cord tumors is less than one-third of 1%, and of these only 1%–3% are high-grade spinal tumors.²⁵ Pediatric glioblastoma multiforme (GBM) differs from adult

GBM in tumor etiology. Pediatric infratentorial GBMs show a molecular karyotype that is more characteristic of pediatric embryonal tumors than adult GBM.⁴⁹ Overall survival (OS) and the management protocol in pediatric GBM also differ from those in adult GBM. Few studies

ABBREVIATIONS CSF = cerebrospinal fluid; CT = chemotherapy; GBM = glioblastoma multiforme; GTR = gross-total resection; HGG = high-grade glioma; NOS = not otherwise specified; OS = overall survival; RT = radiotherapy; STR = subtotal resection.

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have been published on the management of and survival outcome in pediatric intracranial GBM.³⁸ Rarer still is the pediatric primary spinal cord GBM. Hence, treatment protocol and OS are difficult to assess in this group of children. Ononiwu et al.,³⁸ in a study of 8 children with a diagnosis of pediatric spinal cord GBM, reported a median survival of 15 months. In another study, Lober et al.²⁵ wrote about 2 patients with primary pediatric spinal cord GBM, citing an average OS of 14 months. The beneficial role of safe resection and radiotherapy (RT) in intracranial GBM is confirmed in the literature.³⁰ Neurosurgeons and pediatric oncologists must determine if the same principle can be applied in spinal GBM. In this context, our aim was to perform integrative survival analysis by extracting each case from the literature and investigating more precisely the degree of association between the various predictive factors and OS by using Kaplan-Meier analysis.

Methods

Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this study. A search on PubMed's electronic database MEDLINE was performed using standard strings such as "malignant spinal cord tumor" and "spinal glioblastoma multiforme" as well as medical subject headings. The particular search strings used in the PubMed search builder and the number of article titles generated by strings are summarized in Fig. 1 and Table 1.^{2,4,5,8–10,13,17–21,25,27–29,31,32,36,38,42–44,46,48,51,54,56,60} To determine which articles to include, 2 separate reviewers (neurosurgeons) read and screened all titles. The abstracts of selected papers were screened, and data were extracted from those papers after matching the inclusion criteria. After scrutinizing the text of the articles and eliminating duplications, 29 articles were chosen for the final analysis. Non-English language papers were included for analysis only if an English language abstract was available. The availability of individual patient information as regards demographics (age at presentation, sex), spinal tumor location, critical events (death), time to events, and treatment characteristics (extent of resection, RT with or without chemotherapy [CT]) was an important inclusion criterion. A case report reporting on an isolated child younger than 18 years was included for analysis, but articles that reported aggregated data were excluded. Similar studies done in the same place were not included in our analysis to exclude the duplicate patients. Reports from the same institution in different time frames were included after careful examination.

Data Extraction

Demographic features (age, sex), location of tumor, extent of resection, use of adjuvant treatment (RT and/or CT), disease recurrence, OS, and time to recurrence or death were extracted from the included articles. Age was categorized into 3 groups to correlate the impact of age on OS: younger than 7 years, 7–12 years, and older than 12 years.²² Tumors were grouped according to loca-

FIG. 1. Literature search criteria in the selection of articles. Figure is available in color online only.

tion: cervical, cervicothoracic, thoracic, conus, and others (holocord, unspecified). Gross-total resection (GTR), subtotal resection (STR), biopsy, and not otherwise specified (NOS) were the subgroups based on extent of resection. Primary treatment had 4 categories: surgery alone, surgery plus RT, surgery plus CT, and surgery plus RT and CT. Available data on cerebrospinal fluid (CSF) dissemination, hydrocephalus, and brain metastasis were extracted and used to assess OS. The OS (death) was documented from respective articles.

Statistical Analysis

Survival outcome was analyzed with the Kaplan-Meier estimator, and comparison was performed using the log-rank test. For univariate analysis, the Cox regression model was used to demonstrate the impact of individual predictive factors on OS outcome. Hazard ratios with 95% confidence intervals were calculated. The Cox multivariate regression model was applied to assess the interrelationship among the predictive factors and the final outcome. Analyses were performed utilizing SPSS software (version 21, IBM Corp.). A $p < 0.05$ was considered statistically significant.

Results

Patients and Tumor Characteristics

Fifty-three children matching inclusion criteria were subjects in the final analysis (Table 2). The mean age at presentation was 10 years. The majority of children were more than 12 years old (45%), followed by those who were 7–12 years (34%) and those younger than 7 years (21%). In

TABLE 1. Review of the literature on primary spinal GBM in pediatric patients

Case No.	Authors & Year	Age (yrs)/Sex	Level of Tumor	Surgery	RT	CT	Survival (mos)
1	Das et al., 2012	9/F	Thoracic	NR	Y	Y	8
2	Narayana et al., 2010	14/M	C2–7	STR	N	N	2
3	Finlay et al., 1995	9/F	Conus	STR	Y	Y	10
4	Perkins et al., 2011	15/F	C6–7	STR	Y	Y	6
5	O'Halloran et al., 2013	10/F	Cervicothoracic	STR	Y	Y	12
6		10/F	Cervical	GTR	Y	Y	14
7		12/M	Cervical	GTR	Y	Y	14
8		2/M	Thoracic	GTR	Y	Y	30
9		17/F	Thoracic	Biopsy	Y	Y	11
10		14/F	Thoracic	STR	Y	Y	15
11		4/F	Cervical	STR	Y	Y	10
12	Merchant et al., 1999	10/F	Conus	Biopsy	Y	Y	14
13	Kawashima et al., 2004	16/F	Thoracolumbar	Biopsy	Y	Y	12
14	Lam et al., 2012	14/F	C6–T5	GTR	Y	Y	10
15		8/F	C3–T4	STR	Y	Y	14
16	Strik et al., 2000	14/M	Conus	STR	NR	NR	16
17	Banczerowski et al., 2003	16/M	Conus	GTR	Y	N	6
18	Lober et al., 2010	16/M	Cervicothoracic	STR	Y	Y	6
19		8/F	Thoracolumbar	STR	Y	Y	10
20		8/M	Cervical	STR	Y	N	4
21		11/M	Cervicothoracic	STR	Y	Y	17
22	Sharma et al., 2010	14/M	Conus	STR	Y	N	10
23	Campbell et al., 1996	6/M	Thoracic	STR	Y	Y	9
24	Prasad et al., 2012	10/F	Cervical	Biopsy	N	N	3
25	Massimino et al., 2005	14/M	Conus	STR	Y	N	11
26	Ansari et al., 2012	12/F	Cervical	STR	Y	N	6
27		14/F	Conus	STR	N	Y	11
28	Russell & Rubinstein, 1959	18/F	C7–T7	GTR	Y	NR	21
29		3/M	T-7	Biopsy	Y	Y	13
30		14/M	C2–7	STR	Y	Y	9
31		18/F	Cervicothoracic	GTR	Y	N	21
32		18/F	Cervicothoracic	GTR	Y	N	21
33		18/F	Cervicothoracic	GTR	Y	N	21
34	Johnson & Schwarz, 1987	8/F	Cervical	STR	Y	Y	1
35	Kim et al., 2011	12	C1–7	STR	N	N	2
36	McGirt et al., 2008	2/F	C7–T7	GTR	Y	N	14
37		1/M	C7–T2	STR	Y	Y	13
38		1/M	C3–T7	Biopsy	Y	Y	24
39	Adams et al., 2016	4/M	Holocord	STR	N	Y	37
40		13/F	Cervical	GTR	Y	Y	15
41		15/M	Cervical	STR	N	Y	8
42	Pollack et al., 2006	18/M	T9–L1	STR	N	N	3
43	Caroli et al., 2005	10/F	C2–7	STR	Y	N	3
44	Ciappetta et al., 1991	16/F	Conus	NR	Y	NR	6
45		14/M	Conus	NR	Y	NR	4
46		17/F	Thoracic	NR	NR	NR	10
47	Wisoff et al., 1998	1/F	C1–T2	NR	Y	N	64
48		13/M	T9–12	STR	Y	N	1

CONTINUED ON PAGE 242 »

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TABLE 1. Review of the literature on primary spinal GBM in pediatric patients

Case No.	Authors & Year	Age (yrs)/Sex	Level of Tumor	Surgery	RT	CT	Survival (mos)
49	Gee et al., 2012	9/F	Thoracolumbar	NR	Y	N	14
50	Sun et al., 2009	12/F	Conus	NR	NR	NR	11
51	Minehan et al., 2009	18/F	Cervical	STR	Y	N	4
52		1/M	Cervical	STR	N	N	10*
53	Raco et al., 2005	11/F	Cervical	NR	N	N	6

NR = not reported.

* Number of days.

the Kaplan-Meier survival analysis, children younger than 7 years of age had better survival (13 months) than those who were older than 7 years (7–12 years: 10 months, > 12 years: 9 months, $p = 0.01$, log-rank test; Fig. 2). Forty-five percent of the children were male and 55% were female. Patient sex did not influence OS. The most common presenting symptom was limb weakness (53%), followed by sensory disturbances (24%), back pain (21%), and bladder and bowel disturbances (17%). Median OS was 10 months. The 6-month survival rate was 67%, the 12-month rate was 35%, and the 18-month rate was only 9%. Thirty-two percent of the tumors were cervical and 28.3% were thoracic; 18.9% were cervicothoracic and 18.9% were at a conus location (Fig. 3). A cervical location (6 months' survival) had the worst outcome in comparison with thoracic (12 months), cervicothoracic (13 months), and conus (10 months; $p = 0.003$, log-rank test).

Univariate analysis (Table 3) also showed that a cervicothoracic location was associated with both 12-month mortality (HR 0.30, 95% CI 0.09–0.99, $p = 0.048$) and 18-month mortality (HR 0.37, 95% CI 0.15–0.91, $p = 0.03$). Even the Cox multivariate hazard model analysis showed a strong correlation between a cervicothoracic tumor location and OS (HR 0.24, 95% CI 0.09–0.62, $p = 0.004$; Table 4). Thoracic (HR 0.27, 95% CI 0.10–0.72, $p = 0.009$) and conus (HR 0.19, 95% CI 0.06–0.56, $p = 0.003$) locations had an influence on OS as well. Cerebrospinal fluid spread was noted in 42% of the patients, and the median OS in those with CSF dissemination was 10 months. There was no significant difference in OS in the patients with or without CSF dissemination ($p = 0.30$, log-rank test; Fig. 4). Hydrocephalus was noted in 13.2% of patients with 8 months of median survival. The local recurrence rate was 15%. Brain metastasis was noted in 22.6% of the patients with 9 months' median survival. Overall spinal metastasis was noted in 9.4% of the children with a median survival of 11 months.

Extent of Surgery

Subtotal resection was performed in 54.7% of the cases, and GTR was achieved in 17% (Fig. 5). Biopsy was done in 13.2% of the cases. Extent of resection was not related to mortality at 6, 12, or 18 months (Table 3). However, in the Cox multivariate hazard model analysis (Table 4), GTR (HR 0.23, 95% CI 0.07–0.77, $p = 0.01$) had a significant association with OS. The OS after GTR was 14 months in comparison with 9 months for STR.

Surgery Alone Versus Surgery With Adjuvant Therapy

Seventeen percent of the children underwent surgery only. Forty-nine percent received both RT and CT after surgery, 28.3% received only RT after surgery, and 6% received only CT after surgery. Gross-total resection with RT had a better outcome than STR with radiation ($p = 0.04$, log-rank test; Fig. 6). Patients who received adjuvant therapy had a better median survival than those who had surgery alone, as shown in the Kaplan-Meier analysis ($p = 0.01$, log-rank test; Fig. 7). In both univariate and multivariate analyses, the addition of RT and/or CT did not have an association with 6, 12, or 18 months' mortality. Prognosis was the worst in those children who underwent STR without adjuvant therapy (9 months).

Discussion

The management protocol for malignant spinal cord glioma in children is controversial, and clear guidelines are not available to neurosurgeons or oncologists. Knowledge about the survival outcome of a child harboring a malignant spinal cord tumor is essential for a physician to guide caregivers about future treatment. The prognosis of primary spinal GBM, in comparison to intracranial GBM, is not clear despite advances in neuroimaging, microsurgical technique, and oncological therapy. Therefore, we performed a comprehensive literature search to determine all factors predictive of survival in GBM of the spinal cord.

Wolff et al.⁵⁹ reported that an age less than 5 years was related to a superior outcome in malignant spinal cord tumor. In a population-based study, Lam et al.²³ found that an age group 13–18 years old had worse survival than other age groups and that patient sex did not affect OS. In our analysis, we found that the survival rate was better in patients with an age less than 7 years. In intracranial GBM, the mean age at presentation was 8.8–13 years in the literature.^{35,47} The present study showed the mean age at presentation for primary spinal GBM was 10 ± 5.1 years. For intracranial GBM, studies have shown a male predominance. In the present study, however, we found a male/female ratio of 1:1.2; therefore, patient sex did not appear to have any influence on overall outcome.

In a retrospective study,³⁸ a child with thoracic tumor (18.7 months) had better OS than a child with cervical (12.5 months) or cervicothoracic (11.5 months) tumors. In another study,⁴⁵ it was evident that patients with tumors lo-

TABLE 2. Demographic and treatment characteristic of 53 pediatric patients with primary spinal GBM

Variable	No. of Patients (%)	Information Available for Analysis	OS (mos)
Age			
<7 yrs	11 (20.7)	100%	13
7–12 yrs	18 (34)		10
>12 yrs	24 (45.3)		9
Sex			
Male	24 (45.3)	98%	9
Female	29 (54.7)		10
Tumor location			
		100%	
Cervical	17 (32)		6
Cervicothoracic	10 (18.9)		13
Thoracic	15 (28.3)		12
Conus	10 (18.9)		10
NOS	1 (1.9)		37
Symptoms			
Back pain	11 (21)	55%	
Sensory involvement	13 (24)	56.6%	
Extremity weakness	28 (53)	56.6%	
Bladder/bowel disturbance	9 (17)	56.6%	
Surgery type			
		100%	
Biopsy	7 (13.2)		13
STR	29 (54.7)		9
GTR	9 (17)		14
NOS	8 (15)		8
Treatment type			
		100%	
Surgery	9 (17)		3
Surgery+RT	15 (28.3)		6
Surgery+CT	3 (6)		10
Surgery+RT+CT	26 (49)		11
CSF dissemination	22 (41.5)	32/53	10
Brain metastases	12 (22.6)	16/53	9
Spine metastases	5 (9.4)	7/53	11
Recurrence	8 (15)	19/53	13
Hydrocephalus	7 (13.2)	24/53	8

FIG. 2. Comparison of OS based on age (< 7, 7–12, and > 12 years) in children with primary spinal GBM. A $p < 0.05$ was considered statistically significant. cat = category; Cum = cumulative. Figure is available in color online only. **FIG. 3.** Comparison of OS based on tumor location (LOC) in the spinal cord. A $p < 0.05$ was considered statistically significant. Figure is available in color online only.

cated in the cervical region had poorer survival than those with a thoracic tumor location. In the present comprehensive analysis, we also showed that cervical (6 months) tumors had the worst outcome in comparison with thoracic (12 months) and cervicothoracic (13 months) locations ($p = 0.003$, log-rank test). This finding may be attributable to tumor infiltration of the high cervical cord and instability of the cervical spine after surgery.⁴⁵

Because of recent advances in microneurosurgical techniques, extent of resection has a major role in determining OS in malignant spinal cord tumors. Ononiwu et al.³⁸ noted a mean survival of 19.2 months in children who underwent GTR as compared with 12.6 months in those who underwent STR. Wolff et al.⁵⁹ reported that extent of

resection was related to OS in spinal GBM. However, Lam et al.¹ published a conflicting report indicating that extent of resection is not related to OS in spinal GBM.

Extent of resection does play a role in the OS of children with intracranial GBM.^{1,7,12,22,40,58} In pediatric intracranial GBM, the mean survival time of children with GTR was 73.5 months ($p = 0.030$) compared with 13 months in children with STR, as reported by Nikitovic et al.³⁵ Children with GBM treated using GTR had a 5-year progression-free survival of 26% compared with 4% for those with an STR ($p = 0.046$).⁵⁸

In our study, we found that extent of resection does not have a direct relationship with OS. However, GTR plus RT had a more positive impact on OS than STR plus RT ($p =$

TABLE 3. Univariate analyses of risk factors for mortality in 53 patients

Variable	6 Mos*				12 Mos†				18 Mos‡			
	HR	95% CI		p Value	HR	95% CI		p Value	HR	95% CI		p Value
		Upper	Lower			Upper	Lower			Upper	Lower	
Age												
<7 yrs	1	1	1		1	1	1		1	1	1	
7–12 yrs	0.15	0.013	1.785	0.13	0.88	0.24	3.20	0.85	1.00	0.41	2.45	0.98
>12 yrs	0.11	0.010	1.325	0.08	0.74	0.21	2.55	0.63	1.29	0.54	3.09	0.55
Sex												
Male	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
Female	0.68	0.25	1.83	0.44	0.52	0.25	1.07	0.07	0.86	0.47	1.59	0.64
Tumor location												
Cervical	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
Cervicothoracic	0.35	0.07	1.67	0.19	0.30	0.09	0.99	0.048	0.37	0.15	0.91	0.03
Thoracic	2.39	0.47	12.17	0.29	0.29	0.10	0.78	0.014	0.58	0.27	1.23	0.157
Conus	0.44	0.12	1.63	0.22	0.31	0.12	0.81	0.017	0.56	0.25	1.24	0.154
Others	NR	NR	NR	NR								
Surgical intervention												
Biopsy	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
STR	0.66	0.08	5.48	0.70	3.29	0.75	14.44	0.11	1.44	0.58	3.56	0.42
GTR	0.27	0.01	4.75	0.37	2.76	0.37	20.66	0.32	.76	0.24	2.41	0.65
NOS	0.33	0.03	3.51	0.35	2.77	0.54	14.21	0.22	1.57	0.52	4.72	0.42
Treatment type												
Surgery	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
Surgery+RT	0.44	0.15	1.31	0.14	0.86	0.34	2.22	0.77	0.92	0.37	2.24	0.85
Surgery+CT	NR	NR	NR	NR	0.51	0.10	2.45	0.40	0.95	0.22	4.52	0.94
Surgery+RT+CT	0.40	0.09	1.66	0.21	0.42	0.17	1.03	0.06	0.48	0.20	1.06	0.07

Boldface type indicates statistical significance.

* Seventeen deaths.

† Thirty-four deaths.

‡ Forty-six deaths.

0.04, log-rank test). The median survival of patients with intracranial GBM is 13–43 months.^{35,40,53,57} In the present study of spinal GBM, we found a median OS of 10 months. The 6-, 12-, and 18-month survival rates for primary spinal GBM were 67%, 35%, and 9%, respectively.

Lam et al.²³ analyzed the Surveillance Epidemiology and End Results (SEER) data in the pediatric population. They found that the median survival in spinal GBM was 7 months and that the addition of RT does not prolong OS. Ononiwu et al.³⁸ and O'Sullivan et al.³⁷ demonstrated that the addition of RT after surgery could prolong OS. In infants and young patients (< 3 years of age), however, adjuvant therapy is reserved for recurrent malignant spinal cord tumors.¹¹ In contrast, according to 2 other reports, median OS for the child with intracranial GBM was 13.5 months³⁵ and 16 months.³ The Children's Cancer Study Group (CCG)-943 results revealed that CT combined with RT had a significant role in intracranial GBM ($p = 0.026$).¹⁶ Another study⁵⁰ revealed that the 5-year event-free survival was 42% with combination therapy as compared to 6% with radiation alone ($p = 0.01$). The role of preoperative or postoperative CT in pediatric high-grade glioma (HGG) is still debatable. Merchant et al.²⁹ opined that preoperative

CT is beneficial because of the undisturbed microvasculature of the tumor. However, Massimo et al.²⁶ recommended postoperative CT in view of the damaged blood-brain barrier. In the present systematic analysis, we found that a child treated with surgery alone had a worse OS than those treated with surgery plus adjuvant therapy ($p = 0.01$, log rank test). A child who received RT or CT after surgery had an OS of 6 and 10 months, respectively. The OS of a child who received combination therapy consisting of surgery, RT, and CT was 11 months.

Reportedly, leptomeningeal spread is more frequent in spinal GBM (39%) than its intracranial counterpart (27%), and it also limits final survival.^{9,52} However, our study did not provide evidence supporting the assertion that leptomeningeal spread limits final survival. We found CSF dissemination in 42% of cases with a median survival of 10 months. However, children who developed hydrocephalus (13.2%) with spinal GBM had a shorter average survival of 8 months.

Various genetic studies have demonstrated that *EGFR* amplification, *PTEN* mutations, *p16* and *p27* expression, and *IDH* alterations have a lower frequency and that *PDGFR*, loss of heterozygosity on 19q and 22q, and *P53*

TABLE 4. Cox multivariate analysis of OS

Variable	HR	95% CI	p Value
Age			
<7 yrs	1	1	1
7–12 yrs	2.31	0.81–6.61	0.11
>12 yrs	2.32	0.80–6.72	0.12
Sex			
Male	1	1	1
Female	0.91	0.44–1.88	0.81
Location			
Cervical	1	1	1
Cervicothoracic	0.24	0.09–0.62	0.004
Thoracic	0.27	0.10–0.72	0.009
Conus	0.19	0.06–0.56	0.003
Others	0.05	0.003–0.81	0.09
Surgery type			
Biopsy	1	1	1
STR	0.99	0.037–2.64	0.99
GTR	0.23	0.07–0.77	0.01
NOS	0.42	0.098–1.79	0.24
Treatment type			
Surgery only	1	1	1
Surgery+RT	0.64	0.21–1.92	0.43
Surgery+CT	0.45	0.08–2.43	0.35
Surgery+RT+CT	0.37	0.11–1.27	0.116

Boldface type indicates significance.

have overexpression in pediatric HGG.^{39,41,55} In pediatric GBM, Nakamura et al.³³ reported that the high frequency of p53 mutations and loss of heterozygosity on 19q and 22q in children 6 years or older, in comparison with a younger age, influences OS. The DNA methylation of GBM has

FIG. 4. Comparison of OS based on CSF dissemination in children with primary spinal GBM. A $p < 0.05$ was considered statistically significant. Figure is available in color online only.

FIG. 5. Comparison of OS based on surgery (Sx) category. A $p < 0.05$ was considered statistically significant. Figure is available in color online only.

been established as a biomarker for anticipating the gain of temozolomide CT, especially in elderly GBM patients. Meanwhile, both the frequency (16%–50%) and the prognostic importance of O⁶-methylguanine-DNA-methyltransferase (MGMT) silencing in pediatric HGG remain controversial.⁵³ The molecular target for pediatric GBM is vascular endothelial growth factor (VEGF). However, the beneficial results of adding bevacizumab to the treatment protocol for intracranial GBM are debatable.³⁴ Other factors—for example, fibroblast growth factor (FGF), epidermal growth factor receptor (EGFR), and platelet-derived growth factor (PDGF)—are under investigation in the management of pediatric malignant tumors.¹⁴ The introduction of Nimotuzumab (humanized IgG1 monoclonal

FIG. 6. Comparison of OS between GTR and RT versus STR and RT. A $p < 0.05$ was considered statistically significant. Figure is available in color online only.

FIG. 7. Comparison of OS between surgery alone versus surgery with adjuvant therapy in children with GBM. A $p < 0.05$ was considered statistically significant. Figure is available in color online only.

antibody), either alone or with RT and CT, is the latest achievement.⁶ It works against EGFR and has shown OS of 32.66 months and a 2-year survival rate of 54.2% in pediatric intracranial HGG. The pending administration of the histone deacetylase (HDAC) inhibitor⁶ vorinostat in the treatment of recurrent GBM may be a new direction even in spinal GBM. Faury et al.¹⁵ compared pediatric and adult GBM samples for activation of Ras and Akt pathways and revealed a subset of pediatric GBMs with activation of the pathways, a neural stem cell phenotype, and a very poor prognosis. This pediatric GBM subset was distinct from the adult subset and showed nuclear overexpression of Y-box binding protein 1 (YB-1). However, as spinal GBM is a rare tumor in the pediatric population, it would be difficult to find out the predictors from molecular data unless more cases are reported in the future. Therefore, we need a large-scale prospective study addressing all of these molecular factors to assess their impact on OS in spinal GBM in the pediatric population.

Study Limitations

Our analysis was primarily based on case reports and small case series because of the very low incidence of primary spinal GBM. Therefore, the inherent bias of treatment selection could not be avoided. Neither does our study include radiological findings such as the presence of a cyst or information regarding radiation dosage. Given the scarcity of information regarding type, duration, and doses of CT, we were unable to include that information in the final analysis. The pooled data may not be an accurate reflection of all pediatric spinal GBM as only articles published in English were included in the study. Moreover, the contradictory results in the univariate and multivariate analyses is possibly attributable to 1) the effect of unequal sample sizes, 2) the impact of missing data, and 3) the presence of interaction with other variables.²⁴ The major strength of our study is that it consists of the largest number of cases of primary GBM of the spinal cord in the pediatric age group.

Conclusions

Determining the optimal management protocol for primary spinal GBM in the pediatric age group is difficult given the rarity of cases. The mainstay of treatment for spinal GBM remains surgery followed by adjuvant therapy. Results of the present study favored RT after GTR of the tumor. Older age, cervical location, and surgery alone are the factors predictive of poor OS.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Konar. Acquisition of data: Konar. Analysis and interpretation of data: Konar, Bir, Maiti. Drafting the article: Konar. Critically revising the article: all authors. Reviewed submitted version of manuscript: Nanda. Approved the final version of the manuscript on behalf of all authors: Nanda. Statistical analysis: Konar, Bir, Maiti. Study supervision: Nanda.

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