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REVIEW ARTICLE

Primary and metastatic glioblastoma of the spine in the pediatric population: a systematic review

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Abstract

Pediatric glioblastoma multiforme (GBM) involving the spine is an aggressive tumor with a poor quality of life for patients. Despite this, there is only a limited number of reports describing the outcomes of pediatric spinal GBMs, both as primary spinal GBMs and metastases from an intracranial tumor. Here, we performed an individual patient meta-analysis to characterize factors affecting prognosis of pediatric spinal GBM. MEDLINE, Embase, and the Cochrane databases were searched for published studies on GBMs involving the spine in pediatric patients (age ≤ 21 years old). Factors associated with the survival were assessed with multi-factor ANOVAs, Cox hazard regression, and Kaplan-Meier analyses. We extracted data on 61 patients with spinal GBM from 40 studies that met inclusion criteria. Median survival was significantly longer in the primary spinal GBM compared that those with metastatic GBM (11 vs 3 months, $p < 0.001$). However, median survival of metastatic GBM patients was 10 months following diagnosis of their primary brain tumor, which was not different from that of primary spinal GBM patients ($p = 0.457$). Among primary spinal GBM patients, chemotherapy (hazard ratio (HR) = 0.255 [0.106–0.615], $p = 0.013$) and extent of resection (HR = 0.582 [0.374–0.905], $p = 0.016$) conferred a significant survival benefit. Younger age (less than 14 years) was associated with longer survival in patients treated with chemotherapy than those who did not undergo chemotherapy ($\beta = -1.12$, 95% CI [− 2.20, − 0.03], $p < 0.05$). In conclusion, survival after presentation of metastases from intracranial GBM is poor in the pediatric population. In patients with metastatic GBM, chemotherapy may have provided the most benefit in young patients, and its efficacy might have an association with extent of surgical resection.

Keywords Glioblastoma multiforme · Grade IV glioma · Spinal metastasis

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Introduction

Glioblastoma (GBM) is an aggressive tumor that affects the central nervous system (CNS) and accounts for up to 7% of all primary CNS tumors in children [1, 2]. The majority of pediatric GBMs are intracranial at presentation [1, 2]. Pediatric spinal GBMs, either as a primary or metastasis from the brain are uncommon [3]. In addition to neuromotor deficits, children with spinal GBMs tend to have debilitating pain, which present significant challenges to their care. There is a considerable volume of literature on the natural history, risk factors, effectiveness of maximum safe resection, and adjuvant chemoradiation, as well as several guidelines to guide the management of adult brain and spinal GBMs. However, other than a limited number of case reports, there has been very minimal focus on pediatric GBMs, especially spinal GBMs. This is likely due in part to a perceived ineffectiveness of standard GBM treatments for pediatric spinal GBMs, or perhaps due to

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paucity of data on the natural history of spinal GBMs in the pediatric population [3, 4]. This study presents a meta-analysis of individual patient data in the literature to characterize the risk factors, natural history, and prognosis of primary and metastatic pediatric spinal GBM, to help guide treatment, end of life care decisions, and future guidelines on the management of affected children.

Methods

Information sources, protocol, and eligibility criteria

MEDLINE, Embase, and Cochrane databases were searched for all peer reviewed papers published in English or French that reported individual data on pediatric patients (age less than 21 years old) who were treated for spinal GBM. Exclusion criteria were non-grade IV astrocytomas (WHO classification [5]), lack of follow-up, and lack of a clear description of GBM treatment regimen. The last search was conducted on December 4, 2019. This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [6].

Search, study selection, and data extraction

A search strategy for all papers related to pediatric spinal GBM was developed in consultation with a research librarian (Z.P.) (Fig. 1, Appendix A). Additional papers were found by manually searching the reference lists of included studies. Utilizing the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) [7], retrieved titles were deduplicated; then, abstract and full-text reviews were performed by two reviewers independently (R.Y. and M.C.). Individual patient data were extracted in duplicate, and all conflicts at each stage of the review were resolved by discussion. For each patient, the following data were retrieved: age, sex, brain region affected by GBM (frontal, temporal, parietal or occipital) and extent of resection (biopsy, subtotal resection, gross total resection), spinal cord segments with GBM (cervical, thoracic, lumbar, or holocord), presence or absence of any non-surgical treatment regimen for brain and/or spinal GBM (chemotherapy or radiation therapy), and length of survival following treatment.

Summary and outcome measures

The primary outcome was survival following initial brain and/or spine GBM diagnosis. Secondary outcomes were time elapsed between diagnoses with brain GBM and spinal metastases, and survival after spinal metastasis diagnosis. Primary (brain or spine) GBM diagnosis required pathological confirmation of tumor. Spinal metastasis was defined as a solid intradural GBM at any level below the brainstem that was not present at the time of initial intracranial GBM diagnosis. Brainstem GBMs were considered to be intracranial tumors. Given the lack of a uniform definition of leptomeningeal disease in the literature [8, 9], leptomeningeal metastases alone without an associated solid tumor were excluded. Treatment modalities for GBM were restricted to biopsy, subtotal resection (STR), gross total resection (GTR), and any use of radiation therapy or chemotherapy. Since majority of patients receive corticosteroid therapy during tumor management, and is often poorly reported, steroids were not included in our treatment outcome analyses.

Statistics

All statistical analyses were performed with *R* v3.6.0 [10]. Normality of data was assessed to determine data heteroscedasticity. Age and gender differences were assessed using an independent *t*-test and Fischer's exact test, respectively. A Cox-proportional hazard model was used to determine the effect of age, extent of resection, and chemotherapy on overall survival. Hazard ratios (HR) were reported with a 95% confidence interval. A two-way ANOVA was subsequently conducted to assess for interactions between age, chemotherapy, and survival. Kaplan-Meier analyses with log-rank testing compared overall survival based on use of chemotherapy, extent of intracranial GBM resection, and outcomes between primary vs metastatic spinal GBM. An alpha value of 0.05 was considered statistically significant.

Results

Patient characteristics

From 40 studies included [11–45], 61 individual patients were retrieved (Fig. 1, Supplemental Table 1 & 2). Of those patients, 47 and 14 presented with a primary spinal GBM or spinal metastases, respectively. There were no age or sex differences between groups ($p = 0.13$ and $p = 1.00$, respectively). The median duration to diagnosis of spinal metastases following the intracranial disease was 5 months (Table 1). Diagnoses of spinal metastases were made with neuroimaging in 12 patients, exploratory laminectomy in one patient, and with an autopsy in one patient. The majority of the primary intracranial tumors within the metastatic group were lobar (64%), whereas the remainders were located in the pons and cerebellum. While the combinations of initial treatment for their intracranial disease varied, majority of the spinal metastatic patients (36%) underwent subtotal resection with adjuvant chemoradiotherapy (Table 1). Similarly, treatment for the primary spinal GBM patients was highly variable with the majority

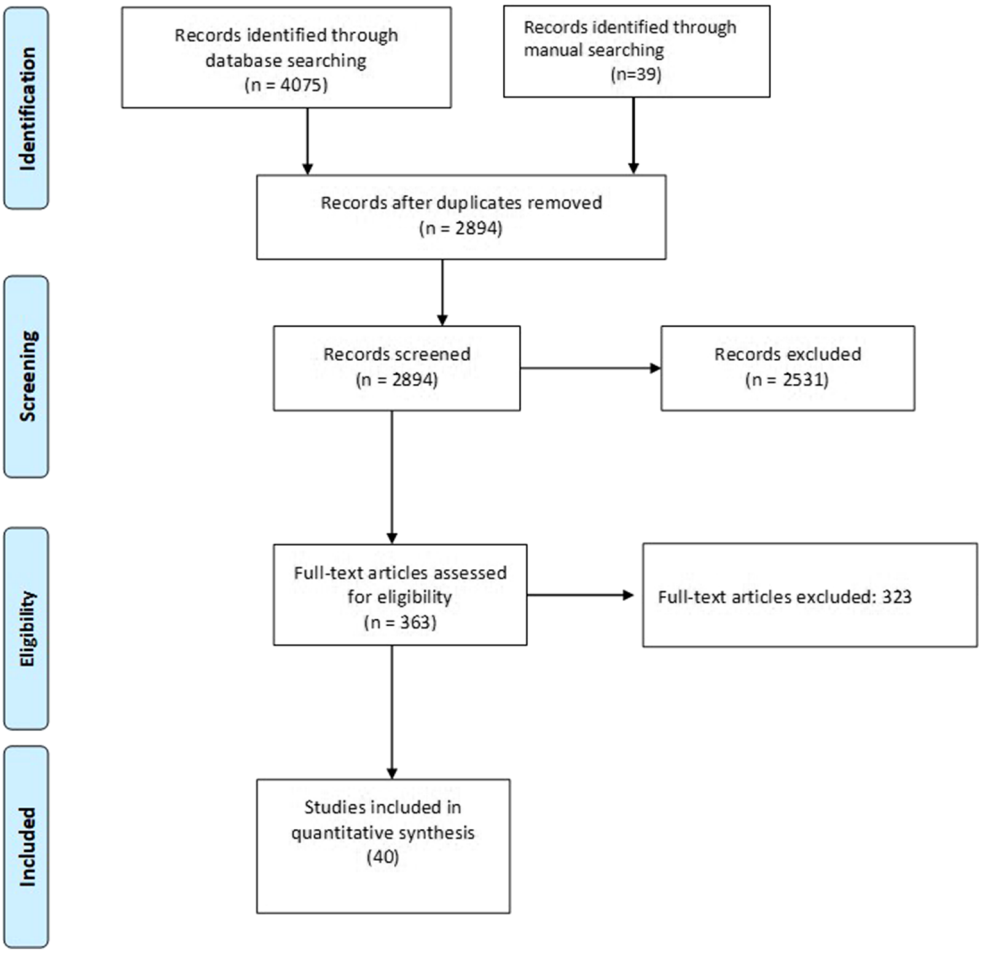

Fig. 1 PRISMA flow diagram. Search algorithm and criteria are described in detail in Appendix A

(38%) of patients undergoing subtotal resection with adjuvant chemoradiotherapy (Table 1).

Patient survival and tumor recurrence

The median duration from diagnosis of spinal GBM to death among the primary spinal GBM group was over 3 times as long as that of the metastatic group, 11 vs 3 months, respectively ($p < 0.001$) (Table 1; Fig. 2a). However, there was no difference in survival times when comparing the durations between their initial presentation with a primary tumor to death, i.e., primary spine GBM group (11 months) vs primary brain in the metastatic group (10 months) ($p = 0.46$, Fig. 2b).

Effects of treatment on survival

A Cox-proportional hazard model revealed that among patients with primary spinal GBM, chemotherapy (HR = 0.25 [0.11–0.62], $p = 0.01$) and aggressive resection (HR = 0.58 [0.37–0.91, $p = 0.02$] had an effect on survival. However, age did not affect survival (HR = 0.98 [0.91–1.05], $p = 0.52$). There was a negative interaction between age at diagnosis and treatment with chemotherapy on overall survival ($\beta = -1.12$, 95% CI [− 2.20, − 0.03], $p < 0.05$), indicating that the impact of chemotherapy on overall survival changes depending on the age of the patient. The survival benefit conferred by chemotherapy declined as age increased, suggesting that chemotherapy provides a significant survival benefit in younger, but not older patients. The 95% confidence interval of the two groups (with and without chemotherapy) converge at 14 years of age, which implies that the use of chemotherapy loses its survival benefits around this age (Fig. 3). For patients treated with biopsy or STR, the use of chemotherapy was associated with longer survival compared to no chemotherapy (Fig. 4). However, the effect of chemotherapy was more pronounced in the biopsy group (median survival 3 months vs 11 months) compared to STR group (median survival 6 months vs 10 months).

Discussion

Pediatric spinal GBM is associated with a decreased quality of life [46]; however, reports on the factors associated with patient prognosis in relation to treatment approaches for spinal GBM are limited, and the only factor associated with an

Table 1 Characteristics of 61 pediatric patients with spinal GBM

	Primary spinal GBM	Metastatic spinal GBM	Total
Number of cases	47	14	61
Sex			
Male	23 (49%)	5 (36%)	28
Female	24 (51%)	7 (50%)	31
Not reported	0 (0%)	2 (14%)	2
Age at first presentation (years)*	13	9.5	-
Spinal tumor location			
Cervical	14 (29%)	3 (21%)	
Cervico-thoracic	6 (13%)	0 (0%)	
Thoracic	11 (23%)	2 (14%)	
Thoracolumbar	2 (4%)	1 (7%)	
Lumbar	0 (0%)	0 (0%)	
Conus	8 (17%)	0 (0%)	
Holocord	3 (6%)	3 (21%)	
Unspecified	3 (6%)	5 (36%)	
Treatment for intracranial GBM			
Biopsy + RTX	-	2 (14%)	
RTX alone	-	2 (14%)	
RTX + CTX	-	2 (14%)	
SX + RTX	-	3 (21%)	
SX + RTX + CTX	-	5 (36%)	
Treatment of spinal GBM			
Biopsy	0 (%)	1 (7%)	
CTX	0 (%)	1 (7%)	
RTX	0 (%)	2 (14%)	
Biopsy + RTX	3 (6%)	0 (0%)	
Biopsy + RTX+ CTX	7 (15%)	0 (0%)	
STR + RTX	6 (13%)	1 (7%)	
STR + CTX	3 (6%)	0 (0%)	
STR + RTX+ CTX	18 (38%)	0 (0%)	
GTR + RTX	1 (2%)	0 (0%)	
GTR + RTX+ CTX	8 (17%)	0 (0%)	
Unspecified	1 (2%)	9 (64%)	
Time to spinal metastases (range) (months)*	N/A	5 [1–16]	
Survival after spinal metastases (range) (months)*	N/A	3 [0.5–10.3]	
Overall survival [Range] (months)*	11 [2.25–37]	10 [1.75–22]	

RTX, radiation therapy; *CTX*, chemotherapy; *GTR*, gross total resection; *STR,* subtotal resection; *SX*, surgery extent of resection not specified

*Medians

improved outcome is younger age [47, 48]. This meta-analysis of individual patient data investigated factors affecting survival in pediatric patients with primary or metastatic spinal GBM. In summary, median survival of those patients with metastatic spinal disease was 10 months after diagnosis of primary brain tumor, and 3 months after diagnosis of spinal metastases. Overall survival in those children with primary spinal GBM was 11 months. Chemotherapy conferred a survival benefit in an age-dependent manner. In addition, use of chemotherapy was associated with relatively longer survival in patients treated with biopsy and to a lesser extent in patients treated with STR.

Pediatric brain GBM typically has a survival of 14 months [49]. Interestingly, as found in this study, intracranial GBM patients who develop spinal metastases tend to have a shorter overall survival of 10 months, and only a 3-month survival

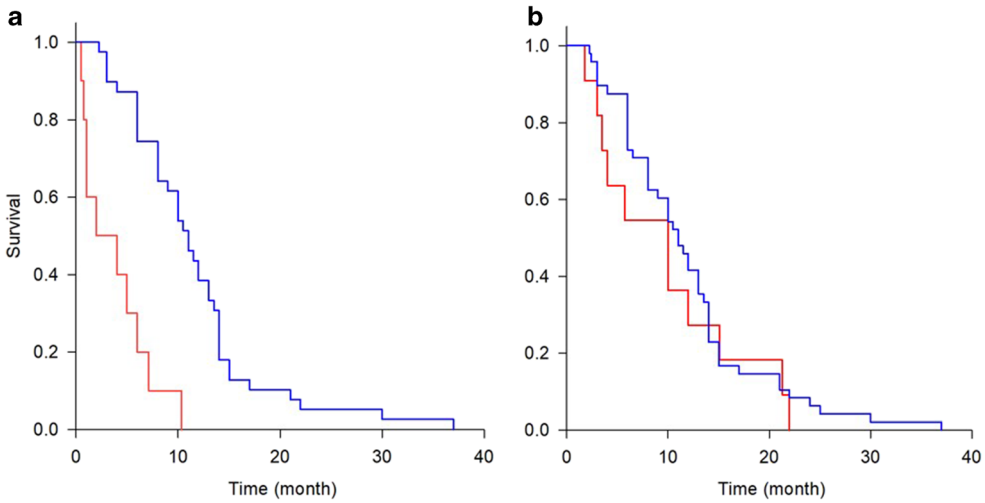

Fig. 2 Kaplan-Meier survival curves comparing the prognosis of pediatric primary spinal GBM patients (blue line) with metastatic spinal GBM patients (red line). Metastatic spinal GBM was associated with poorer survival after presentation compared with primary spinal disease ($p < 0.001$) (**a**). However, when incorporating the metastatic group's initial intracranial presentation into their survival calculations, there was no difference in overall survival between the two groups ($p = 0.46$) (**b**)

following spinal metastasis diagnosis. Perhaps, the shorter survival among metastatic patients is to be expected because development of metastatic disease is likely associated with a relatively greater tumor burden of the primary tumor. It is also possible that intracranial GBM with the propensity to metastasize to the spine may be more aggressive and could potentially have different molecular characteristics. Indeed, it has been shown that *H3F3A*, a gene important in histone methylation, is an important gene associated with the location of GBMs [50]. Sturm et al. showed that tumors harboring mutations in *H3F3A* were likely to occur in pediatric patients, with the tumors arising predominantly from midline structures

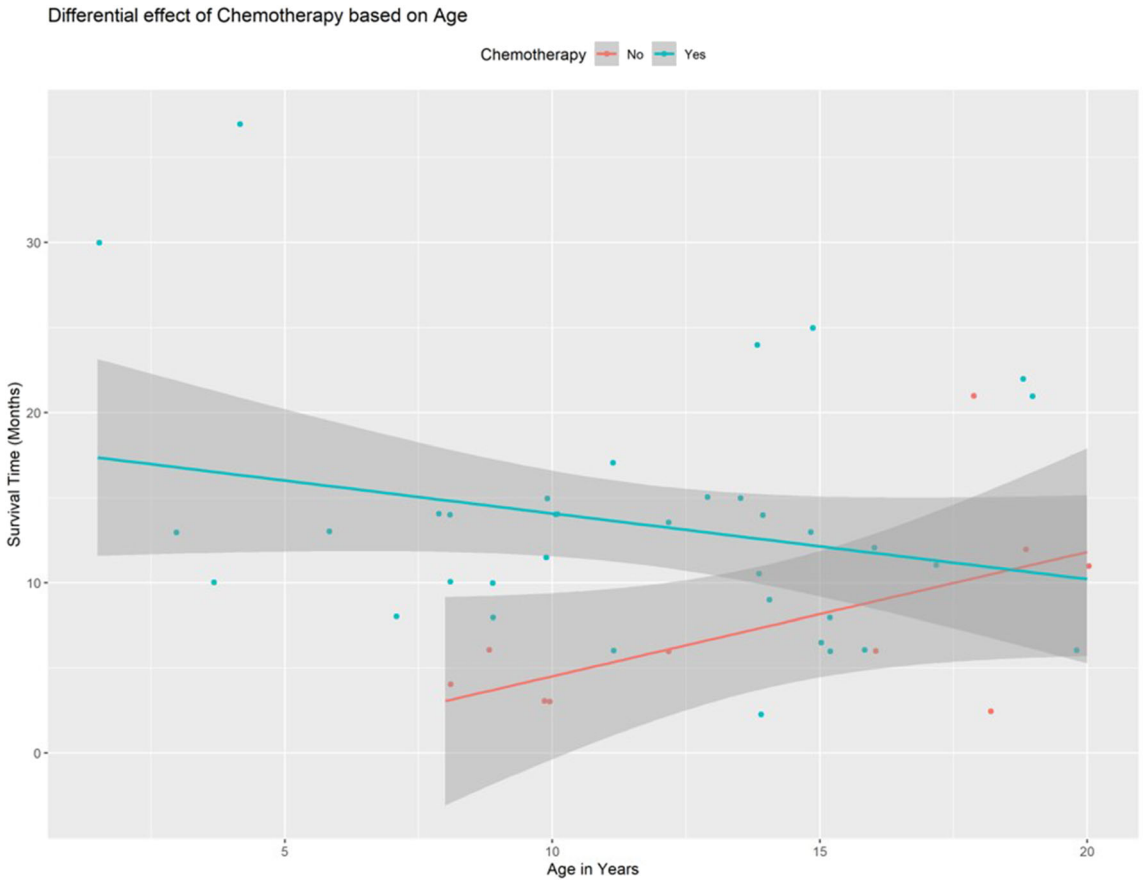

Fig. 3 Differential effect of CTX and age of presentation on survival. There was a significant interaction effect between the presence of chemotherapy and patient age. The data revealed that chemotherapy improves survival at young ages, and the impact on survival diminishes as age increases. The 95% confidence intervals overlap at 14 years of age, suggesting that the benefit of chemotherapy is likely lost around this age

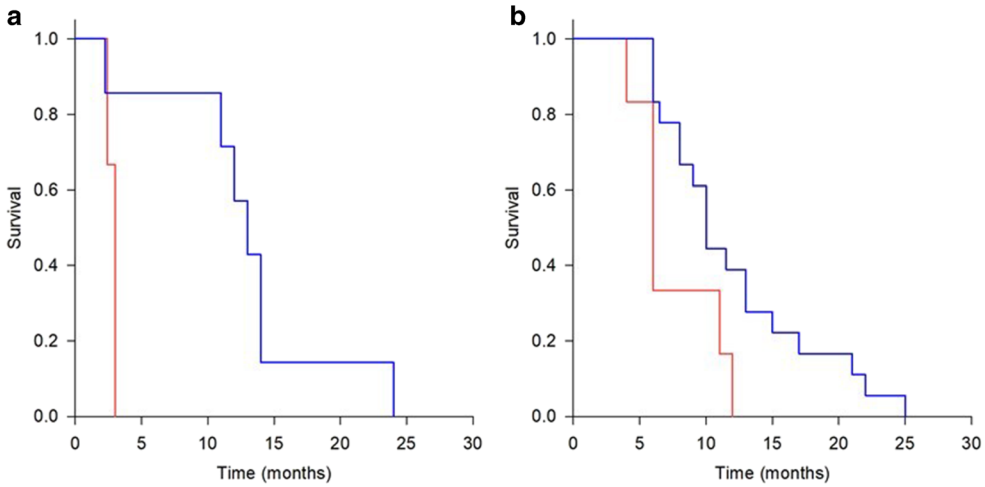

Fig. 4 Chemotherapy has a significant impact on survival in primary spinal GBM patients that were concurrently treated with radiation. Patients treated with biopsy and chemotherapy had significantly prolonged survival compared to biopsy alone (median survival 3 months without chemotherapy vs 13 months with chemotherapy, $p = 0.03$) (**a**). Chemotherapy significantly prolonged survival in patients receiving subtotal resection of the tumor (median survival 6 months without chemotherapy, vs 10 months with chemotherapy $p = 0.04$) (**b**)

(thalamus, pons, spinal cord). These tumors behave very aggressively and are associated with poor prognoses [50]. Although the mechanism of extracranial metastases remains unclear, two main mechanisms of spread have been suggested [51]. Frank et al. suggested iatrogenic seeding following surgery as a major mechanism for GBM spread. In addition, tumor cells could also spread via the CSF pathways and lymphatics [51]. Therefore, the faster time to metastasis in the pediatric metastatic patients could be due to residual tumor spread through the CSF following STRs.

Modeling the effect of age and chemotherapy on survival in primary spinal GBM patients suggested that chemotherapy may have had the largest benefit on overall survival in young patients, and after 14 years of age, chemotherapy did not have a significant impact on survival. Thus, the age-chemotherapy interaction could be explained by the fact that various GBM subtypes respond differently to chemotherapy. This notion is supported by previous studies that compared the molecular profiles of pediatric high-grade gliomas (pHGG) to adults, and to sub-categorize pHGG [52, 53]. Paugh et al. showed several distinct differences between pHGGs and their adult counterpart. Gain of function of chromosome 1q gain was more common, while chromosome 7 gain and 19q loss were less common in pHGGs compared to adults [52]. Within pHGGs, evidence suggests that tumors of children aged 14 or older show much more resemblance to adult secondary GBMs compared to primary pHGGs [52–54]. Furthermore, Paugh et al. found that children below 3 years old had overall significantly longer survival, and no associated 1q gain, representing a distinct subtype of tumors. Children aged 3–14 represent another distinct group and can be further divided into one of 3 sub-groups with overexpression genes involved in cell cycle regulation, neuronal differentiation, and cell adhesion, respectively. Thus, it would appear that there are three distinct entities among pediatric GBMs, and evidence supporting this could also be seen in the Surveillance, Epidemiology, and End Results (SEER) database [52–54].

Age is also an important prognostic factor in high-grade pediatric spinal cord astrocytoma. Luksik et al. and Lam et al. reported that patients above 14 years old had a significantly shorter survival compared to younger patients, further supporting the notion that the genetics of pediatric gliomas change with age [47, 48]. Thus, it is possible that the age-chemotherapy interaction that we observed is driven by the differential response to chemotherapy by the different subtypes of GBMs. Further studies with larger sample sizes are needed to examine relationships between age, chemotherapy, genetic subtypes, and survival and to further characterize the impact of these variables on prognosis.

In this study, extent of spinal cord tumor resection was associated with an increase in survival in primary spinal GBM patients; the larger the percent volume of tumor resected, the better the survival. Among all patients who underwent radiation therapy, the survival advantage conferred by chemotherapy was associated with extent of spinal cord tumor resection. Chemotherapy was associated with longer survival in patients who had a biopsy than those who underwent STR. These findings may reflect a selection bias in that patients who do not undergo tumor excision surgery typically present with unresectable lesions and would have had higher disease burden at the start of chemotherapy, making any strides made with medical management more noticeable.

A major limitation of our study is the small sample size, which limited our ability to rigorously assess several important factors, especially the effect of extent of resection on survival. Patient treatments were heterogeneous across studies, with a variety of chemotherapy agents (ranging from

methotrexate to temozolomide to CCNU) and varying radiation doses employed. Given the heterogeneous chemotherapy regimen, we were not able to assess the interaction of chemotherapy with the extent of surgery. These limitations underscore the need for larger multi-centered study designs.

Conclusion

Spinal GBM in the pediatric population is rare, and little is known about the prognostic factors. We reviewed all available cases from the literature and found the prognosis of spinal GBM to be poor, with a median survival of 11 months in primary spinal GBMs and a 3-month survival after diagnosis with GBM metastases to the spine. We found that for primary spinal cord GBM, chemotherapy significantly increased overall survival in patients 14 years and younger, and its efficacy decreased with increasing age. These novel findings are an important first step to defining the prognostic factors of pediatric spinal GBM, and future studies with larger, homogenous sample sizes are needed to explore the spectrum of the disease as well as viable treatment options to improve patient outcomes.

Appendix. Searches were run in December 4th, and references were downloaded in ris format and uploaded to Covidence for deduplication

Table 2. Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to December 03, 2019

Number	Searches	Results
1	Glioblastoma/	24046
2	(glioblastoma* or glyoblastoma* or spongioblastoma or gliosarcoma* or ((“high grade” or malignant or “grade IV” or “grade V” or “grade 4” or “grade 5” or brain*) adj5 glioma*) or GBM or “WHO grade IV”).tw,kf.	53420
3	((“high-grade” or malignant or “grade IV” or “grade 4”) adj3 astrocytoma*).tw,kf.	2270
4	(glioma* adj15 metasta*).tw,kf.	1965
5	1 or 2 or 3 or 4	58170
6	Spinal Neoplasms/or exp Spinal Cord Neoplasms/	23717
7	(spinal or spine or intramedullary or intradural or extradural or “dura mater” or intraspinal or dural or leptomening* or vertebr* or holocord* or thoracolumb* or cervico* or conus or (cerebrospinal adj5 (metasta* or spread*))).tw,kf.	539926
8	6 or 7	545656
9	5 and 8	1567
10	animals/ not humans/	4615227
11	9 not 10	1484

Table 3. Database(s): Embase 1974 to 2019 December 03. Search strategy:

Number	Searches	Results
1	exp glioblastoma/	63852
2	(glioblastoma* or glyoblastoma* or spongioblastoma or gliosarcoma* or ((“high grade” or malignant or “grade IV” or “grade V” or “grade 4” or “grade 5” or brain*) adj5 glioma*) or GBM or “WHO grade IV”).tw,kw.	80467
3	((“high-grade” or malignant or “grade IV” or “grade 4”) adj3 astrocytoma*).tw,kw.	2985
4	(glioma* adj15 metasta*).tw,kw.	2827
5	1 or 2 or 3 or 4	95512
6	exp spine tumor/or spinal cord tumor/or exp spinal cord cancer/	22963
7	(spinal or spine or intramedullary or intradural or extradural or “dura mater” or intraspinal or dural or leptomening* or vertebr* or holocord* or thoracolumb* or cervico* or conus or (cerebrospinal adj5 (metasta* or spread*))).tw,kw.	664224
8	6 or 7	668684
9	5 and 8	2682
10	exp animal/ not human/	4696271
11	9 not 10	2547

Table 4. Database(s): EBM Reviews–Cochrane Database of Systematic Reviews 2005 to November 20, 2019. Search strategy:

Number	Searches	Results
1	(glioblastoma* or glyoblastoma* or spongioblastoma or gliosarcoma* or (("high grade" or malignant or "grade IV" or "grade V" or "grade 4" or "grade 5" or brain*) adj5 glioma*) or GBM or "WHO grade IV").ti,ab.	17
2	(("high-grade" or malignant or "grade IV" or "grade 4") adj3 astrocytoma*).ti,ab.	0
3	(glioma* adj15 metasta*).ti,ab.	1
4	1 or 2 or 3	17
5	(spinal or spine or intramedullary or intradural or extradural or "dura mater" or intraspinal or dural or leptomening* or vertebr* or holocord* or thoracolumb* or cervico* or conus or (cerebrospinal adj5 (metasta* or spread*))).ti,ab.	190
6	4 and 5	0

Table 5. Database(s): EBM Reviews–Cochrane Central Register of Controlled Trials October 2019. Search strategy:

Number	Searches	Results
1	Glioblastoma/	596
2	(glioblastoma* or glyoblastoma* or spongioblastoma or gliosarcoma* or (("high grade" or malignant or "grade IV" or "grade V" or "grade 4" or "grade 5" or brain*) adj5 glioma*) or GBM or "WHO grade IV").tw,kw.	2709
3	(("high-grade" or malignant or "grade IV" or "grade 4") adj3 astrocytoma*).tw,kw.	136
4	(glioma* adj15 metasta*).tw,kw.	84
5	1 or 2 or 3 or 4	2835
6	Spinal Neoplasms/ or exp Spinal Cord Neoplasms/	122
7	(spinal or spine or intramedullary or intradural or extradural or "dura mater" or intraspinal or dural or leptomening* or vertebr* or holocord* or thoracolumb* or cervico* or conus or (cerebrospinal adj5 (metasta* or spread*))).tw,kw.	39524
8	6 or 7	39547
9	5 and 8	44

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00381-021-05098-8.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Sanchez-Herrera F, Castro-Sierra E, Gordillo-Dominguez LF, Vaca-Ruiz MA, Santana-Montero B, Perezpena-Diazconti M, Gonzalez-Carranza V, Torres-Garcia S, Chico-Ponce de Leon F (2009) Glioblastoma multiforme in children: experience at Hospital Infantil de Mexico Federico Gomez. Childs Nerv Syst 25:551–557
2. States CBTRotU (2010) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in. Central Brain Tumor Registry of the United States, Hinsdale, IL, pp 2004–2006
3. Behmanesh B, Setzer M, Konczalla J, Harter P, Quick-Weller J, Imoehl L, Franz K, Gessler F, Seifert V, Marquardt G (2017) Management of patients with primary intramedullary spinal cord glioblastoma. World Neurosurg 98:198–202
4. Mansha MA, Khan AMH, Abbasi ANN, Tariq MUU, Mushtaq N, Tariq M, Waheed A (2018) Glioblastoma multiforme involving conus medullaris in a child. Cureus 10:e2863
5. Louis DN, Ohgaki H, Wiestler OD, Cavenee DK (2016) World Health Organization histological classification of tumours of the central nervous system. International Agency for Research on Cancer France
6. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097
7. Innovation VH (2019) Covidence systematic review software. Melbourne, Australia
8. Le Rhun E, Ruda R, Devos P, Hoang-Xuan K, Brandsma D, Perez Segura P, Soffietti R, Weller M (2017) Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across Europe. J Neuro-Oncol 133:419–427
9. Pan Z, Yang G, He H, Yuan T, Wang Y, Li Y, Shi W, Gao P, Dong L, Zhao G (2018) Leptomeningeal metastasis from solid tumors: clinical features and its diagnostic implication. Sci Rep 8:10445
10. Team RDC (2018) A language and environment for statistical computing, in, ed 3.5.0. Vienna, Australia R Foundation for Statistical Computing
11. Allen JC, Aviner S, Yates AJ, Boyett JM, Cherlow JM, Turski PA, Epstein F, Finlay JL (1998) Treatment of high-grade spinal cord astrocytoma of childhood with "8-in-1" chemotherapy and radiotherapy: a pilot study of CCG-945. Children's Cancer Group. J Neurosurg 88:215–220
12. Banczerowski P, Simo M, Sipos L, Slowik F, Benoist G, Veres R (2003) Primary intramedullary glioblastoma multiforme of the spinal cord: report of eight cases. Ideggyogy Sz 56:28–32
13. Battaglia S, Albini Riccioli L, Bartiromo F, Galassi E, Marliani AF, Leonardi M (2007) Childhood spinal glioblastoma multiforme with intracranial dissemination. A case report. Neuroradiol J 20:500–503
14. Bonde V, Balasubramaniam S, Goel A (2008) Glioblastoma multiforme of the conus medullaris with holocordal spread. J Clin Neurosci 15:601–603
15. Broniscer A, Chintagumpala M, Fouladi M, Krasin MJ, Kocak M, Bowers DC, Iacono LC, Merchant TE, Stewart CF, Houghton PJ, Kun LE, Ledet D, Gajjar A (2006) Temozolomide after radiotherapy for newly diagnosed high-grade glioma and unfavorable low-grade glioma in children. J Neuro-Oncol 76:313–319
16. Caroli E, Salvati M, Ferrante L (2005) Spinal glioblastoma with brain relapse in a child: clinical considerations. Spinal Cord 43:565–567
17. Ciappetta P, Salvati M, Capoccia G, Artico M, Raco A, Fortuna A (1991) Spinal glioblastomas: report of seven cases and review of the literature. Neurosurgery 28:302–306
18. Derinkuyu BE, Boyunaga O, Okur A, Alimli AG, Oztunali C, Damar C, Ucar M (2015) Primary intraspinal glioblastoma multiforme in a child. Spine J 15:e37–e38
19. Etherton MR, Neagu MR, Oakley DH, Koch MJ, Shin JH, Frosch MP, Berkowitz AL, Dietrich J (2015) A 20-year-old man with back pain and lower extremity weakness. JAMA Neurol 72:363–366
20. Gee TS, Ghani AR, Idris B, Awang MS (2012) Case report: a rare case of pediatric conus medularis glioblastoma multiforme. Med J Malaysia 67:438–441
21. Johnson DL, Schwarz S (1987) Intracranial metastases from malignant spinal-cord astrocytoma. Case report. J Neurosurg 66:621–625
22. Kim WH, Yoon SH, Kim CY, Kim KJ, Lee MM, Choe G, Kim IA, Kim JH, Kim YJ, Kim HJ (2011) Temozolomide for malignant primary spinal cord glioma: an experience of six cases and a literature review. J Neuro-Oncol 101:247–254
23. Lober R, Sharma S, Bell B, Free A, Figueroa R, Sheils CW, Lee M, Cowell J (2010) Pediatric primary intramedullary spinal cord glioblastoma. Rare Tumors 2:e48
24. Medhkour A, Chan M (2005) Extremely rare glioblastoma multiforme of the conus medullaris with holocord and brain stem metastases, leading to cranial nerve deficit and respiratory failure: a case report and review of the literature. Surg Neurol 63:576–582 discussion 582-573
25. Morais N, Mascarenhas L, Soares-Fernandes JP, Silva A, Magalhaes Z, Costa JA (2013) Primary spinal glioblastoma: a case report and review of the literature. Oncol Lett 5:992–996
26. Mori K, Imai S, Shimizu J, Taga T, Ishida M, Matsusue Y (2012) Spinal glioblastoma multiforme of the conus medullaris with holocordal and intracranial spread in a child: a case report and review of the literature. Spine J 12:e1–e6
27. O'Halloran PJ, Farrell M, Caird J, Capra M, O'Brien D (2013) Paediatric spinal glioblastoma: case report and review of therapeutic strategies. Childs Nerv Syst 29:367–374
28. Ononiwu C, Mehta V, Bettegowda C, Jallo G (2012) Pediatric spinal glioblastoma multiforme: current treatment strategies and possible predictors of survival. Childs Nerv Syst 28:715–720
29. Prasad GL, Borkar SA, Subbarao KC, Suri V, Mahapatra AK (2012) Primary spinal cord glioblastoma multiforme: a report of two cases. Neurol India 60:333–335
30. Przybylski GJ, Albright AL, Martinez AJ (1997) Spinal cord astrocytomas: long-term results comparing treatments in children. Childs Nerv Syst 13:375–382
31. Raco A, Piccirilli M, Landi A, Lenzi J, Delfini R, Cantore G (2010) High-grade intramedullary astrocytomas: 30 years' experience at the Neurosurgery Department of the University of Rome "Sapienza". J Neurosurg Spine 12:144–153
32. Santi M, Mena H, Wong K, Koeller K, Olsen C, Rushing EJ (2003) Spinal cord malignant astrocytomas. Clinicopathologic features in 36 cases. Cancer 98:554–561
33. Shen CX, Wu JF, Zhao W, Cai ZW, Cai RZ, Chen CM (2017) Primary spinal glioblastoma multiforme: a case report and review of the literature. Medicine (Baltimore) 96:e6634
34. Yan C, Kong X, Yin H, Wang Y, He H, Zhang H, Gao J, Li Y, Ma W (2017) Glioblastoma multiforme in conus medullaris with intracranial metastasis after postoperative adjuvant therapy. Medicine (Baltimore) 96:e6500
35. Biswas R, Gupta S, Haresh KP, Halder A, Rath GK (2018) Giant cell glioblastoma with spinal and spinal leptomeningeal metastasis

in a child: a rare presentation of a rare tumor. J Craniovertebr Junct Spine 9:202–204
36. Erlich SS, Davis RL (1978) Spinal subarachnoid metastasis from primary intracranial glioblastoma multiforme. Cancer 42:2854–2864
37. Jahraus CD, Dishop MK, Bayliff SL, Lee C, St Clair WH (2003) Atypical presentation and progression of glioblastoma multiforme in a 6-year-old girl: multidisciplinary case report. J Pediatr Hematol Oncol 25:243–247
38. Kandt RS, Shinnar S, D'Souza BJ, Singer HS, Wharam MD, Gupta PK (1984) Cerebrospinal metastases in malignant childhood astrocytomas. J Neuro-Oncol 2:123–128
39. Kepes JJ, Striebinger CM, Brackett CE, Kishore P (1976) Gliomas (astrocytomas) of the brain-stem with spinal intra- and extradural metastases: report of three cases. J Neurol Neurosurg Psychiatry 39:66–76
40. Khan MB, Riaz M, Bari ME (2014) Is surgical spinal decompression for supratentorial GBM symptomatic drop down metastasis warranted? A case report and review of literature. Surg Neurol Int 5:40
41. Kulkarni AV, Becker LE, Jay V, Armstrong DC, Drake JM (1999) Primary cerebellar glioblastomas multiforme in children. Report of four cases. J Neurosurg 90:546–550
42. Momota H, Iwami K, Fujii M, Motomura K, Natsume A, Ogino J, Hasegawa T, Wakabayashi T (2011) Rhabdoid glioblastoma in a child: case report and literature review. Brain Tumor Pathol 28:65–70
43. Saad AG, Sachs J, Turner CD, Proctor M, Marcus KJ, Wang L, Lidov H, Ullrich NJ (2007) Extracranial metastases of glioblastoma in a child: case report and review of the literature. J Pediatr Hematol Oncol 29:190–194
44. Tinkle CL, Orr BA, Lucas JT Jr, Klimo P, Patay Z, Baker SJ, Broniscer A, Qaddoumi I (2017) Rapid and fulminant leptomeningeal spread following radiotherapy in diffuse intrinsic pontine glioma. Pediatr Blood Cancer 64
45. Vaidya SJ, Hargrave D, Saran F, Britton J, Soomal R, Bouffet E (2007) Pattern of recurrence in paediatric malignant glioma: an institutional experience. J Neuro-Oncol 83:279–284
46. McGirt MJ, Goldstein IM, Chaichana KL, Tobias ME, Kothbauer KF, Jallo GI (2008) Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. Neurosurgery 63:55–60 discussion 60-51
47. Lam S, Lin Y, Melkonian S (2012) Analysis of risk factors and survival in pediatric high-grade spinal cord astrocytoma: a population-based study. Pediatr Neurosurg 48:299–305
48. Luksik AS, Garzon-Muvdi T, Yang W, Huang J, Jallo GI (2017) Pediatric spinal cord astrocytomas: a retrospective study of 348 patients from the SEER database. J Neurosurg Pediatr 19:711–719
49. Perkins SM, Rubin JB, Leonard JR, Smyth MD, El Naqa I, Michalski JM, Simpson JR, Limbrick DL, Park TS, Mansur DB (2011) Glioblastoma in children: a single-institution experience. Int J Radiat Oncol Biol Phys 80:1117–1121
50. Sturm D, Witt H, Hovestadt V, Khuong-Quang DA, Jones DT, Konermann C, Pfaff E, Tonjes M, Sill M, Bender S, Kool M, Zapatka M, Becker N, Zucknick M, Hielscher T, Liu XY, Fontebasso AM, Ryzhova M, Albrecht S, Jacob K, Wolter M, Ebinger M, Schuhmann MU, van Meter T, Fruhwald MC, Hauch H, Pekrun A, Radlwimmer B, Niehues T, von Komorowski G, Durken M, Kulozik AE, Madden J, Donson A, Foreman NK, Drissi R, Fouladi M, Scheurlen W, von Deimling A, Monoranu C, Roggendorf W, Herold-Mende C, Unterberg A, Kramm CM, Felsberg J, Hartmann C, Wiestler B, Wick W, Milde T, Witt O, Lindroth AM, Schwartzentruber J, Faury D, Fleming A, Zakrzewska M, Liberski PP, Zakrzewski K, Hauser P, Garami M, Klekner A, Bognar L, Morrissy S, Cavalli F, Taylor MD, van Sluis P, Koster J, Versteeg R, Volckmann R, Mikkelsen T, Aldape K, Reifenberger G, Collins VP, Majewski J, Korshunov A, Lichter P, Plass C, Jabado N, Pfister SM (2012) Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell 22:425–437
51. Frank S, Kuhn SA, Brodhun M, Mueller U, Romeike B, Kosmehl H, Regenbrecht CR, Ewald C, Reichart R, Kalff R (2009) Metastatic glioblastoma cells use common pathways via blood and lymphatic vessels. Neurol Neurochir Pol 43:183–190
52. Paugh BS, Qu C, Jones C, Liu Z, Adamowicz-Brice M, Zhang J, Bax DA, Coyle B, Barrow J, Hargrave D, Lowe J, Gajjar A, Zhao W, Broniscer A, Ellison DW, Grundy RG, Baker SJ (2010) Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. J Clin Oncol 28:3061–3068
53. Qaddoumi I, Sultan I, Gajjar A (2009) Outcome and prognostic features in pediatric gliomas: a review of 6212 cases from the Surveillance, Epidemiology, and End Results database. Cancer 115:5761–5770
54. Jones C, Perryman L, Hargrave D (2012) Paediatric and adult malignant glioma: close relatives or distant cousins? Nat Rev Clin Oncol 9:400–413