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ORIGINAL ARTICLE

Predictors of mortality in patients with primary spinal cord glioblastoma

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Abstract

Purpose Primary spinal cord glioblastoma (GBM) is a rare and devastating disease. Little attention was ever paid to this rare disease. As a result, the standard treatment protocol and prognostic factors of primary spinal cord GBM were not well established. The aim of this study was to determine the predictors associated with survival in patients with primary spinal cord GBM.

Methods A total of 122 patients with primary spinal cord GBM from Surveillance, Epidemiology, and End Results database and our institution were included in this retrospective analysis. Information about age, sex, race, tumor invasion, extent of resection, radiation, chemotherapy and year of diagnosis was collected. Univariate and multivariate accelerated failure time (AFT) regression model was performed to identify prognostic factors.

Results Of the 122 patients, 102 (83.6%) expired at the time of data collection. Overall survival at 1 year, 2 years, 3 years and 5 years was 48.4%, 22.8%, 17.1% and 8.4%, respectively, and median survival time was 12 months. Only radiation was found to be associated with survival in the AFT regression model (time ratio 1.94, 95% CI 1.01–3.72, $p < 0.05$). Radiotherapy could improve survival slightly; patients who received RT survived approximately two times as long as patients who did not receive RT, but the advantage was short term.

Conclusion The survival of primary spinal cord GBM is poor in the current treatment strategy. Radiotherapy was associated with better survival, but the advantage was short term.

Keywords Spinal cord · Glioblastoma · Prognostic factors · Radiotherapy · Survival

Abbreviations

AIC	Akaike's information criterion
AFT	Accelerated failure time model
CSF	Cerebrospinal fluid
IQR	Interquartile range
GBM	Glioblastoma
GTR	Gross total resection
PH	Proportional hazards assumption
RT	Radiotherapy
S/PR	Subtotal/partial resection
TMZ	Temozolomide
95% CI	95% Confidence interval

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Introduction

Primary spinal cord glioblastoma (GBM) is a rare disease, just accounting for approximately 1.4% of intraspinal tumors [1]. However, in contrast to its intracranial counterpart, which has standard management guideline, the primary spinal cord GBM has no management consensus to refer to and often cause even more devastating outcome. The median survival time for spinal cord GBM is about 9 months, shorter than that of 15–23 months for intracranial GBM [2–4]. With respect to treatment, less well-defined margins between tumor and normal spinal cord make gross total resection a great challenge, and the effect of chemotherapy, like Temozolomide(TMZ) which was proved to be effective

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for intracranial GBM, remains controversial on spinal cord GBM [5, 6]. In addition, the rarity of this disease makes it difficult to conduct a comprehensive and in-depth clinical study and underlying mechanism research. To date, most of the studies focusing on spinal cord GBM were published in the form of case series. As a result, the clinical factors associated with survival are still unclear and inconsistent across the limited studies. Data are needed for accurate prognostication for patients, for the option of treatment strategy and for the design of clinical trials.

In the present study, we aimed to identify the risk factors associated with primary spinal cord GBM.

Methods

Data retrieval

Data were obtained from Surveillance, Epidemiology, and End Results (SEER) registries (source database: Incidence-SEER 18Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying)). We only included patients diagnosed with glioblastoma (ICD-O-3 code: 9940, 9941) and lesion sited at the spinal cord and Cauda equina (ICD-O-3 code: C72.0 for "spinal cord", C72.1 for "cauda equina"). Only primary intramedullary lesion instead of metastasis from intracranial GBM was included and identified by sequence number, which describes the number and sequence of primary tumors that occur over the lifetime of a patient, a sequence number of "one primary only" or "1st of 2 or more primaries" denotes primary lesion. The following data were collected: demographic characteristics, tumor invasion, extent of resection, adjuvant treatments, year of diagnosis and survival outcome. Patients of whom the diagnosis of primary spinal cord GBM was not confirmed by tissue pathology, the surgery was not performed, the surgical strategy was unknown, or the survival time was unknown were excluded. Corresponding coding rule can be found in *SEER Research Data Recorded Description Case Diagnosed in 1975–2016*. In addition, patients with primary spinal cord GBM treated in our institution from 2015 to 2019 were pooled into the analysis after being approved by the hospital ethical board. Detailed screening flow chart is shown in Fig. 1.

Variables stratification

Age groups were divided into pediatric (≤ 18 year/o) and adult group (> 18 year/o). The race was grouped into white, black and others. Tumor invasion was divided into

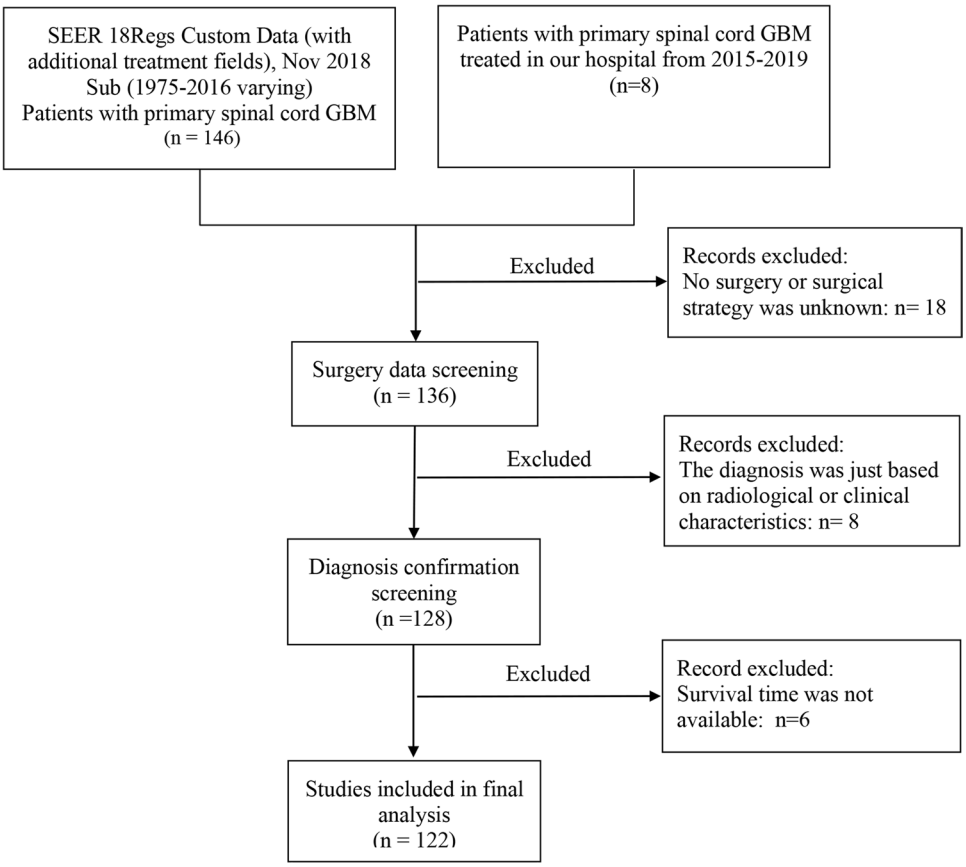


Fig. 1 Flow diagram of patients screening

"localized", "extensive", "metastatic", "unknown", localized lesion was defined as tumor that just involved spinal cord without adjacent tissue invasion, like nerve root, adjacent dura etc., otherwise, tumor without metastasis was classified as an extensive group, while tumor with CSF dissemination was classified as a metastatic group and unknown tumor invasion as an unknown group. The extent of resection was categorized as autopsy/biopsy (auto/biopsy), subtotal/partial resection (S/PR) and gross total resection (GTR). Year of diagnosis was stratified into four levels with an interval of 6 years. Unfortunately, vertebral location of the tumor, numbers of involved vertebra and radiological characteristics were not available. Survival outcome was dichotomized into alive and all-cause death.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical data are presented as the frequency (percentage). Two-tailed *t*-test was used for continuous variables and χ^2 test or Fisher test for categorical variables to compare the differences. Survival rates at 1 year, 2 years, 3 years and 5 years were calculated. Kaplan–Meier curves were constructed for survival by stratified variables and compared using the Gehan–Breslow test (also known as Wilcoxon test), which places more weight on events that occur at earlier time points and is considered more powerful than the log-rank test when the proportional hazards (PH) assumption is violated [7, 8]. Considering the violation of PH assumption for several variables (age groups, radiation and chemotherapy) in an exploratory analysis, accelerated failure time (AFT) regression model, instead of Cox proportional hazard regression, was applied for univariate and multivariate analysis. As to detailed model selection, the selection was based on survival time distribution and Akaike's information criterion (AIC), which is a measure of goodness of fit and the smaller the value, the better the model. In our study, the survival time distribution followed a log-normal distribution, and the log-normal model provided the best fit to the data with the smallest AIC. Consequently, a log-normal AFT model was chosen to perform univariate and all-included multivariate regression analysis. In the AFT model, the effect of covariates estimated was reported as time ratio (95% confidence interval), which represents the estimated delay until an event occurs in one group relative to another group. Furthermore, to evaluate the specific time-dependent effect of statistically significant covariates identified in the AFT model, a post hoc analysis using piecewise hazards model was further performed, whereby the follow-up time was split into two segments at 18 months, with the hazard ratio calculated separately for events that occurred up to 18 months and that occurred after 18 months by using a Cox PH model. A p-value < 0.05 was defined as statistical significance. All statistical analysis was performed using R language software (version 3.6.1).

Results

Baseline characteristics of patients

A total of 122 patients with primary spinal cord GBM were identified (SEER database: 114 cases; Our institution: 8 cases). 64 (52.5%) were male, with a median age at diagnosis (IQR) of 35 (32) years. The tumor invasion of most patients (69.7%) was unknown, 16.4% lesion was localized, 9.8% extensive and 4.1% of patients suffered from tumor dissemination; hence, a subset analysis of patients with available tumor invasion included only was performed (supplement Table 1). A total of 65 (53.3%) patients received subtotal or partial resection, whereas 41 (33.6%) and 16 (13.1%) patients underwent auto/biopsy and GTR, respectively. A total of 87 (71.3%) patients and 82 (67.2%) patients received radiation chemotherapy, respectively. Only 20 (16.4%) patients were alive at the time of data collection. When conducting a comparison between subgroups stratified by survival status, age groups and year at diagnosis presented significant difference ($p < 0.05$) (Table 1).

Variables associated with survival

Overall survival at 1 year, 2 years, 3 years and 5 years was 48.4%, 22.8%, 17.1% and 8.4%, respectively, and median survival time was 12 months (Fig. 2A). Kaplan–Meier survival curves by variable categories demonstrated that only radiation was possibly associated with survival (Gehan–Breslow test $p = 0.01$) (Fig. 2B–I). Univariate AFT analysis showed that radiation was associated with better survival with a time ratio of 1.95 (95% CI 1.20–3.17, $p < 0.05$), while age groups, sex, race, tumor invasion, extent of resection and year of diagnosis each did not present a significant association with survival. After adjusting the confounding effect of each covariate, the multivariate AFT model revealed that radiation was an independent predictor of favorable survival (time ratio 2.15, 95% CI 1.13–4.08, $p < 0.05$), whereas other variables showed no association with survival (Table 2). Consistently, radiation was also identified to be a predictor of favorable survival outcome in the subset analysis of patients with available tumor invasion included (supplement Table 2).

Table 1 Demographic and treatment characteristics of patients

	Total		Alive		All-cause death		*p*
	(*n* = 122)		(*n* = 20)		(*n* = 102)		
Age, median (IQR)	35	(32)	34	(17)	35	(34)	0.863
Age groups, *n* (%)							0.026
≤ 18	38	(31.1)	2	(10.0)	36	(35.3)	
> 18	84	(68.9)	18	(90.0)	66	(64.7)	
Sex, *n* (%)							0.803
Male	64	(52.5)	11	(55.0)	53	(52.0)	
Female	58	(47.5)	9	(45.0)	49	(48.0)	
Race, *n* (%)							0.814
White	96	(78.7)	16	(80.0)	80	(78.4)	
Black	9	(7.4)	2	(10.0)	7	(6.9)	
Others	17	(13.9)	2	(10.0)	15	(14.7)	
Tumor invasion, *n* (%)							0.745
Localized	20	(16.4)	2	(10.0)	18	(17.6)	
Extensive	12	(9.8)	2	(10.0)	10	(9.8)	
Metastatic	5	(4.1)	0	(0)	5	(4.9)	
Unknown	85	(69.7)	16	(80.0)	69	(67.6)	
Extent of resection, *n* (%)							0.225
Auto/biopsy	41	(33.6)	5	(25.0)	36	(35.3)	
S/PR	65	(53.3)	14	(70.0)	51	(50.0)	
GTR	16	(13.1)	1	(5.0)	15	(14.7)	
Radiation, *n* (%)							0.690
Yes	87	(71.3)	15	(75.0)	72	(70.5)	
No	35	(28.7)	5	(25.0)	30	(29.4)	
Chemotherapy, *n* (%)							0.818
Yes	82	(67.2)	13	(65.0)	69	(67.6)	
No	40	(32.8)	7	(35.0)	33	(32.4)	
Year of diagnosis, *n* (%)							0.008
1988–1994	7	(5.7)	1	(5.0)	6	(5.9)	
1995–2001	19	(15.6)	1	(5.0)	18	(17.6)	
2002–2008	33	(27.0)	1	(5.0)	32	(31.4)	
2009–2016	63	(51.6)	17	(85.0)	46	(45.1)	

Post hoc analysis

Radiation presented significant association with favorable survival, but its effect on survival changed over time. The piecewise hazards model showed that radiotherapy was more beneficial in the initial 18 months after diagnosis than 18 months later (HR 0.51 95% CI 0.31–0.84, $p < 0.008$ vs. HR 1.91 95% CI 0.69–5.26, $p > 0.2$). Additionally, the median survival time was 13 months in patients who received radiotherapy compared with that of 8 months in patients who did not receive radiotherapy (Table 3).

Discussion

Primary spinal cord GBM is a devastating disease and, unlike its intracranial counterpart, it predominately occurs in earlier decades of life without gender predilection [6, 9–11], as documented in our studies. Additionally, the prognosis of primary spinal cord GBM is worse than that of brain GBM. In our study, the overall survival was 48.4% at 1 year and dropped to less than 20% at 3 years, and the median survival time was 12 months, which was consistent with the results reported in the literature [2, 3, 10, 12]. Besides its aggressive nature of primary spinal cord GBM, tumor residuals burden partially contributes to the unfavorable prognosis. In our entire cohorts, only 16 (13.1%) patients received GTR. Similarly, a systematic review by Konar SK et al. [10] demonstrated that only 15 out of 128 patients obtained GTR. In our clinical practice, we observed that no distinct border between tumor and normal spinal cord made GTR without permanent neurological function injury a great challenge. The reported main causes of death were intracranial metastasis and respiratory failure, which may indicate that CSF dissemination and rapid growth along the nerve fiber tracts toward the upper cervical spinal cord are the two main exacerbation patterns of this disease [13–15].

Predictors associated with primary spinal cord GBM were ever not well established. In the present study, age groups, sex, race, tumor invasion, extent of resection, chemotherapy and year of diagnosis were not associated with survival. Only radiation was the independent predictor of survival, and patients who received radiotherapy had approximately two times the survival time of those who did not receive radiotherapy. Cheng et al. [11] found that radiotherapy could increase the overall survival time from 9 to 17 months. Similarly, Shen et al. [6] reported that the mean survival time was 12.8 months for patients who underwent subtotal resection plus radiation compared with 5.7 months for patients who received subtotal resection only. Santi et al. [2] and Minehan et al. [16] also showed the effect of radiation on improved survival in infiltrative astrocytoma of spinal cord. On the contrary, Fakhreddine et al. [17], Lam et al. [18] and Adams [12] consistently did not find the significant benefit of radiation on overall survival in patients with infiltrative spinal cord astrocytoma. Several factors, such as varying dose and modality of radiation, sample size, tumor grade (In some studies, WHO III astrocytoma was pooled into analysis) and statistical analysis method, may contribute to this discrepancy. Of note, although radiation showed an effect on improving survival in patients with spinal cord GBM, the effect was time dependent and its advantage over no radiation was short term (Table 3). Generally, the long-term

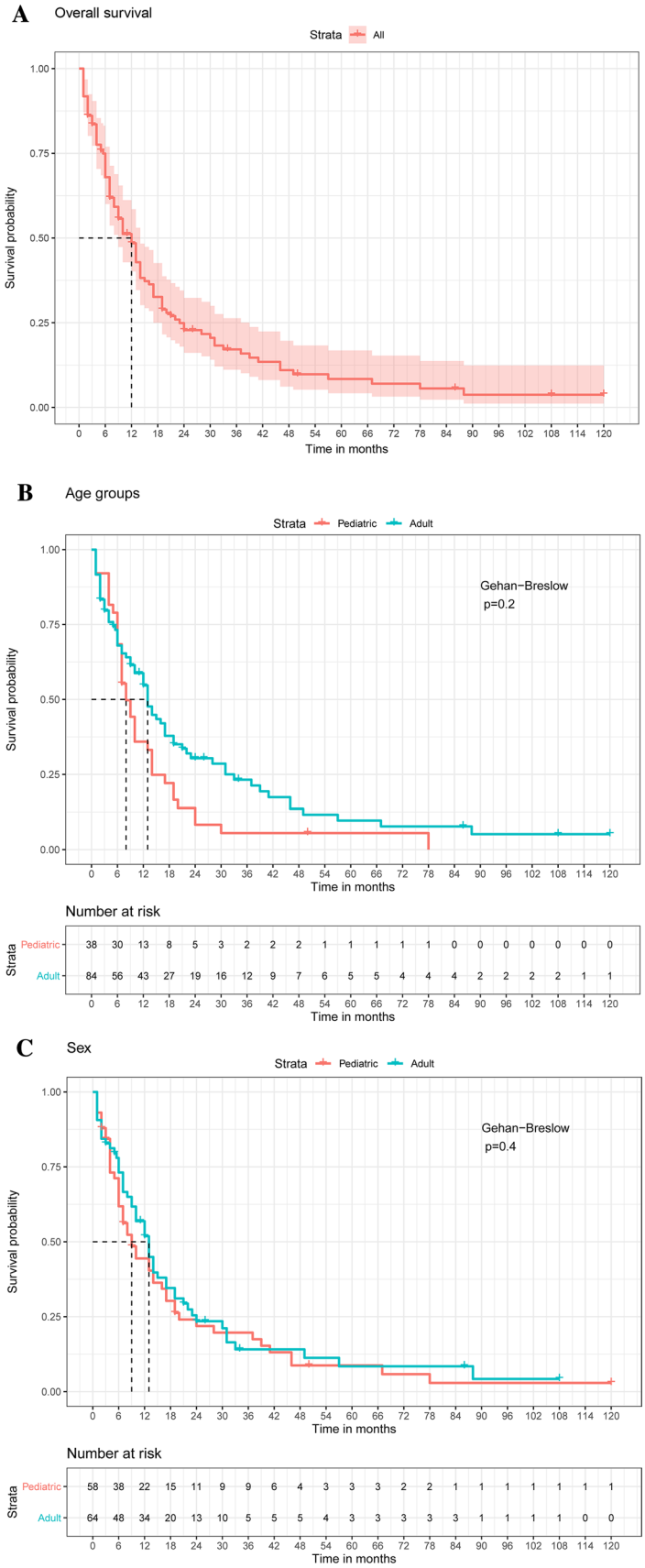
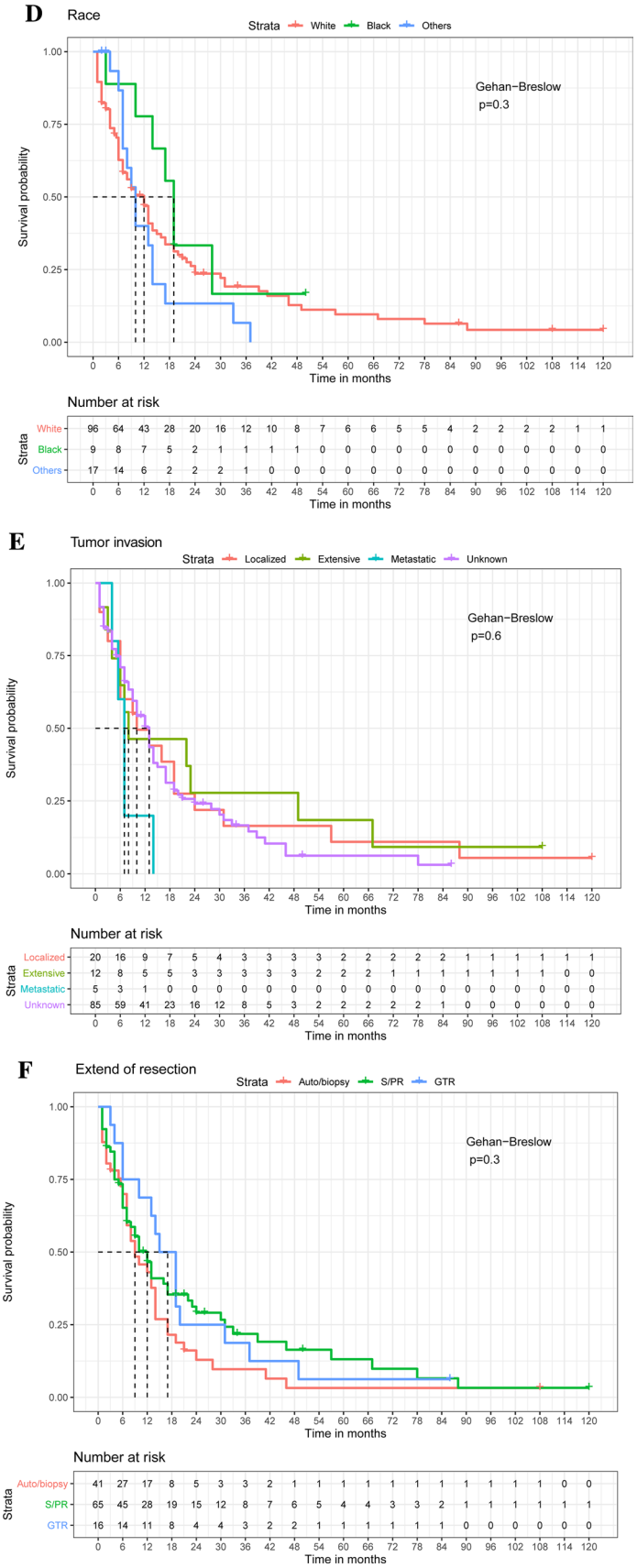


Fig. 2 **a** Kaplan–Meier survival curves of overall survival for all 122 patients showed that the overall survival at 1 year, 2 years, 3 years and 5 years was 48.4%, 22.8%, 17.1% and 8.4%, respectively; **b–i** Kaplan–Meier survival curves by variables, including age groups, sex, race, tumor invasion, extent of resection, radiation, chemotherapy and year of diagnosis, respectively, revealed that only radiotherapy reached significant difference

Fig. 2 (continued)



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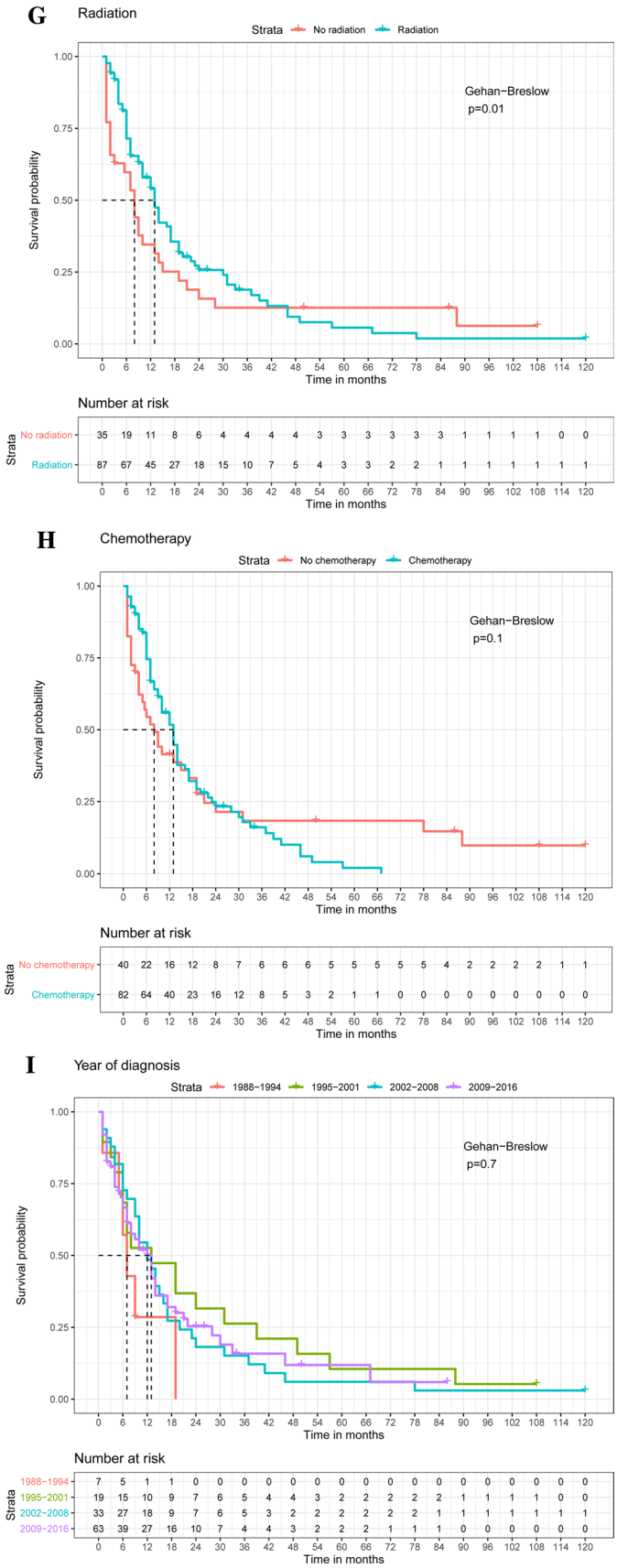
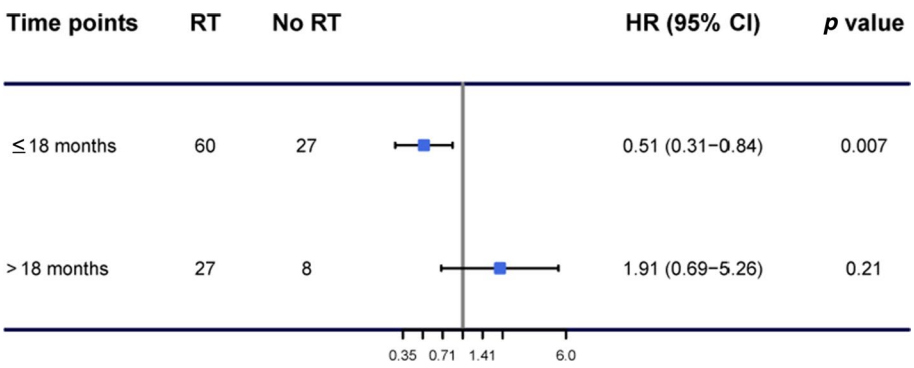


Table 2 Univariate and multivariate AFT analysis

	Univariate analysis			Multivariate analysis		
	Time ratio	95% CI	*p* value	Time ratio	95% CI	*p* value
Age groups	1.31	0.81–2.14	0.267	1.63	0.98–2.71	0.057
Sex	1.14	0.72–1.80	0.567	1.41	0.90–2.21	0.137
Race						
White	Ref.			Ref.		
Black	1.91	0.80–4.56	0.148	2.63	0.96–6.30	0.130
Others	1.10	0.57–2.14	0.773	1.48	0.71–3.08	0.290
Tumor invasion						
Localized	Ref.			Ref.		
Extensive	1.15	0.46–2.86	0.769	1.10	1.04–5.97	0.837
Metastatic	0.61	0.18–2.07	0.428	0.62	0.19–2.06	0.435
Unknown	0.96	0.52–1.77	0.885	0.87	0.41–1.86	0.726
Extent of resection						
Auto/biopsy	Ref.			Ref.		
S/PR	1.36	0.83–2.23	0.228	1.05	0.61–1.80	0.860
GTR	1.86	0.91–3.82	0.089	1.13	0.52–2.46	0.765
Radiation	1.95	1.20–3.17	0.007*	2.15	1.13–4.08	0.020*
Chemotherapy	1.42	0.88–2.30	0.150	0.98	0.54–1.80	0.958
Year at diagnosis						
1988–1994	Ref.			Ref.		
1995–2001	1.83	0.62–5.44	0.276	1.90	0.65–5.59	0.243
2002–2008	1.66	0.59–4.62	0.336	1.63	0.57–4.66	0.361
2009–2016	1.48	0.55–3.99	0.437	1.37	0.47–4.04	0.562

Table 3 Piecewise hazard ratios for radiation versus no radiation



prognosis of primary spinal cord GBM was still dismal regardless of whether adjuvant radiotherapy was prescribed.

Several studies have shown that age was a prognostic factor [19–21]. The study conducted by Adams et al. [12] revealed that the survival in adult cohorts with malignant spinal cord astrocytoma was significantly better than that in pediatric cohorts. Conversely, Santi et al. [2] found that young aged patients with malignant spinal cord astrocytoma presented better survival as compared to old aged patients. However, these studies did not restrict their cohorts to spinal cord GBM. As to the association between sex and survival outcome, consistently, most studies reported no significant relation between gender and survival except the study by Adams et al. [12] which saw a tendency of worst survival in females.

In our study, no significant association between tumor invasion and survival was observed, which was most likely ascribed to a high proportion of cases with unknown tumor invasion. In a systematic review by Benes et al. [22], the results unexpectedly showed that no significant association of tumor invasion with survival was noted in the majority of studies included. Ardeshiri et al. [23] demonstrated that tumor extending more than three segments was a predictor of an unfavorable outcome. And exophytic and metastatic

spinal GBM was reported to carry poor survival [24, 25]. In our study, small number of cases might result in difficulty in finding out the statistical difference.

The effect of the extent of resection on survival was not well understood in previous published studies. The majority of studies did not observe larger scope of surgery benefited better survival [2, 17, 18, 22, 26–28], while several studies found GTR could provide a better outcome than non-GTR cohorts [12, 29]. McGirt et al. [3] found that GTR was associated with poor survival. Surgery without radical removal of the tumor may be not beneficial for the outcome; on the contrary, debulking of spinal cord GBM presumably increases the risk of CSF dissemination. But it does not mean GTR is recommended in the sacrifice of major neurological function; the pursuit of GTR must lie in the premise of preservation of major neurological function; for patients with the preserved independent living ability or sphincter function, the maximum safe resection should be given priority rather than GTR in the sacrifice of neurological function. In contrast to GTR under a microscope, cordectomy as an extended resection could achieve truly radical removal of the tumor in the sacrifice of adjacent "normal" tissue and was reported to provide favorable survival [30, 31]. It probably can serve as a final salvage treatment strategy in the premise of strict case selection.

Chemotherapy has not shown an association with survival in our study, and the chemotherapeutic protocol was not recorded in the SEER database. Varying chemotherapeutic modalities were ever reported in the literature [29, 32–35]. Of those, the most commonly used chemotherapeutic agent was TMZ [5, 36–38]. However, although TMZ was proved to be effective in improving brain GBM, the effect of TMZ on spinal cord TMZ is debated. Hernández-Durán et al. [5] noted that there was no significant advantage of the addition of TMZ to treat spinal cord GBM. Conversely, Kim et al. [36], Kaley et al. [38] and Chamberlain et al. [37] consistently found that TMZ could elongate the survival time. In addition to TMZ, bevacizumab was also applied to treat spinal cord GBM and showed promising effects [38, 39]. Of note, these studies were case reports or series and, in addition, different molecular profiling between spinal cord GBM and brain GBM may result in a different response to TMZ or bevacizumab [40–42]. Thus, the effect of TMZ and bevacizumab on spinal cord GBM should be confirmed in a prospective study with a large sample size.

Several limitations to our studies should be noted. Firstly, covariate data, for instance, symptomatic characteristics, numbers of involved vertebral segments, radiological characteristics, dose of radiotherapy, chemotherapeutic agents, etc., all of which probably are strong predictors, unfortunately, were not recorded in SEER database. Secondly, the time span of the database was approximately 30 years, and microsurgical skills and chemoradiotherapy modality evolved over that period. Finally, taking into account the limitation to the respective study, predictors associated with survival identified in our study should be validated in the prospective study before it was used as evidence of treatment efficacy. However, considering the paucity of spinal cord GBM, a collaborative, multiple-institutional study group is needed to conduct a prospective, large sample-size study.

Conclusion

The outcome of primary spinal cord GBM is dismal in the current treatment strategy. Radiotherapy was identified to be protective, and patients who received radiotherapy may survive approximately two times as long as patients who did not receive radiotherapy. However, the advantage that radiotherapy could provide was short term.

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Compliance with ethical standards

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

Ethical approval The study was approved by the ethical board of Xuanwu Hospital.

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