Assessment of treatment approach and survival outcomes in a modern cohort of patients with primary gliosarcoma using the national cancer database

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ABSTRACT

Background: Primary gliosarcoma is a rare malignant brain tumor with dismal prognosis. Previous reports are limited to case reports and small retrospective case series.

Objective: To evaluate treatment and survival outcomes in a large cohort of primary gliosarcoma patients treated in the United States.

Results: 1622 patients met the inclusion criterion. Median age was 63 years. The 3-year OS rate for the entire cohort was 11.9%. Patients aged 18 to 60 years were significantly more likely to receive trimodality therapy (defined as the use of surgery, radiotherapy [RT] and chemotherapy [CT]) than patients older than 60 (68.1% vs. 56.7%, $p < 0.001$). The utilization of trimodality therapy significantly increased during the study period (57.5% in 2004–2008 vs. 65.1% in 2009–2013; $p = 0.002$). On multivariate Cox regression analysis, GTR, surgery followed by RT and the use of trimodality therapy were associated with longer OS, while older age, Charlson-Deyo score ≥ 1 and multi-focal tumor were associated with shorter OS. The use of trimodality therapy was consistently associated with longer OS in subgroup analyses based on age and extent of resection.

Materials and Methods: The National Cancer Database was used to identify all primary gliosarcoma patients aged 18 to 90 years who were diagnosed between 2004 and 2013. Overall survival (OS) was evaluated by Kaplan-Meir analysis, univariate and multivariate Cox proportional hazard regression analysis.

Conclusions: The use of trimodality therapy significantly increased during the study period and was associated with improved outcomes regardless of age and extent of resection.

INTRODUCTION

Gliosarcoma (GSM) is a rare, primary malignant brain tumor that accounts for 4% of all malignant gliomas [1]. Its morphology is characterized as a well-circumscribed lesion with clearly identifiable biphasic glial and mesenchymal components histologically [1, 2]. The mesenchymal component of the tumor may display a variety of morphologies with origins from fibroblastic, cartilaginous, osseous, smooth muscle, striated muscle, or adipose cell lineage [3, 4]. Clinical guidelines for diagnosis are poorly defined. In the 2007 World Health Organization (WHO) classification of central nervous system (CNS) tumors, the glial component of GSM meets the histological criteria for grade IV astrocytoma (glioblastoma) [5]. The new 2016 WHO classification, with its incorporation of molecular markers, has placed GSM under the category of IDH-wild type glioblastoma [6].

Clinically similar to glioblastoma, GSM usually affects patients in their sixth to eighth decade of life, with a male preponderance [7, 8]. The median age at diagnosis was approximately 60 years [7, 9–12].Current treatment options include surgery, radiotherapy (RT) and chemotherapy (CT) [13]. Due to its low incidence, the current literature is limited to case reports and small cases series with insufficient evidence to guide treatment decisions. A previous study using the National Cancer Data Base (NCDB) compared patient demographics, treatment regimen, and survival among glioblastoma, giant cell glioblastoma, and GSM [14]. However, the study was limited to patients diagnosed before 2006 and did not provide focused analysis on the GSM patients.

The primary aim of this study was to examine treatment approach and survival outcomes in patients with primary GSM using data from the NCDB.

RESULTS

Demographic, patient, and tumor characteristics

A total of 1622 patients were included with a median follow-up of 10.2 months. Our patient flowchart is shown in Supplementary Figure 1. The median age was 63 years (range, 18–90 years). A summary of patient and tumor characteristics for the entire cohort is shown in Table 1. Information on the extent of resection was available for 524 patients, among whom 309 underwent gross total resection (GTR) and 215 subtotal resection (STR) (Supplementary Table 1). A comparison of baseline characteristics of patients diagnosed before and after 2007 is shown in Supplementary Table 2.

Treatment

One thousand patients (61.7%) received trimodality therapy (defined as the use of surgery, RT and CT), while 365 patients received surgery alone, 164 patients surgery followed by RT, and 30 patients surgery followed by CT. Sixty-three patients did not undergo surgery. Patients aged 18 to 60 years were significantly more likely to receive trimodality therapy than patients older than 60 (68.1% vs. 56.7%, $p < 0.001$).The use of trimodality therapy significantly increased during the study period (57.5% in 2004–2008 vs. 65.1% in 2009–2013; $p = 0.002$). Patients aged 18–60 years were significantly more likely to receive RT (77.0% vs. 67.7%, $p < 0.001$) and CT (69.2% vs. 59.1%, $p < 0.001$) than patients aged 61–90 years. The use of RT (69.4% for 2004–2008 vs. 73.7% for 2009–2013, $p = 0.06$) and CT (59.9% in 2004–2008 vs. 65.5% in 2009–2013, $p = 0.007$) increased significantly during the study period.

Survival outcomes

The median OS and the 3-year OS rate for the entire cohort was 10.2 months and 11.9%, respectively (Figure 1). Patients diagnosed after 2007 had significant longer OS than those diagnosed before 2007 (Supplementary Figure 2). On multivariate analysis, older age (HR, 1.032, 95% CI, 1.028–1.037, $p < 0.001$), Charlson-Deyo score ≥1 (HR, 1.262, 95% CI, 1.125–1.416, $p < 0.001$) and multi-focal tumor (HR, 1.417, 95% CI, 1.105–1.817, $p = 0.006$) were associated with shorter OS, while GTR (HR, 0.784, 95% CI, 0.659–0.933, $p = 0.006$), surgery followed by RT (HR, 0.783, 95% CI, 0.645–0.950, $p = 0.01$) and the use of trimodality therapy (HR, 0.514, 95% CI, 0.451–0.585, $p < 0.001$) were associated with longer OS (Table 2 and Figure 2). Compared to surgery alone, surgery followed by CT alone did not result in improved OS on multivariate analysis.

Subgroup analysis based on extent of resection

There was no significant difference in baseline characteristics between STR and GTR groups except for tumor size (Supplementary Table 1). Patients who received GTR had significantly longer OS than those who received STR (median OS: 13.2 vs. 9.6 months, $p < 0.001$; Figure 2B). On multivariate analysis, among the 215 patients who underwent STR, older age (HR, 1.021, 95% CI, 1.008–1.034, $p = 0.002$) and multi-focal tumor (HR, 1.912, 95% CI, 1.236–2.958, $p = 0.004$) were associated with shorter OS, while the use of trimodality therapy was associated with longer OS (HR, 0.375, 95% CI, 0.259–0.543, $p < 0.001$) (Supplementary Table 3 and Supplementary Figure 3).

Among the 309 patients who underwent GTR, older age (HR, 1.029, 95% CI, 1.017–1.041, $p < 0.001$) and a Charlson-Deyo score > 1 (HR, 1.391, 95% CI, 1.044–1.854, $p = 0.02$) were associated with shorter OS, while the use of trimodality therapy was associated with longer OS (HR, 0.545, 95% CI, 0.388–0.764, $p < 0.001$) on multivariate analysis (Supplementary Table 4 and Supplementary Figure 4).

Table 1: Demographics and clinical characteristics of the entire cohort

Category		No. (%)
Age (range, 18–90 y)	18–40 y	102 (6.3)
	41–50 y	203 (12.5)
	51–60 y	400 (24.7)
	61–70 y	484 (29.8)
	71–90 y	433 (26.7)
Gender	Male	987 (60.9)
	Female	635 (39.1)
Race	White	1426 (87.9)
	Black	133 (8.2)
	Asian	31 (1.9)
	Other	13 (0.8)
	Unknown	19 (1.2)
Year of diagnosis	2004–2008	739 (45.6)
	2009–2013	883 (54.4)
Tumor size	0–4 cm	502 (30.9)
	> 4.1 cm	818 (50.4)
	Unknown	302 (18.6)
Tumor location	Supratentorial	1282 (79.0)
	Infratentorial	10 (0.6)
	Unknown	330 (20.3)
Metastasis at diagnosis	M0	1486 (91.6)
	M+	21 (1.3)
	Unknown	115 (7.1)
Charlson-Deyo score	0	1140 (70.3)
	≥ 1	482 (29.7)
Treatment	No surgery	63 (3.9)
	Surgery alone	365 (22.5)
	Surgery with RT	164 (10.1)
	Surgery with CT	30 (1.8)
	Trimodality therapy	1000 (61.7)
Extent of Resection	Subtotal resection/biopsy	344 (21.2)
	Gross total resection	309 (19.1)
	Other	969 (59.7)
Lesion Number	Unifocal tumor	568 (35.0)
	Multifocal tumor	83 (5.1)
	Other	971 (59.9)

Abbreviations: M0, no metastatic disease at diagnosis; M+, metastatic disease at diagnosis; RT, radiation therapy; CT, chemotherapy.

Subgroup analysis based on age

The age distribution of the entire cohort is shown in Supplementary Figure 5. There was no significant difference in baseline characteristics between the 18–60 y and 61–90 y age groups except for race, Charlson-Deyo score and treatment (Supplementary Table 5). Older patients were more likely to be white and with more comorbidities, but less likely to receive trimodality than younger patients. In the 18–60 age group, older age (HR, 1.030, 95% CI, 1.019–1.040, $p < 0.001$), a Charlson-Deyo score > 1 (HR, 1.219, 95% CI, 1.002–1.482, $p = 0.047$)

and multi-focal tumor (HR, 1.747, 95% CI, 1.173–2.601, $p = 0.006$) were associated with shorter OS, while trimodality therapy (HR, 0.599, 95% CI, 0.481–0.745, $p < 0.001$) and GTR (HR, 0.761, 95% CI, 0.580–0.999, $p = 0.049$) were associated with longer OS on multivariate analysis (Supplementary Table 6 and Supplementary Figure 6).

In the 61–90y group, trimodality therapy (HR, 0.469, 95% CI, 0.397–0.554, $p < 0.001$) was associated with longer OS, while older age (HR, 1.045, 95% CI, 1.034–1.055, $p < 0.001$) and a Charlson-Deyo score > 1 (HR, 1.316, 95% CI, 1.138–1.522, $p < 0.001$) were associated with shorter OS (Supplementary Table 7 and Supplementary Figure 7).

DISCUSSION

Due to the rarity of GSM, insufficient literature has been published on this tumor to guide clinical treatment [15]. The current treatment recommendations for GSM are largely based on those for the more common glioblastoma. Using the NCDB, we evaluated treatment approaches and survival outcomes in 1622 adult patients diagnosed with primary GSM. We found that the use of trimodality therapy significantly increased during the study period and was associated with longer OS. Compared to surgery alone, surgery followed by RT alone also resulted in improved OS, but not to the same extent as trimodality therapy. Surgery followed by CT alone did not result in an OS benefit. These results were consistent in subgroup analyses as well.

The improved survival during the study period could be attributed to the increased use of trimodality therapy. We found that the use of both RT ($p = 0.06$) and CT ($p = 0.007$) increased significantly during the time period. These changes could be attributed to the improved understanding of underlying tumor biology as well as tumor response to these adjuvant therapies in recent years [16–18], or more importantly the clinical findings in both GSM and the clinically similar glioblastoma that more favorable outcomes often result from treatment with adjuvant RT and/or CT [19, 20]. This same trend has started to apply to low-grade gliomas as well, after a randomized controlled trial of 251 patients was published in 2016 that demonstrated longer progression-free survival and OS among patients who received trimodality when compared to RT alone [21]. However, there are well-known side effects of RT and CT which are especially prominent for elderly cancer patients treated with these therapies [22, 23]. Thus, these treatments should only be offered when the benefits outweigh the risks.

A number of studies on glioblastomas have demonstrated the efficacy of RT and CT, in addition to surgery, as the treatment of choice [19, 24, 25]. The question that remains, which was investigated in our study, is whether or not this standard of treatment can be applied to GSM patients, given that GSM has a worse prognosis than glioblastoma [20, 25]. In our cohort of GSM patients, we found that although surgery followed by RT alone was associated with longer OS, trimodality therapy resulted in the greatest OS benefit. Despite the increasing use of RT and CT in recent years, the current literature has mixed results on the effectiveness of adjuvant therapy in GSM. Some studies have demonstrated the benefit of adjuvant RT and CT [25, 26], while others questioned their utility [25, 26]. A literature summary of treatment, survival and prognostic factors in GSM studies greater than 10 patients is presented in Supplementary Table 8 [2, 7–12, 20, 24–35]. In many of these studies, the sample size was small, and there was a lot of heterogeneity in the treatment regimen used. In a study of 353 GSM patients from the Surveillance, Epidemiology, and End Results database, the largest study published in the literature prior to the current study, Kozak et al. suggested that tumor resection, as opposed to biopsy only, and adjuvant RT may improve

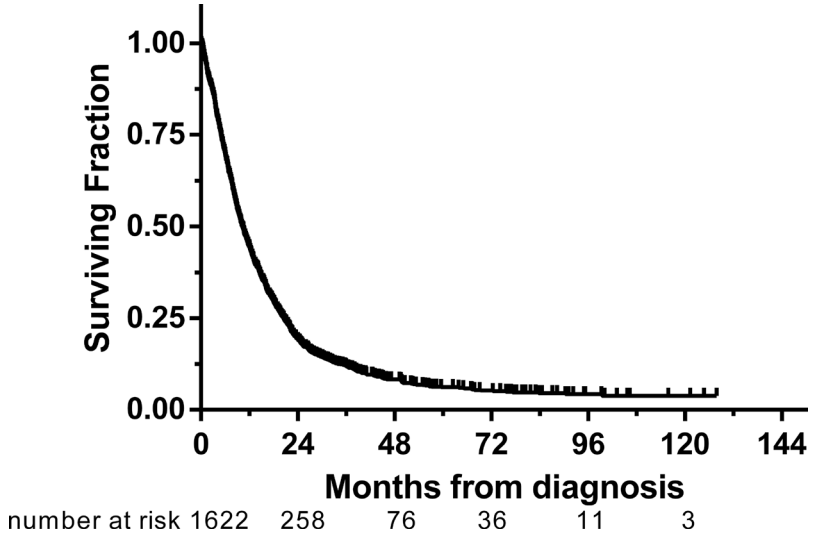

Figure 1: Kaplan-Meier curve of overall survival for the entire cohort.

Table 2: Univariate and multivariate Cox proportional hazards analyses of the overall survival for the entire cohort

	Univariate Analysis		Multivariate Analysis	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age (range, 18–90 y)				
As continuous variable	1.035 (1.030–1.039)	< 0.001	1.032 (1.028–1.037)	< 0.001
Gender				
Male	Reference group		-	
Female	0.934 (0.840–1.040)	0.21	-	
Race				
White	Reference group		-	
Nonwhite	0.873 (0.742–1.027)	0.10	-	
Year of diagnosis				
2004–2008	Reference group		-	
2009–2013	0.890 (0.801–0.988)	0.03	-	
Tumor size				
0–4.0 cm	Reference group		-	
> 4.0 cm	1.064 (0.945–1.199)	0.30	-	
Tumor location				
Supratentorial	Reference group		-	
Infratentorial	0.574 (0.273–1.207)	0.14	-	
Metastasis at diagnosis				
M0	Reference group		-	
M+	1.074 (0.674–1.710)	0.76	-	
Charlson-Deyo score				
0	Reference group		Reference group	
≥ 1	1.398 (1.248–1.566)	< 0.001	1.262 (1.125–1.416)	< 0.001
Treatment				
Surgery alone	Reference group		Reference group	
No surgery	1.096 (0.827–1.452)	0.52	1.136 (0.851–1.518)	0.39
Surgery with RT	0.849 (0.700–1.031)	0.10	0.783 (0.645–0.950)	0.01
Surgery with CT	1.036 (0.704–1.525)	0.86	0.895 (0.607–1.318)	0.57
Trimodality therapy	0.507 (0.446–0.577)	< 0.001	0.514 (0.451–0.585)	< 0.001
Extent of resection				
Subtotal resection/Biopsy	Reference group		Reference group	
Gross total resection	0.722 (0.608–0.858)	< 0.001	0.784 (0.659–0.933)	0.006
Other	0.959 (0.839–1.095)	0.53	1.028 (0.806–1.311)	0.82
Lesion number				
Unifocal tumor	Reference group		Reference group	
Multifocal tumor	1.461 (1.141–1.872)	0.003	1.417 (1.105–1.817)	0.006
Other	1.136 (1.014–1.272)	0.03	0.992 (0.783–1.256)	0.95

Abbreviations: CI, confidence interval; HR, hazard ratio; M0, no metastatic disease at diagnosis; M+, metastatic disease at diagnosis; RT, radiation therapy; CT, chemotherapy.

survival outcomes [20]. However, this study was limited by the lack of data on CT. In a retrospective study of 75 GSM patients by Castelli et al., the second-largest of its kind, patients were treated with a combination of surgery, RT and/or CT. A high total dose of RT and treatment at recurrence were found to be good prognostic factors, while temozolomide (TMZ)-based CT was not associated with an improvement in OS when compared to patients who received RT alone [9]. A smaller retrospective study of 27 GSM patients from 2009–2013 by Kumar et al. found that the addition of TMZ to RT did not significantly improve OS when compared to RT alone [33]. Using a much larger cohort, we were able to show definitively the benefit of trimodality therapy in both the entire cohort and subgroups of GTR and STR.

Age has been shown to be an important predictor of survival in both GSM and glioblastoma. We found that patients over the age of 60 years were less likely to receive adjuvant therapies than younger patinets. Similar trends have been observed in glioblastoma patients, in which age was the most significant predictor of the type of treatment received, with elderly patients less likely to receive adjuvant RT and CT [36, 37]. As expected, the survival outcomes for younger patients were significantly better than those for older patients (median OS: 14.5 vs. 8.2 months; $p < 0.001$). In addition to the less favorable tumor biology and comorbidities associated with advanced age, it is possible that the shorter OS in older patients can be partly attributed to their lesser likelihood of receiving trimodality therapy, which has been shown in our study to improve OS regardless of age. The concern about adjuvant RT in elderly glioblastoma patients is neurotoxicity, which would outweigh any survival benefit conferred by RT [38–40]. The link between comorbidity and receipt of treatment remains unclear, even in glioblastoma patients. For example, Iwamoto et al. found that though higher

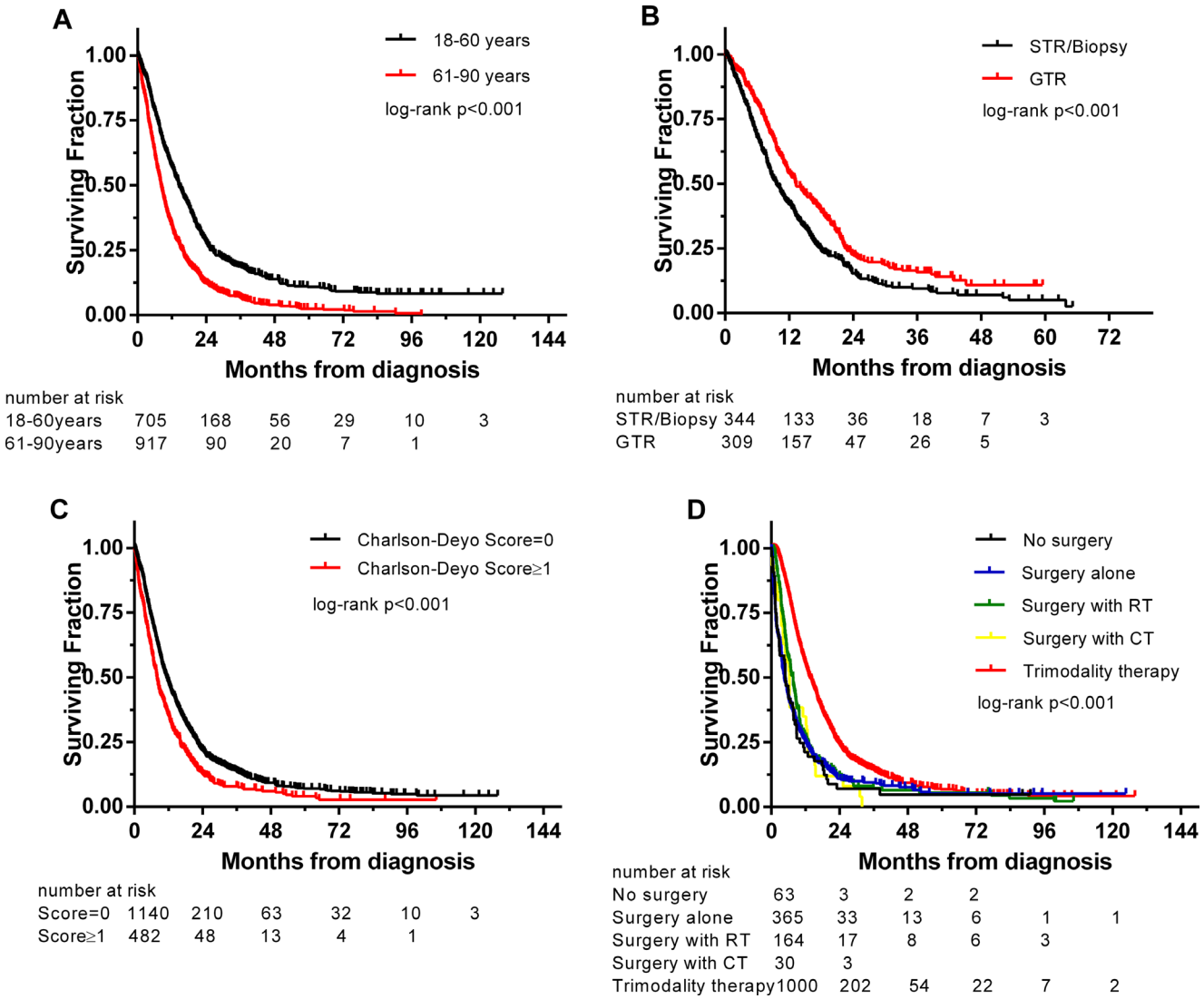

Figure 2: Kaplan-Meier curve comparing overall survival in patients (**A**) aged 18 to 60 years and 61 to 90 years, (**B**) who underwent subtotal resection/biopsy and gross total resection, (**C**) with Charlson-Deyo score of 0 and ≥ 1, (**D**) treated with no surgery, surgery alone, surgery followed by radiation therapy, surgery followed by chemotherapy and trimodality therapy.

comorbidity was associated with decreased RT treatment, comorbidities were not strong predictors of treatment receipt [41].

We would like to acknowledge several limitations of our study. First, there was no central pathology review so presumably some samples may have been misdiagnosed as GSM. Second, data on rescue therapies post primary course of treatment was not available in the NCDB. Third, the NCDB lacked data on important molecular markers in glioblastoma such as IDH1 mutation and MGMT promoter methylation. However, IDH1 mutation and MGMT promoter methylation have been reported to be rare in GSM [2]. Even though our study includes a large number of patients with relatively complete information on patient demographics and treatments, the inherent bias of a retrospective study can only be excluded with a prospective randomized control trial.

MATERIALS AND METHODS

Data source and study population

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Established in 1989, the NCDB is a comprehensive, nationwide, facility-based oncology data set that captures approximately 70% of all newly diagnosed malignancies in the United States. The data used in this study are derived from a deidentified participant user file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or for the conclusions drawn, from these data by the investigators.

Deidentified data for patients diagnosed with primary GSM who were 18 years or older and diagnosed between 2004 and 2013 with follow-up were extracted from the NCDB. We excluded patients with incomplete treatment data. Demographic and clinical data extracted included age, gender, race, primary tumor site, tumor size, presence of metastatic disease, Charlson-Deyo score, extent of resection (GTR versus STR/biopsy), lesion number (unifocal versus multifocal) and type of treatment (surgery, RT, and CT). Neither institutional review board/ethics committee nor patient consent was required for this study since the study used de-identified data from a public database.

Statistical analysis

OS was calculated from diagnosis until death with censoring at the last follow-up for patients who were alive. Patients' co-morbidity, or the lack of, was evaluated by the Charlson-Deyo score. Charlson-Deyo score (0, 1, or 2) was assigned according to NCDB guidelines based on how many co-morbid conditions were reported and their relative severity. The chi-square test was used to evaluate contingency tables as appropriate. Univariate Cox regression followed by multivariate Cox proportional hazard regression was used to calculate hazard ratios (HRs) for survival and identify independent prognostic factors for OS. Variables with p values < 0.05 on univariate cox regression were entered into the multivariate Cox proportional model. Significance was defined as a value of $p < 0.05$. All levels of significance were 2-sided. SPSS Statistics V22.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

CONCLUSIONS

In conclusion, the use of trimodality therapy significantly increased during the study period and was associated with longer survival regardless of age or extent of resection.

Abbreviations

NCDB, National Cancer Database; OS, overall survival; CI, confidence interval; GSM, gliosarcoma; CNS, central nervous system; WHO, World Health Organization; RT, radiotherapy; CT, chemotherapy; GTR, gross total resection; STR, subtotal resection; HR, hazard ratio; TMZ, temozolomide.

Author contributions

Li Yang, Harrison X. Bai and Lu Deng conceptualized the project. Harrison X. Bai obtained the data used for this study. All authors contributed to data analysis and editing of the manuscript.

CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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