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Clinical study

Treatment patterns and outcomes for cerebellar glioblastoma in the concomitant chemoradiation era: A National Cancer database study

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ABSTRACT

Cerebellar glioblastoma (GB) is much rarer than its supratentorial counterpart, and potentially of different molecular origin. Prior database studies are of limited size and reported on patients who preceded the validation of temozolomide. Thus, we provide an updated population-based analysis of the treatment trends and outcomes since the standardization of GB adjuvant chemoradiation. Patients diagnosed with primary cerebellar and supratentorial GB were identified from the National Cancer Database spanning 2005–2015. Patients were characterized by demographics, extent of resection, and adjuvant chemotherapy or radiation status. Cohorts were primarily and secondarily assessed for overall survival by tumor site and treatment history, respectively. A total of 655 patients with cerebellar GB were identified (0.6%). Cerebellar GB patients, compared to supratentorial GB were more likely to undergo a biopsy or subtotal resection (13.4% vs 9.3% and 16.0% vs 13.4%, p-value < 0.001), and less likely to pursue adjuvant therapy (48.4% vs 52.7%, p-value < 0.001). Overall median survivals were 9.3 and 9.4 months, respectively. On multivariable analysis, gross total resection, radiation, and chemotherapy were found to be predictors of improved overall survival (HR 0.77, p = 0.038; HR 0.67, p < 0.001; and HR = 0.77, p = 0.030, respectively). While many management principles are currently shared between cerebellar and supratentorial GB, aggressive regimens appear less frequently prescribed. Survival continues to match supratentorial outcomes and may benefit from future, systemic guidance by distinguishing molecular features.

1. Introduction

Glioblastoma (GB) is the most common primary brain tumor in adults, but only 0.5–1% of cases initially arise from the cerebellum [1,2]. Although cerebellar GB represents a much rarer subset of primary central nervous system (CNS) tumors, they have had comparable outcomes with their supratentorial counterparts [1–4]. This may be since treatment recommendations for surgical resection with adjuvant chemoradiation among supratentorial lesions have commonly been extrapolated [5,6]. However, prior large database series reported on populations that included patients from primarily before 2005, when concomitant temozolomide and radiation-based protocol was formally reported [1,2,7].

Additionally, the recent movement towards molecularly based diagnosis of supratentorial GB has enabled identification of subgroups with prolonged survival [8,9]. The same robust, molecular characterization has not been duplicated within cerebellar GB [10]. There is a scarcity of data comparing outcomes in cerebellar versus supratentorial GB treated using modern treatment techniques. In order to provide an update to prior smaller and older outcome studies, we use the National Cancer Database (NCDB) to report on the trends in treatment preferences and associated outcomes in a contemporary cohort of cerebellar GB patients.

2. Methods

The NCDB is a national oncology database sponsored by the American College of Surgeons and the American Cancer Society which captures > 70% of newly diagnosed cancer cases in the United States [11]. Patients diagnosed with primary brain tumors from 2005 to 2015 were identified in the National Cancer Database. Patients were included if they had primary GB; histology of glioma was defined using the International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] codes, including 9380–9382, 9400–9401, 9440–9445, 9450–9451 [12]. Brainstem tumors were excluded using the primary site code. Inclusion and exclusion criteria for our patient cohort are illustrated in Fig. 1.

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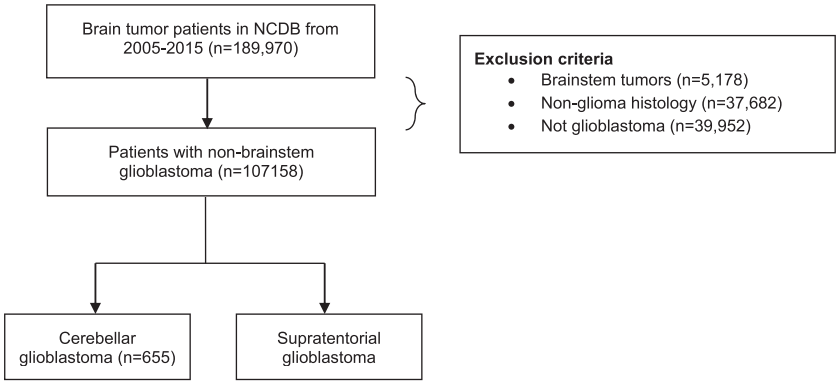


Fig. 1. Inclusion and exclusion criteria for the patient cohort. Abbreviations: NCDB = National Cancer Database.

Table 1
Comparative demographics for patients with cerebellar glioblastoma and supratentorial glioblastoma.

	Cerebellar (n = 655)	Supratentorial (n = 106,503)	p-value of Chi-square test
Sociodemographic Factors			
Year of Diagnosis			
2005-2006	108 (16.5%)	17198 (16.1%)	
2007-2009	162 (24.7%)	27671 (26.0%)	
2010-2012	193 (29.5%)	29632 (27.8%)	
2013-2015	133 (20.3%)	21305 (20.0%)	0.77
Sex			
Female	280 (42.7%)	45373 (42.6%)	
Male	375 (57.3%)	61130 (57.4%)	0.938
Charlson-Deyo Comorbidity Score			
0	486 (74.2%)	76087 (71.4%)	
1	118 (18.0%)	18491 (17.4%)	
≥ 2	51 (7.8%)	11925 (11.2%)	0.022*
Age			
<65 years	406 (62.0%)	58303 (54.7%)	
≥65 years	249 (38.0%)	48200 (45.3%)	< 0.001***
Race			
Non-Hispanic White	522 (79.7%)	91799 (86.2%)	
Black	48 (7.3%)	5772 (5.4%)	
Hispanic	44 (6.7%)	5275 (5.0%)	
Other	41 (6.3%)	3657 (3.4%)	< 0.001***
Facility Type			
Academic/Research	320 (48.9%)	56091 (52.7%)	
Community/Comprehensive Community	212 (32.4%)	45408 (42.6%)	
Unknown	123 (18.8%)	5004 (4.7%)	< 0.001***
Insurance Status			
Government	340 (51.9%)	54146 (50.8%)	
Private	266 (40.6%)	45981 (43.2%)	
None	32 (4.9%)	3850 (3.6%)	
Unknown	17 (2.6%)	2526 (2.4%)	0.243
Region			
Midwest	123 (18.8%)	25159 (23.6%)	
Northeast	220 (33.6%)	42886 (40.3%)	
South	81 (12.4%)	16262 (15.3%)	
West	108 (16.5%)	17192 (16.1%)	
Unknown	123 (18.8%)	5004 (4.7%)	< 0.001***
Treatment Factors			
Surgical resection status			
No surgery	125 (19.1%)	26524 (24.9%)	
Biopsy only	88 (13.4%)	9914 (9.3%)	
Subtotal resection	105 (16.0%)	14238 (13.4%)	
Gross total resection	128 (19.5%)	22457 (21.1%)	
Surgery, not otherwise specified	209 (31.9%)	33370 (31.3%)	< 0.001***
Received radiation			
No	227 (34.7%)	31649 (29.7%)	
Yes	428 (65.3%)	74854 (70.3%)	0.003**
Received chemotherapy			
No	279 (42.6%)	38056 (35.7%)	
Yes	376 (57.4%)	68447 (64.3%)	< 0.001***
Treatment paradigm			
Surgical resection, adjuvant therapy	317 (48.4%)	55608 (52.2%)	
Surgical resection, no adjuvant therapy	125 (19.1%)	14457 (13.6%)	
Chemotherapy and/or radiation alone	136 (20.8%)	22633 (21.3%)	
No treatment	77 (11.8%)	13805 (13.0%)	< 0.001***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The overall patient cohort was stratified into cerebellar and supratentorial GB cohorts. All variables were selected *a priori*. Demographic variables including age, year of diagnosis, race, insurance status, facility type, Charlson-Deyo comorbidity score were defined according to their respective data fields in the NCDB data dictionary [13]. Race was categorized as non-Hispanic white, Black, or other (including Hispanic, Asian, and other). Insurance status was grouped into government (Medicare/Medicaid/other), private, or uninsured.

For treatment variables, extent of resection (EOR) was defined using the surgery of primary site code in the NCDB data dictionary. Receipt of chemotherapy and radiation were defined by their respective fields in the data dictionary. Sequencing of treatment was determined according to the time between diagnosis and initiating that modality of treatment.

Descriptive statistics were generated for each cohort, with Chi-square test used for comparisons. Logistic regression was used to predict adjuvant therapy use in the management of cerebellar GB patients. Kaplan-Meier survival curves were generated, and a log-rank test was performed for comparison between cerebellar and supratentorial GB. Cox proportional-hazards regression was performed to evaluate predictors of overall survival in the cerebellar GB cohort.

All statistical analyses were performed using the open-source R statistical environment (version 3.4.2; R Core Team 2017) and SPSS statistical software (version 23.0; IBM Corporation, Armonk, NY).

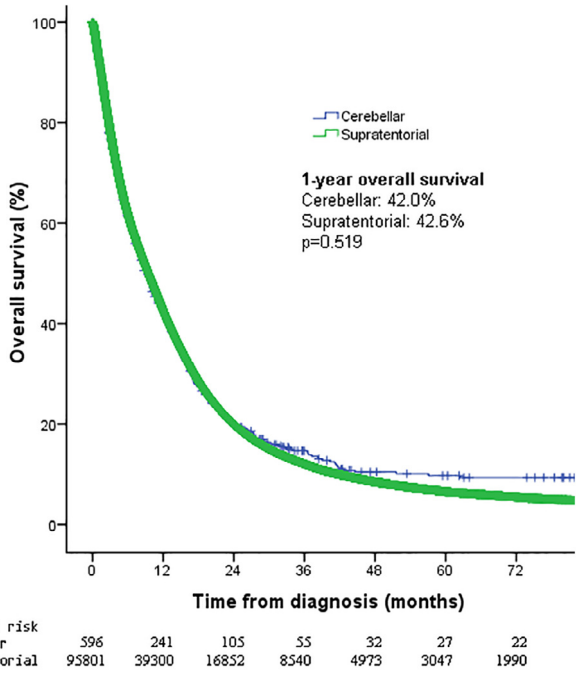


Fig. 2. Kaplan-Meier survival curves comparing patients with cerebellar glioblastoma with supratentorial glioblastoma.

3. Results

3.1. Patient population

A total of 655 patients with cerebellar GB were identified over the study period (0.6%, Table 1). A comparison between the study population with patients presenting for supratentorial GB management 2005–2015 suggested patients with cerebellar disease were proportionally of a younger age (<65 years among 62% vs 54.7%, p-value < 0.001, Chi squared) and fewer comorbidities (≥2 points among 7.8% vs 11.2%, p-value = 0.022, Chi squared). Cerebellar GB patients, compared to supratentorial GB were more likely to undergo a biopsy or subtotal resection (13.4% vs 9.3% and 16.0% vs 13.4%, p-value < 0.001, Chi squared) Additionally, cerebellar GB were less likely to receive chemotherapy (57.4% vs 64.3%, p-value < 0.001) or radiation (65.3% vs 70.3%, p-value = 0.003). When considering possible combination treatments, cerebellar GB were most like to receive surgical intervention with some form of adjuvant therapy (chemotherapy or radiation), but at a lower rate, relative to patients with supratentorial diagnoses (48.4% vs 52.7%, p-value < 0.001, Chi squared).

3.2. Survival

The 1- and 2- year survival rates for cerebellar GB and supratentorial GB were 42.6% and 20% vs 42% and 20.2% (p = 0.5186, Log-rank, Fig. 2). Overall median survivals were 9.3 and 9.4 months for cerebellar and supratentorial GB, respectively. We further investigated outcomes for patients who received any adjuvant therapy, among whom survival between cerebellar and supratentorial GB were 12.4 and 14.3 months, respectively. The median follow-up for the overall patient population was 9 months; median follow-ups were 8.6 and 9.0 months in the cerebellar and supratentorial GB cohort, respectively.

Survival outcomes associated with surgical management were further analyzed. The 1-year survival rates for patient undergoing no surgery, biopsy, subtotal resection, and gross total resection were 33.9%, 40.2%, 35.2%, and 52.4%. The 2-year survival rates were 14.3%, 22.5%, 15.4%, and 27.8% respectively (p-value < 0.001 Log rank, Fig. 3**A**). Among patients receiving radiation, relative to those not receiving radiation, the 1- and 2- year OS were 51.2% vs 25.1% and 23.5% vs 13.7% (p-value < 0.001, Log rank, Fig. 3**B**).

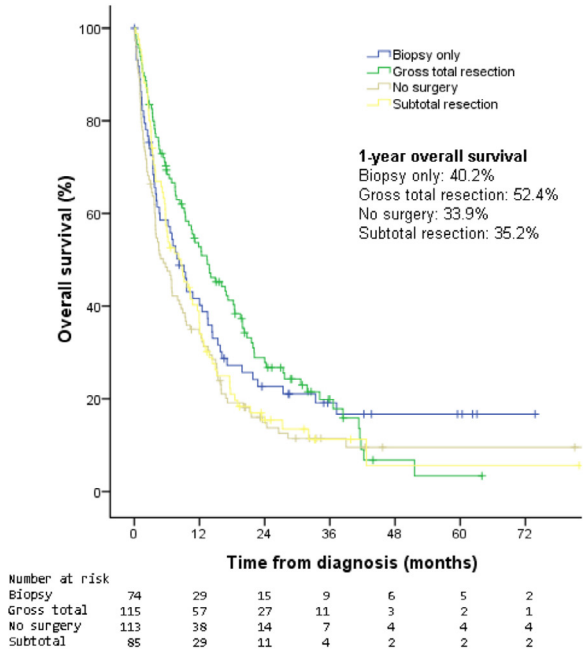
Additional multivariable Cox proportional hazards analysis was conducted to identify predictors of overall survival (Table 2). Age ≥ 65 was a negative predictive feature (HR = 1.08, CI 1.01–1.17, p = 0.030). Meanwhile both radiation and chemotherapy were found to be protective (HR 0.67, CI 0.52–0.85, p < 0.001 and HR = 0.77, CI 0.60–0.98, p = 0.030, respectively). Regarding EOR, there were no statistically significant differences between either STR or biopsy, relative to no intervention, but there was improved survival seen between GTR and no intervention (HR 0.67, CI 0.5–0.9, p = 0.007).

Finally, an additional multivariable analysis on possible predictors of receipt of adjuvant therapy was performed specifically on cerebellar GB patients (Table 3). Older age and a comorbidity score ≥ 2 were less likely to receive adjuvant treatment (HR 0.56, CI 0.37–0.85, p = 0.007 and HR 0.35, CI 0.18–0.69, p = 0.002). Patients treated in the community were also less likely to get additional chemotherapy or radiation (HR 0.77, CI 0.60–0.98, p = 0.030).

4. Discussion

In this study we characterize the population-level landscape of cerebellar GB treatment and outcomes since the academic introduction of concomitant temozolomide and radiation in 2005. Most notably survival between cerebellar and supratentorial GB have remain matched, with prolonged survival associated with additional interventions. The EOR achieved for cerebellar GB appears less than that achieved for supratentorial GB, perhaps giving insight on how the former are triaged. With regards to adjuvant therapy, this is the first database study to confirm that chemotherapy has associated survival benefits, which is important given the increasing role of molecularly guided therapies.

(A)



(B)

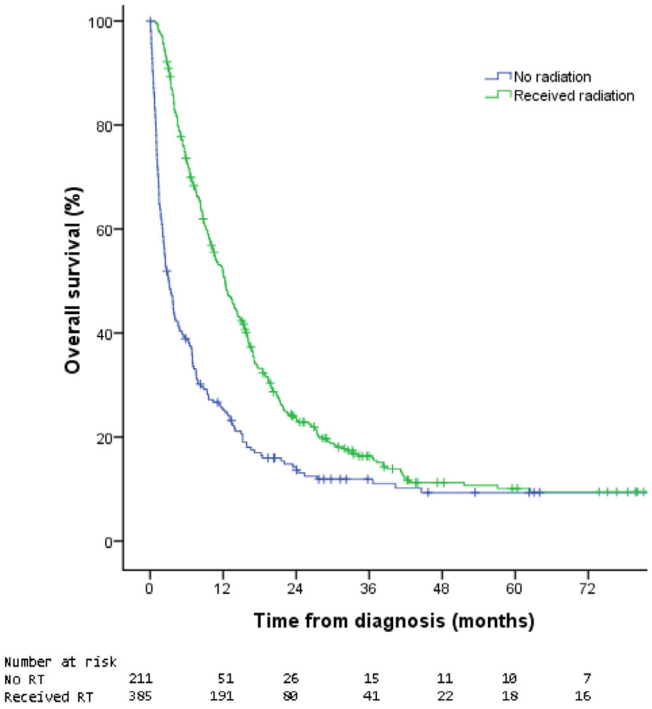


Fig. 3. Kaplan-Meier survival curves in patients with cerebellar glioblastoma. (A) Survival curves stratified by extent of resection. (B) Survival curves stratified by receipt of radiation. Abbreviations: RT = radiation therapy.

4.1. Predictors of survival

We identified a median survival period approximating 9 months which was comparable between supratentorial and cerebellar GB, and similar to Surveillance, Epidemiology, and End Results (SEER) database studies covering an earlier period [1,2]. There may be signs of marginal gains, as these studies, inclusive of populations

Table 2
Multivariable Cox proportional hazards regression for overall survival in patients with cerebellar glioblastoma.

Significant Factors	Hazard of death (95% Confidence)	P Value
Age		
< 65 years	Reference	
≥ 65 years	1.08 (1.01–1.17)	0.030*
Charlson-Deyo Comorbidity Score		
0	Reference	
1	1.26 (1.00–1.58)	0.051
≥ 2	1.13 (0.81–1.57)	0.482
Race		
Non-Hispanic White	Reference	
Black	0.57 (0.39–0.83)	0.003**
Other	0.67 (0.45–0.99)	0.045*
Unknown	0.81 (0.56–1.18)	0.269
Received radiation		
No	Reference	
Yes	0.67 (0.52–0.85)	0.001**
Received chemotherapy		
No	Reference	
Yes	0.77 (0.60–0.98)	0.030*
Extent of surgical resection		
None	Reference	
Biopsy only	0.77 (0.55–1.08)	0.128
Subtotal resection	0.90 (0.66–1.22)	0.502
Gross total resection	0.67 (0.50–0.90)	0.007**
Surgery, not otherwise specified	0.77 (0.60–0.99)	0.038*

* p < 0.05, ** p < 0.01.

Table 3
Logistic regression for utilization of surgery with adjuvant therapy in patients with cerebellar glioblastoma.

Significant Factors	Hazard of death (95% Confidence)	P Value
Year of Diagnosis		
2005–2006	Reference	
2007–2009	1.27 (0.76–2.12)	0.357
2010–2012	0.65 (0.40–1.07)	0.090
2013–2015	0.68 (0.41–1.11)	0.123
Sex		
Female	Reference	
Male	0.81 (0.59–1.13)	0.216
Age		
< 65 years	Reference	
≥ 65 years	0.56 (0.37–0.85)	0.007**
Charlson-Deyo Comorbidity Score		
0	Reference	
1	0.89 (0.58–1.36)	0.588
≥ 2	0.35 (0.18–0.69)	0.002**
Race		
Non-Hispanic White	Reference	
Black	1.19 (0.63–2.22)	0.593
Hispanic	0.65 (0.34–1.26)	0.205
Other	1.07 (0.55–2.08)	0.838
Insurance		
Government	Reference	
Private	1.16 (0.78–1.73)	0.458
Uninsured	0.76 (0.34–1.69)	0.499
Facility Type		
Academic/Research	Reference	
Community/Comprehensive Community	0.77 (0.60–0.98)	0.030*
Extent of surgical resection		
None	Reference	
Biopsy only	0.77 (0.55–1.08)	0.128
Subtotal resection	0.90 (0.66–1.22)	0.502
Gross total resection	0.67 (0.50–0.90)	0.007**
Surgery, not otherwise specified	0.77 (0.60–0.99)	0.038*

* p < 0.05, ** p < 0.01.

through 2009, cited 1-year survival rates of 21% and 34%. Most prior small series on adult cerebellar GB have argued equal or worse outcomes to supratentorial counterparts, also citing median overall survival spanning 5–9 month [1,2,4–6,14,15]. Among the best performing cohorts, Tsung et al. and Cho et al. described median overall survivals of over 18 months [3,16]. This is perhaps attributed to a higher rate of adjuvant care [16]. Alternatively, the availability of sequencing data may have been helpful with personalized treatment [3]. As we demonstrate in our own analysis, the commitment to additional postoperative therapy may promote better outcomes.

We also continue to give evidence to substantiate GTR when safely possible [1,15]. Prior SEER studies were equivocal, demonstrating only suggestive trends, only after post hoc analyses [1,2]. Our database findings seem to resolve this ambiguity, as GTR was associated with better survival outcomes. However, no statistically significant difference was observed in the multivariate HRs between biopsy and STR.

Interestingly in Tsung et al. EOR was not a predictor; however, in their series EOR was uniformly high with mean of 93.8%. The small cohort could preclude measuring a small effect size [16]. Nevertheless, there may still be a threshold EOR to see survival benefits among cerebellar GB, as is the case with supratentorial GB [17]. Alternatively, the EOR may inherently be limited among cerebellar GB due to lesion locations involving the brainstem and leptomeninges [6,16]. We further saw in our analysis that comorbidities strongly predicted adjuvant management. These anatomic and clinical attributes could explain our findings of more frequent subtotal resections and less frequent adjuvant regimens in cerebellar GB. In prior series, authors have also frequently commented how not all patients underwent aggressive care due to quality of life concerns [5,6].

There seems to be consistent evidence for an association between the coordination of post-surgical care and improved outcomes. Since prior SEER data could not report on chemotherapy information and preceded the standardization of the temozolomide-based care, these works did not address treatments' relationship with outcomes. Our median survival among those receiving adjuvant care is comparable to the temozolomide-era data. Despite the guidelines by Stupp et al., the literature on cerebellar GB still reflects a heterogeneity in chemotherapy regimens [2,3,5–7,16]. Although a subset of patients understandably pursue palliative measures, our data suggests some may benefit from earlier engagement at academic centers. Given the described benefits conferred by chemotherapy and radiation, we speculate such institutions are essential to coordinating post-surgical cancer care.

Histological Implications and Relationship to Supratentorial Glioblastoma

It is important to interpret these findings in the context of an increased emphasis for molecularly based diagnosis of GB. MGMT-status alone is insufficient for personalized glioma care. Moreover, although MGMT-mutation is of similar incidence between cerebellar and supratentorial GB, traditional concurrent chemoradiation according to the Stupp protocol has not always outperformed other regimens [3,16]. The WHO 2016 guidelines have helped to standardize the diagnostic algorithm for supratentorial GB, and there is increasing clarity of the genetic drivers among cerebellar lesions. The divergent outcomes of epithelial GB and IDH-mutant GB are evidence that future trials should be designed with cohorts containing more homogenous driver mutations [18,19].

The current literature on cerebellar GB has shown a unique molecular entity but is still investigating which mutations are most relevant for guiding care. Although histologically similar to supratentorial GB, cerebellar GB are commonly p53 mutated, EGFR-negative, and TERT-negative. These suggest an etiology different from traditional supratentorial GB [3,4,6,9,20]. Meanwhile, many cerebellar GB are also IDH-wildtype, and therefore distinct from low grade gliomas [3,4,6,20]. Additional genetic screening has demonstrated an anatomic predilection. Expression-level data of cerebellar GB identified a gene signature for oligodendroglial, specific to the posterior fossa [3,21]. Further involvement of H3K27M in about 20% has supported a potential bias in younger populations or brainstem involvement [3,5,6,14,15,22,23].

Future care and studies are moving towards more personalized capabilities. In a drug screening study, Cho et al. reported on cerebellar GB's overexpressed mutations and susceptibilities to chemotherapies [3]. Notable associations included loss of NF1 and vulnerability to MEK inhibitor, absence of EGFRvIII and poor responsiveness to EGFR-targeting agents, as well as PDGFRA alterations and increased responsiveness to tyrosine kinase inhibitors have all been proposed. Cerebellar GB may also benefit from alternative different treatment field array arrangements [24]. Unfortunately, this remains a rare pathology. Slow recruitment will likely preclude robust statistical conclusions about treatment regimens for cerebellar GB. Thus, current treatment paradigms will still realistically be guided by those for supratentorial GB. Fortunately hierarchical clustering analysis of genomic data shows cerebellar GB to be closer to supratentorial GB than other posterior fossa brain tumors [3].

5. Limitations

The NCDB database is an improvement given the larger population size and coverage of hospitalized patients with new oncologic diagnoses [25]. Nevertheless this study demonstrates the expected limitations of a national registry database. Particularly for the NCDB, it is subject to the participation and precision of contribution institutions. Several clinical features that could further elucidate the natural history of cerebellar GB are not captured here such as molecular diagnosis, tumor size, multifocality, recurrence, secondary status, and disposition. Likewise, certain variables were disproportionately missing in some variables such as race or geographic region, precluding a dedicated analysis on these population effects. We note that although multifocality and MGMT methylation status can be found in the data dictionary, this data was available for <10% of patients in the cohort, which we felt was insufficient for substantive analyses based on these factors. Finally, in part because of the rarity of cerebellar GB, direct comparison between sub-cohorts such as those describing EOR, were underpowered for subset analyses.

6. Conclusion

Overall, we continue to see that traditional treatment arms of surgery, radiation, and chemotherapy provide beneficial contributions to outcomes. However, this study notably identifies that providers do not uniformly apply all multi-modality treatment to and may be less aggressive with cerebellar GB, compared to supratentorial GB. Although it is reassuring to see that cerebellar GB outcomes have maintained pace with supratentorial GB, the muted survival gains in the last decade indicates room for improvement. Ongoing histological characterization are likely essential to selecting therapies and such registry studies as this will continue to be necessary monitor feedback.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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