Comparative Analysis of Survival Outcomes and Prognostic Factors of Supratentorial versus Cerebellar Glioblastoma in the Elderly: Does Location Really Matter?

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■ BACKGROUND: **Cerebellar glioblastomas (cGBMs) are rare tumors that are uncommon in the elderly. In this study, we compare survival outcomes and identify prognostic factors of cGBM compared with the supratentorial (stGBM) counterpart in the elderly.**

■ METHODS: **Data from the SEER 18 registries were used to identify patients with a glioblastoma (GBM) diagnosis between 2000 and 2016. The log-rank method and a multivariable Cox proportional hazards regression model were used for analysis.**

■ RESULTS: **Among 110 elderly patients with cGBM, the median age was 74 years (interquartile range [IQR], 69–79 years), 39% were female and 83% were white. Of these patients, 32% underwent gross total resection, 73% radiotherapy, and 39% chemotherapy. Multivariable analysis of the unmatched and matched cohort showed that tumor location was not associated with survival; in the unmatched cohort, insurance status (hazard ratio [HR], 0.11; IQR, 0.02–0.49; $P = 0.004$), gross total resection (HR, 0.53; IQR, 0.30–0.91; $P = 0.022$), and radiotherapy (HR, 0.33; IQR, 0.18–0.61; $P < 0.0001$) were associated with better survival. Patients with cGBM and stGBM undergoing radiotherapy (7 months vs. 2 months; $P < 0.001$) and chemotherapy (10 months vs. 3 months; $P < 0.0001$) had improved survival. Long-term mortality was lower for cGBM in the elderly at 24 months compared with the stGBM cohort ($P = 0.007$).**

■ CONCLUSIONS: **In our study, elderly patients with cGBM and stGBM have similar outcomes in overall survival, and those undergoing maximal resection with adjuvant therapies, independent of tumor location, have improved outcomes. Thus, aggressive treatment should be encouraged for cGBM in geriatric patients to confer the same survival benefits seen in stGBM. Single-institutional and multi-institutional studies to identify patient-level prognostic factors are warranted to triage the best surgical candidates.**

INTRODUCTION

Glioblastoma (GBM) is the most common primary brain malignancy, accounting for >60% of all primary brain tumors. Median survival is 15 months and 5-year survival is 5% despite aggressive therapies.[1-3] GBM is considered a disease of the elderly, with a median age of patients at diagnosis of 65 years and a peak incidence in individuals aged 75–84 years.[4] According to the National Institute on Aging, the global elderly population is expected to double from 8% to 16% by 2050, leading to an increase in GBM prevalence and a heightened challenge in the care of this population.[5]

Key words
- Cerebellum
- Elderly
- GBM
- Glioblastoma
- Infratentorial
- Supratentorial

Abbreviations and Acronyms
cGBM: Cerebellar glioblastoma
CI: Confidence interval
CT: Chemotherapy
GBM: Glioblastoma
GTR: Gross total resection
HR: Hazard ratio
IQR: Interquartile range
OS: Overall survival
RT: Radiotherapy
SEER: Surveillance Epidemiology and End Results
stGBM: Supratentorial glioblastoma
STR: Subtotal resection

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Despite significant advancements in our understanding of tumor biology and therapeutics, there remains significant heterogeneity in GBM survival because of factors such as age, tumor size, extent of resection, and baseline neurologic performance.[6-9] Tumor location is also believed to be an important prognostic factor, although the literature is inconclusive. For example, cerebellar GBM (cGBM) has been reported to have worse, better, and similar prognosis compared with supratentorial GBM (stGBM).[10-13] Few studies have compared stGBM and cGBM survival, in part because of the scarcity of data on elderly patients with cGBM.[11,12] To our knowledge, no study has extensively investigated survival outcomes and prognostic factors of cGBM in the elderly population.

Given that more than half of all GBMs occur in elderly patients, we sought to characterize prognostic factors, survival outcomes, and treatment patterns for elderly patients with cGBM using the SEER (Surveillance Epidemiology and End Results) cancer registry.

METHODS

Study Design and Population

SEER*Stat software (www.seer.cancer.gov/seerstat) was used to query the SEER 18 registries data set[14] for patients aged ≥65 years with a histologic GBM diagnosis between 2000 and 2016. GBM was defined by International Classification of Diseases for Oncology, Third Edition, with codes 9440/3, 9441/3, and 9442/3.[15] Intracranial location was identified with topography codes C71.0-C71.9. Patients diagnosed before 2000 were excluded because of inconsistent data availability (Figure 1). Among 30,419 elderly patients diagnosed with GBM identified in the SEER 18 registries, 20,959 patients had an stGBM and 243 had an infratentorial GBM, 71 of whom had a brainstem GBM. Among 13,339 patients (44%) included in the cohort for analysis, as per criteria in Figure 1, 13,229 patients (99%) were in the stGBM group and 110 (1%) in the cGBM group.

Covariates and Outcomes

Sociodemographic characteristics included age at diagnosis, gender, race, ethnicity, marital status, insurance status (available from 2007 onward), year of diagnosis, and geographic area. Age at diagnosis was categorized as an ordinal variable. Clinicopathologic characteristics included tumor location, tumor size, and histologic subtype. Tumor location was categorized as supratentorial (topography codes C71.1–C71.4) or infratentorial (topography codes C71.6–C71.7). Patients with topography codes C71.0, C71.5, and C71.8–C71.9, which refer to nonspecific tumor locations, were excluded. Because brainstem GBMs have a

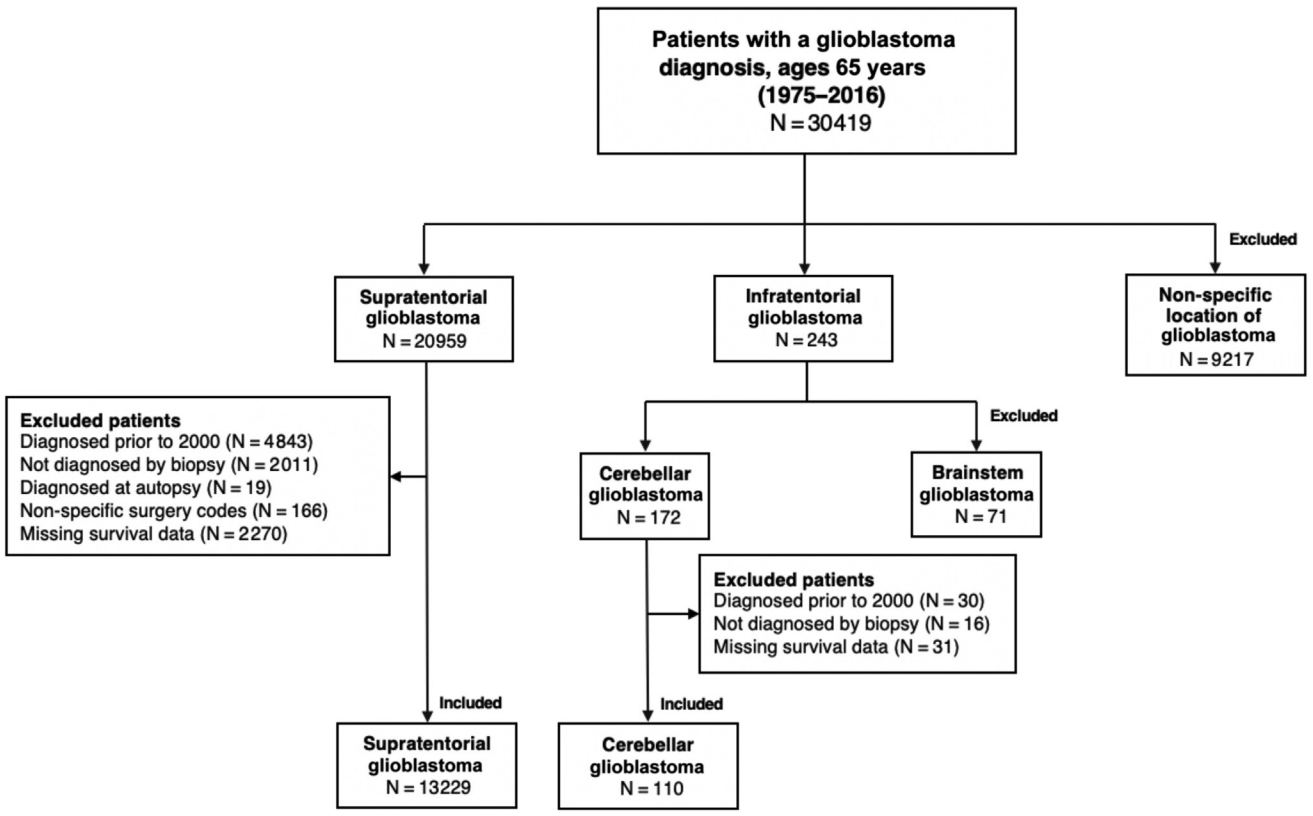

Figure 1. Flow diagram detailing reasons for the exclusion of patients with glioblastoma reported in the SEER database (18 registries).

different natural history and biology, these patients were also excluded. Tumor size was categorized into 0–39 mm, ≥40 mm, and unknown. Patients with missing data on tumor size (37%) and those with miscoding were included in the unknown group. For records with tumor size coded as a range, the midpoint of the range was used for analysis (e.g., 20 mm size was assigned for 0–40 mm range). Year of diagnosis was categorized into quartiles. Geographic area was categorized into Northeast, South, North Central, and West using state codes.

The first course of treatment data, including surgical resection, radiotherapy (RT), and chemotherapy (CT), were available in SEER. Extent of resection was defined using the site-specific codes as biopsy/local excision defined by codes 00 and 20, subtotal resection (STR) defined by codes 21 and 40, and gross total resection (GTR) defined by codes 30 and 55. We excluded patients with nonspecific surgery data (codes 10, 22, 90, 99), as shown in Figure 1. Receipt of CT and RT was categorized as a binary variable (yes vs. no/unknown). The reason for not undergoing certain treatments, data on specific chemotherapeutics, performance status, and radiation dose are not available in SEER.

The primary end point was overall survival (OS), defined as the time in months from diagnosis to death or last follow-up.

Statistical Analysis

Patients were categorized into 2 groups by tumor location: stGBM and cGBM. Analyses of continuous and discrete variables were performed using the Mann-Whitney U test and Fisher exact test, respectively.

A propensity score model was used to match patients with stGBM to the cGBM group by covariates considered to affect outcome. A logistic regression model was used to calculate the propensity score for each patient in the cohort. These covariates included age, gender, race, ethnicity, geographic area, insurance status, year of diagnosis, histologic type, tumor size, extent of resection, CT, and RT. A nearest-neighbor algorithm was used to match 3 patients with stGBM to 1 patient with cGBM.

OS was calculated using the Kaplan-Meier method. Survival was compared between cohorts using the univariable log-rank and Wilcoxon-Breslow-Gehan tests. For the unmatched cohort, multivariable Cox proportional hazard regression was used to calculate the hazard ratio (HR) estimates with 95% confidence intervals (CIs). We then performed a subanalysis in the stGBM and cGBM groups, respectively.

Statistical analyses were performed using STATA version 14.0 (StataCorp LLC, College Station, Texas, USA). All P values were 2 sided and considered statistically significant as $P < 0.05$.

Ethics Statement

This study adheres to the SEER data use policies. Access to the SEER database was requested by 2 authors (A.C. and V.L.-R.), for whom a user-specific reference number was given to access these data. Ethical approval was waived by the committee for the protection of human subjects because this study is not considered as human subjects research.

RESULTS

Patient Characteristics of the Unmatched Cohort

Among 30,419 elderly patients diagnosed with GBM identified in the SEER 18 registries, 20,959 patients had an sGBM and 243 an infratentorial GBM, 71 of whom had a brainstem GBM. Among 13,339 patients (44%) included in the cohort for analysis (Figure 1), 13,229 (99%) were in the stGBM group and 110 (1%) cGBM group. Among patients in the cohort, the median age was 73 years (interquartile range, 68–78 years), 44% were female, 92% white, and 8% Hispanic. Most patients were insured (60%) and 61% were treated in the Western region of the United States. GTR was achieved in one third of patients, and 72% and 56% underwent RT and CT, respectively. Patients with cGBM showed more Asian/Pacific islanders (14% vs. 4%; $P < 00001$), smaller tumor size (36 vs. 43 mm; $P = 0.0004$), and were less frequently treated with CT (39% vs. 56%; $P < 0.0001$) than did patients with stGBM. Demographic, clinical, and treatment characteristics of the unmatched cohort are shown in Table 1.

Median follow-up for the study cohort was 6 months (interquartile range, 3–12 months). In univariable analysis, OS did not significantly differ between stGBM and cGBM (6 months vs. 6 months; $P = 0.8946$) (Table 2; Figure 2A). Mortality of patients with stGBM was 50%, 75%, 92%, and 97% at 6, 12, 24, and 36 months, respectively. In univariable survival analysis, tumor location was not associated with survival (cGBM HR, 1.01; 95% CI, 0.83–1.23; $P = 0.900$), and this was maintained in multivariable analysis (HR, 0.91; 95% CI, 0.75–1.10; $P = 0.319$).

Case-Control Analysis and OS

We performed a case-control analysis accounting for covariates known to affect outcomes. Demographic, clinical, and treatment characteristics of the matched patients with stGBM and patients with cGBM are shown in Table 3.

Median OS for the matched cohort was 5 months (95% CI, 4–6). There was no difference in OS between stGBM ($n = 330$) and cGBM ($n = 110$) patients in univariable analysis (5 vs. 6 months, respectively; $P = 0.409$) (Figure 2B). In univariable analysis, both patients with stGBM and patients with cGBM who received RT (7 months vs. 2 months; $P < 0.001$) and CT (10 months vs. 4 months, $P < 0.0001$ in stGBM and 10 months vs. 3 months, $P < 0.001$ in cGBM) had better survival compared with those who did not receive these treatments (Figure 3A and B and Table 2). However, there were survival differences between patients with stGBM versus patients with cGBM. Mortality of patients with stGBM rates was 55%, 78%, 94%, and 97% at 6, 12, 24, and 36 months, respectively. In elderly patients with cGBM, mortality was 52%, 74%, 89%, and 96%, at 6, 12, 24, and 36 months ($P = 0.8$, $P = 0.03$, $P = 0.007$, and $P = 0.6$, respectively), respectively (Table 4).

Independent Factors Associated with Survival in the Elderly

Sensitivity analysis of the unmatched cohort by tumor location (Table 5) showed that age ≥80 years (HR, 1.5; 95% CI, 1.43–1.57; $P < 0.0001$), tumor ≥40 mm (HR, 1.12; 95% CI, 1.07–1.17; $P < 0.0001$), and a geographic location other than Northeast were associated with decreased survival for patients with stGBM.

Table 1. Sociodemographic, Clinical, and Treatment Characteristics of the Unmatched Cohort of Patients with Glioblastoma

Characteristic	All (N = 13,339)	Supratentorial Glioblastoma (n = 13,229)	Cerebellar Glioblastoma (n = 110)	*P* Value
Age at diagnosis (years), median (IQR)	73 (68–78)	73 (68–78)	74 (69–79)	0.1328
Female	5883 (44)	5840 (44)	43 (39)	0.335
Race				<0.0001
White	12,214 (92)	12,123 (92)	91 (83)	
Black	579 (4)	575 (4)	NA	
Asian or Pacific islander	492 (4)	477(4)	15 (14)	
American Indian/Alaska native/unknown	36 (<1)	36 (<1)	NA	
Spanish or Hispanic or Latino	1017 (8)	1005 (8)	NA	0.203
Marital status				0.983
Single/unmarried or domestic partner	980 (7)	973 (7)	NA	
Married (including common law)	8561 (64)	8490 (64)	71 (65)	
Divorced/separated	974 (7)	967 (7)	NA	
Widowed	2371 (18)	2350 (18)	21 (19)	
Unknown	453 (3)	449 (4)	NA	
Insurance status (2007+)				0.309
Any Medicaid	580 (4)	577 (4)	NA	
Insurance status unknown	4659 (35)	4615 (35)	44 (40)	
Insured/insured, NOS	8052 (60)	7990 (60)	62 (56)	
Uninsured	48 (<1)	47 (<1)	NA	
Year of diagnosis				0.770
2000–2003	2434 (18)	2410 (18)	24 (22)	
2004–2007	2838 (21)	2814 (21)	24 (22)	
2008–2011	3289 (25)	3264 (25)	25 (23)	
2012–2016	4778 (36)	4741 (36)	37 (34)	
Geographic location				0.843
Northeast	2518 (19)	2501 (19)	17 (16)	
South	1313 (10)	1302 (10)	NA	
North Central	1430 (11)	1418 (11)	NA	
West	8078 (61)	8008 (61)	70 (64)	
Histologic type				0.573
Glioblastoma, NOS	12,900(97)	12,792 (97)	108 (98)	
Giant cell glioblastoma	114 (1)	113 (1)	NA	
Gliosarcoma	325 (2)	324 (2)	NA	
Tumor size (mm), median (IQR) (2004+)	43 (31–55)	43 (31–55)	36 (30–44)	0.0004
Tumor size, categorical				0.004
0–39 mm	3448 (26)	3407 (26)	41 (37)	
>39 mm	5020 (37)	4993 (38)	27 (25)	
Unknown	4871 (37)	4829 (37)	42 (38)	
Extent of resection				0.906

Continues

Table 1. Continued

Characteristic	All (N = 13,339)	Supratentorial Glioblastoma (n = 13,229)	Cerebellar Glioblastoma (n = 110)	*P* Value
Biopsy/local excision	5022 (38)	4980 (38)	42 (38)	
Subtotal resection	3823 (29)	3790 (29)	33 (30)	
Gross total resection	4494 (34)	4459 (32)	35 (32)	
Radiotherapy	9618 (72)	9538 (72)	80 (73)	1.000
Chemotherapy	7432 (56)	7389 (56)	43 (39)	<0.0001

Values are number (%) except where indicated otherwise. Data were suppressed if less than a certain number according to the privacy policy of SEER.
IQR, interquartile range; NA, not available; NOS, not otherwise specified.

Patients who were Asian or Pacific islanders (HR, 0.74; 95% CI, 0.67–0.82; $P < 0.0001$) had improved survival compared with white patients. Patients who underwent GTR (HR, 0.65; 95% CI, 0.62–0.68; $P < 0.0001$) and STR (HR, 0.86; 95% CI, 0.82–0.90; $P < 0.001$) had improved survival compared with biopsy/local excision. RT (HR, 0.61; 95% CI, 0.58–0.64; $P < 0.0001$) and CT (HR, 0.58; 95% CI, 0.55–0.61; $P < 0.0001$) were also associated with improved survival.

In contrast to stGBM findings, elderly patients with cGBM treated in the West had improved survival compared with those treated in the Northeast (HR, 0.38; 95% CI, 0.20–0.74; $P = 0.004$). Similarly, patients with cGBM treated with GTR (HR, 0.53; 95% CI, 0.30–0.92; $P = 0.023$) and RT (HR, 0.32; 95% CI, 0.17–0.60; $P < 0.0001$) had better outcome. Patients with cGBM with a giant cell GBM histology had a poor prognosis (HR, 38.98; 95% CI, 3.64–417.45; $P = 0.002$).

DISCUSSION

cGBMs are rare tumors, comprising 0.4%–3.4% of all GBMs.[16,17] As a result, cGBM is poorly characterized and lacks a well-established natural history and accurate prognostic data. The literature has shown that patients with cGBM are typically younger than patients with stGBM, with a median diagnosis age of 50.3 years compared with 65 years.[4,18] Additional differences between these 2 tumors, such as their unique imaging characteristics, clinical presentation, progression patterns, surgical challenges, and risks, make it essential to characterize cGBM particularly in the elderly, who have a poorer prognosis despite aggressive treatment.

Babu et al.[10] conducted the largest cohort study of adult patients with cGBM ($n = 247$), showing a median age at diagnosis of 56.6 years and OS of 7 months, a cohort younger with shorter survival compared with patients with stGBM. Other recent studies have reported similar findings.[11,12] However, none of these studies extensively investigated outcomes in the elderly population, obscuring the applicability of their findings to this population. In our novel study, we compared elderly patients with cGBM with their counterparts with stGBM to characterize outcomes and prognostic factors for cGBM in the elderly.

Patient Characteristics Unique to Elderly Patients with cGBM

There was no difference in the sex distribution or median age between the 2 cohorts. The cohort with cGBM had fewer white patients, had smaller tumor size at diagnosis, and had lower rates of CT treatment in contrast to their counterparts with stGBM.

Table 2. Median Overall Survival of the Unmatched (N = 13,339) and Matched (N = 440) Cohorts

	Supratentorial Glioblastoma	95% CI	*P* Value	Cerebellar Glioblastoma	95% CI	*P* Value
Unmatched cohort	6	6–6	—	6	3–7	—
Treated with RT	8	8–8	<0.0001	7	6–10	<0.0001
Not treated with RT	3	3–3		2	2–3	
Treated with CT	9	9–10	<0.0001	10	6–14	<0.001
Not treated with CT	3	3–4		3	2–4	
Matched cohort	5	4–6		6	3–7	—
Treated with RT	7	2–3	<0.0001	7	6–10	<0.0001
Not treated with RT	2	6–8		2	2–3	
Treated with CT	10	7–12	<0.0001	10	6–14	<0.001
Not treated with CT	4	3–5		3	2–4	

CI, confidence interval; RT, radiotherapy; CT, chemotherapy.

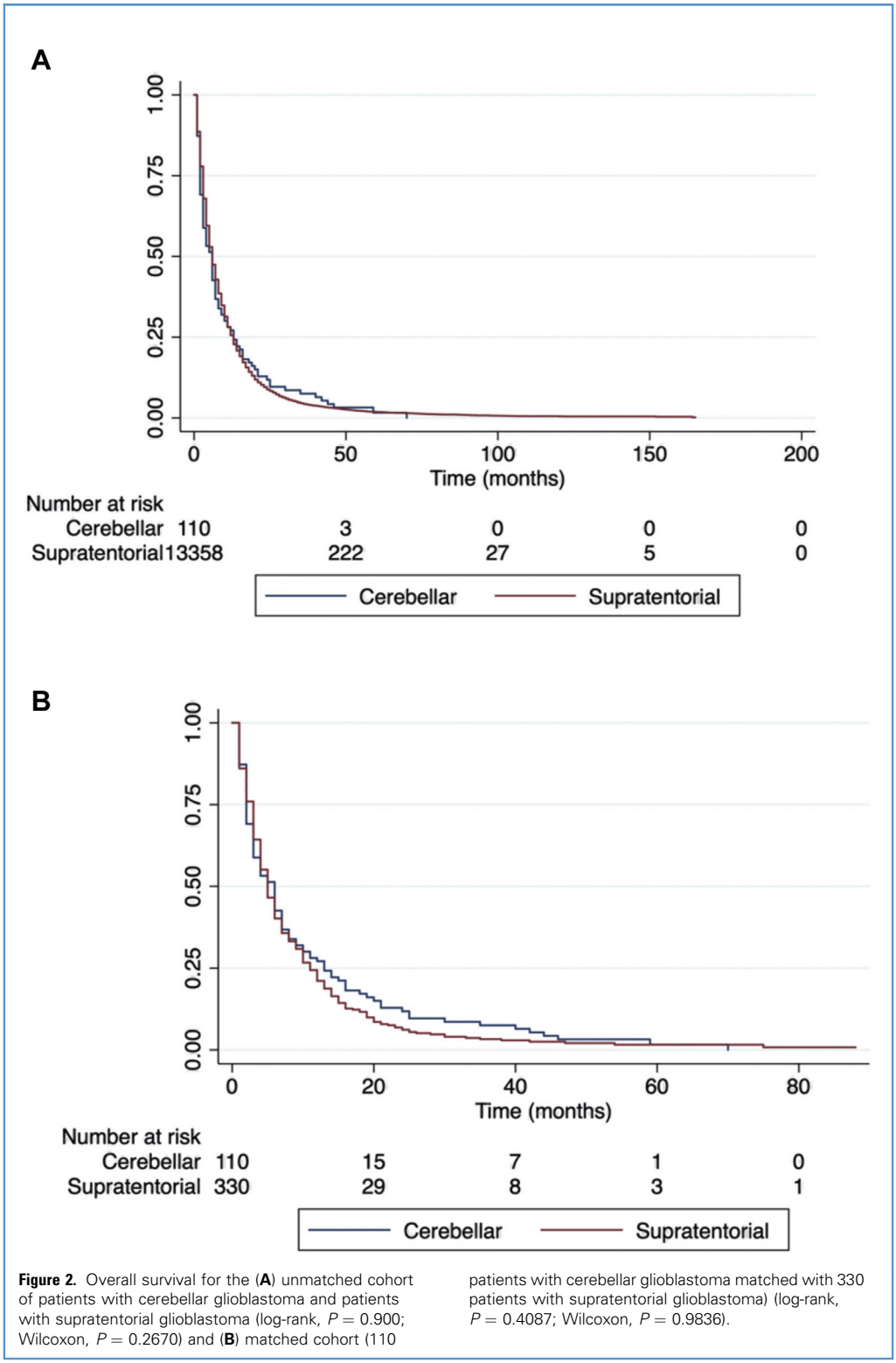

Figure 2. Overall survival for the (**A**) unmatched cohort of patients with cerebellar glioblastoma and patients with supratentorial glioblastoma (log-rank, $P = 0.900$; Wilcoxon, $P = 0.2670$) and (**B**) matched cohort (110 patients with cerebellar glioblastoma matched with 330 patients with supratentorial glioblastoma) (log-rank, $P = 0.4087$; Wilcoxon, $P = 0.9836$).

Table 3. Sociodemographic, Clinical, and Treatment Characteristics of the Matched Cohort of Patients with Glioblastoma

Characteristic	All (N = 440)	Supratentorial Glioblastoma (n = 330)	Cerebellar Glioblastoma (n = 110)	*P* Value
Age at diagnosis (years), median (IQR)	74 (69–79)	74 (69–79)	74 (69–79)	0.7314
Female	173 (39)	130 (39)	43 (39)	1.000
Race				0.363
White	371 (84)	280 (85)	91 (83)	
Black	21 (5)	17 (5)	NA	
Asian or Pacific islander	42 (10)	27 (8)	15 (14)	
American Indian/Alaska native/unknown	NA	NA	NA	
Spanish or Hispanic or Latino	52 (12)	40 (12)	12 (11)	0.865
Marital status				0.959
Single/unmarried or domestic partner	25 (6)	26 (8)	NA	
Married (including common law)	280 (64)	209 (63)	71 (65)	
Divorced/separated	33 (8)	26 (8)	NA	
Widowed	88 (20)	67 (20)	21 (19)	
Unknown	14 (3)	NA	NA	
Insurance status (2007+)				0.471
Any Medicaid	13 (3)	NA	NA	
Insurance status unknown	172 (39)	128 (39)	44 (40)	
Insured/insured, NOS	254 (58)	192 (58)	62 (56)	
Uninsured	NA	NA	NA	
Year of diagnosis				0.714
2000–2003	88 (20)	64 (19)	24 (22)	
2004–2007	109 (25)	85 (26)	24 (22)	
2008–2011	108 (25)	83 (25)	25 (23)	
2012–2016	135 (31)	98 (30)	37 (34)	
Geographic location				0.330
Northeast	64 (15)	47 (14)	17 (16)	
South	32 (7)	21 (6)	NA	
North Central	38 (9)	26 (8)	12 (11)	
West	306 (70)	236 (72)	70 (64)	
Histologic type				0.569
Glioblastoma, NOS	435 (99)	327 (99)	108 (98)	
Giant cell glioblastoma	NA	NA	NA	
Gliosarcoma	NA	NA	NA	
Tumor size (mm), median (IQR) (2004+)	38 (30–51)	39 (29–55)	36 (30–44)	0.1111
Tumor size, categorical				0.414
0–39 mm	153 (35)	112 (34)	41 (37)	
>39 mm	130 (30)	103 (31)	27 (25)	
Unknown	157 (36)	115 (35)	42 (38)	

Values are number (%) except where indicated otherwise. Data were suppressed if less than a certain number according to the privacy policy of SEER.
IQR, interquartile range; NA, not available; NOS, not otherwise specified.

Continues

Table 3. Continued

Characteristic	All (N = 440)	Supratentorial Glioblastoma (n = 330)	Cerebellar Glioblastoma (n = 110)	*P* Value
Extent of resection				0.932
Biopsy/local excision	176 (40)	121 (36)	42 (38)	
Subtotal resection	130 (30)	104 (32)	33 (30)	
Gross total resection	134 (30)	105 (32)	35 (32)	
Radiotherapy	324 (74)	244 (74)	80 (73)	0.804
Chemotherapy	177 (40)	134 (41)	43 (39)	0.823

Values are number (%) except where indicated otherwise. Data were suppressed if less than a certain number according to the privacy policy of SEER.
IQR, interquartile range; NA, not available; NOS, not otherwise specified.

Smaller tumor size at diagnosis and fewer white patients in cGBM is consistent with the literature.[12] On the other hand, lower rates of CT may be explained by undertreatment to ensure a higher quality of life by avoiding side effects secondary to CT in elderly patients, who may be frail and at a higher risk of toxicity and low drug tolerability.

Survival Outcomes in the Elderly with cGBM

The median OS for the study cohort was 6 months, with a mortality of 92%. Our reported overall OS is shorter than that reported by Stupp et al.,[19] with the survival of 15 months in GBM patients undergoing chemoradiotherapy with temozolomide after surgery. This discrepancy can be explained by 2 reasons: first, our study period began before the Stupp protocol was published in 2005, and thus, many patients may have not received CT and/or RT. Second, our study cohort exclusively includes elderly patients with GBM, who have been shown to have poorer survival in several studies.[20-22] Therefore, the lower OS is a result of the natural history of GBM in an older population.

The median OS for elderly patients with stGBM and elderly patients with cGBM in the matched cohort study was similar, with 5 and 6 months, respectively. Moreover, similar to Jeswani et al.,[11] we found that elderly patients with cGBM had slightly lower mortality at 12 and 24 months than their stGBM counterparts, showing a long-term survival benefit in the cGBM elderly cohort, despite similar median survival timescomparable to patients with stGBM.

The median OS in our elderly cGBM group was lower than the survival time reported in the literature. In the largest study of cGBM conducted by Babu et al.,[10] the median OS was 7-months, whereas Adams et al.[12] reported a median OS of 8 months. Other cGBM studies have reported a median OS of 18.4 months.[11,18,23,24] Only 2 studies reported a median OS in the elderly (4 months),[10,11] which is lower than the median OS in our study (6 months). However, the periods of these studies ended in 2008 and 2009, thereby capturing only a small subset of Stupp protocol era patients compared with our study, which included patients until 2016. Moreover, in our study, elderly patients with cGBM treated with CT and RT showed 2.5 times and 3.5 times longer median OS, respectively, than did untreated patients. This finding is consistent with previous studies, including some landmark clinical trials such as the Canadian Cancer trial, NOA-08 trial, and Nordic trials.[25-31]

Factors Independently Associated with Survival in Elderly Patients with cGBM

On univariable analysis, we found that age and tumor size ≥40 mm were associated with worse outcomes, whereas STR/GTR, RT, and CT were each associated with improved survival. Multivariable analysis showed that insurance status, treatment in the Western region, GTR, and RT were associated with better survival; having giant cell GBM histology was associated with poorer survival outcomes.

Recent studies have shown a strong correlation between insurance coverage and improved survival outcomes in patients with GBM,[7,32] because insured patients are more likely to have an assigned primary care physician and may receive more timely diagnosis and treatment for cGBM. Patients with cGBM may have poorer survival outcomes secondary to obstructive hydrocephalus and/or compression of critical and essentials structures in the brainstem without acute intervention, which may be driven by access to health care. Xu et al.[33] reported geographic variations in incidence and survival outcomes in GBM in the United States with the Northeast having the best survival outcomesamong all geographic regions. Although this finding is similar to ours for elderly patients with stGBM, improved outcomes in elderly patients with cGBM being treated in the West can be attributed to geographically distinct access to health care, lifestyle factors, and variations in neurosurgical practices.'[34]

As expected, GTR was associated with improved survival in elderly patients with cGBM. Several studies have reported that GTR significantly improves survival outcomes in GBM,[8,35] including in elderly GBM.[20,21,36,37] Moreover, some cGBM studies have shown similar results in elderly patients.[10-12] This finding goes along with the dogma of maximal safe tumor resection decreasing the risk of disease recurrence and progression.[38] RT leads to significant improvement in elderly patients with GBM and based on our findings, it might confer the same survival benefit in elderly patients with cGBM.

Giant cell GBM is an extremely rare tumor overall and is exceptionally rare in the cerebellum. It portends better survival

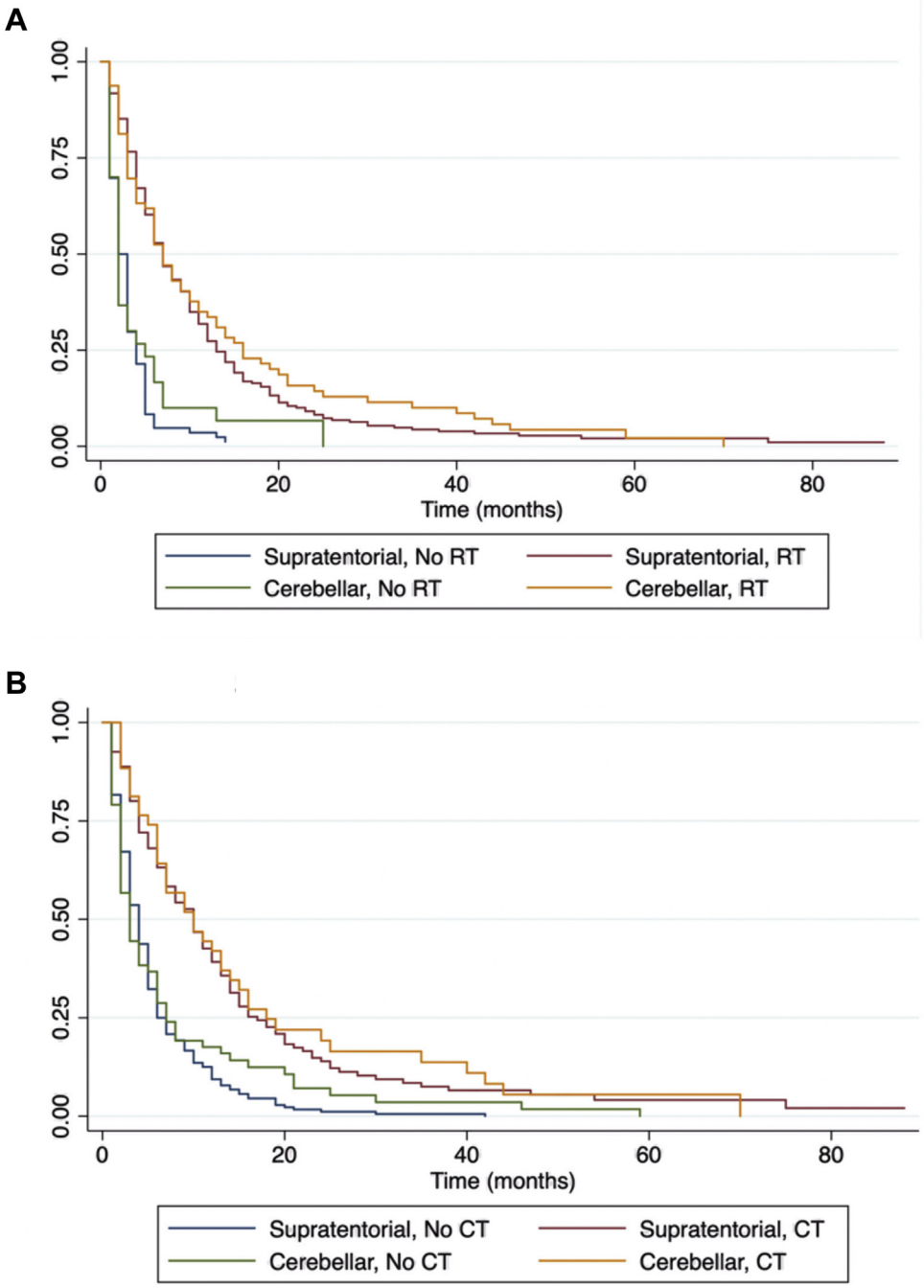

Figure 3. Overall survival for 110 patients with cerebellar glioblastoma matched with 330 patients with supratentorial glioblastoma by treatment strategy. (**A**) Comparison of survival by radiotherapy treatment (RT) stratified by tumor location (log-rank, $P < 0.0001$ for all; Wilcoxon, $P < 0.0001$ for all). (**B**) Comparison of survival by chemotherapy treatment stratified by tumor location (log-rank, $P < 0.001$ for all; Wilcoxon, $P < 0.001$ for all).

Table 4. Mortality at 6, 12, 24, and 36 Months for the Unmatched and Matched Cohorts by Tumor Location (Supratentorial Glioblastoma vs. Cerebellar Glioblastoma)

Months	All (%)	Supratentorial Glioblastoma (%)	Cerebellar Glioblastoma (%)	*P* Value
Unmatched cohort				
6	49	50	52	0.2005
12	74	75	74	0.826
24	92	92	89	0.2047
36	97	97	96	0.0964
Matched cohort				
6	55	55	52	0.8265
12	77	78	74	0.03637
24	93	94	89	0.0077
36	96	97	96	0.59

outcomes than does cGBM.[39,40] Our findings are contradictory to those reported in the literature, with a diagnosis of giant cell cGBM associated with poor survival outcomes in the elderly. However, in the 2 most extensive studies[41,42] investigating the outcomes of giant cell GBM, older age was associated with poor survival, and that interaction could explain our contradictory findings.

Age and CT were not significantly associated with survival in elderly patients with cGBM. Studies have consistently showed an association between age and survival outcomes in stGBM, which is consistent with our findings in elderly patients with stGBM.[43] However, conflicting results have been reported for cGBM. Some reports have shown a significant association between age and OS,[10,11] whereas others did not identify this association and were consistent with our findings.[18,24] A plausible explanation might be that octogenarian patients with cGBM do not have worse outcomes than 65-year-old to 79-year-old patients; however, it might also be that the rarity of this disease, with a scarce number of cases in octogenarians, underpowered our analysis. Although CT prolongs survival in elderly patients with cGBM in our univariable analysis, it was not significantly associated with any survival benefit on multivariable analysis. This finding may be the result of age-related changes in the elderly. Elderly patients tend to have more comorbidities and increased frailty, with significantly lower body reserves. Therefore, drug-related adverse effects severely affecting the quality of life are more likely in this patient cohort, which can prevent treatment of this population.

The molecular genetics of cGBM and how they compare with stGBM are unknown because of the rarity of this lesion.[44-46] SEER was also limited in the availability of molecular data. Small case series have shown that cGBMs are immunopositive for p53 with absent *EGFR* and *IDH1*/*IDH2* mutations, suggesting cGBM to be molecularly different from stGBMs, although Utsuki et al.[47] found evidence of "low grade" or "secondary" GBM while analyzing the histology.[48] More recent studies have performed molecular genetic analysis on cGBM, showing unique molecular features that may aid in targeted therapy of cGBM. Cho et al. observed that cGBM has frequent *ATRX*, *PDGFRA*, *NF1*, and RAS alteration with the absence of *EGFR* alterations. In addition, high susceptibility of this rare entity to mitogen-activated protein kinase kinase (MEK) inhibitors was seen. Moreover, studies have confirmed the absence of *EGFR* and *IDH1* mutations in cGBM.[49] It has been reported that patients with cGBM harbor H3K27M mutations more frequently than stGBM.[50] The presence of this mutation would reconsider the diagnosis of cGBM as an even more dire disease, the diffuse midline glioma H3K27M mutant. Although this disease is more frequent in the pediatric population, it is known to occasionally occur in adults.[51] However, the genetic landscape of cGBM, especially in the elderly, is largely unknown. More studies are warranted to identify the molecular characteristics of this rare disease, because these findings may help develop targeted and effective treatment strategies for the best survival outcomes of the increasing elderly population with cGBM.

Limitations

Although our study is among the first to investigate survival outcomes and associated prognostic factors in elderly patients with cGBM using a large national database, it is subject to several limitations, including those related to its retrospective observational design. In addition, our population includes patients treated before the temozolomide era, the standard of care for GBM; however, we performed a controlled analysis by year of diagnosis in both the unmatched and matched cohorts to address this issue. Given the lack of granular data at the level of the patients and institutions in the SEER database, we were unable to collect and assess the impact of other factors that affect survival, such as performance status, patient comorbidities, tumor volumetric, and treatment characteristics. Such prognostic factors play an important role in determining the best surgical candidates in the elderly population with cGBM who could undergo aggressive therapies. Also, we were unable to assess progression-free survival and tumor recurrence because of the lack of such information in the SEER database. Moreover, imaging diagnostics, characteristics, and molecular data (isocitrate dehydrogenase and methylguanine methyltransferase status) are not available in the SEER registry. This information might show insight into the tumor biology specific to cGBM in the elderly. However, SEER is a large national database that reflects actual practice and thus findings from this study should be broadly applicable to the study cohort of interest.

CONCLUSIONS

In our study, elderly patients with cGBM have similar OS compared with their supratentorial counterparts in a case-control analysis. GTR and adjuvant therapies (RT and CT) are all associated with improved survival outcomes in the elderly cGBM cohort. Thus, these findings should encourage physicians to aggressively treat GBM in the elderly with maximal safe resection and adjuvant therapy independent of tumor location (supratentorial or cerebellum) to confer the

Table 5. Multivariable Cox Proportional Hazards Regression Model for Survival Analysis by Tumor Location of Elderly Patients with Glioblastoma

	Supratentorial Glioblastoma			Cerebellar Glioblastoma		
Factor	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age group						
65–79 years	Reference	—	—	Reference	—	—
≥80 years	1.50	(1.43–1.57)	<0.0001	0.96	(0.55–1.68)	0.888
Gender						
Male	Reference	—	—	Reference	—	—
Female	0.98	(0.94–1.01)	0.185	1.40	(0.85–2.32)	0.190
Race						
White	Reference	—	—	Reference	—	—
Black	0.99	(0.91–1.08)	0.811	0.32	(0.08–1.32)	0.116
Asian or Pacific islander	0.74	(0.67–0.82)	<0.0001	0.62	(0.31–1.24)	0.178
American Indian/Alaska native	1.35	(0.96–1.92)	0.088	—	—	—
Unknown	0.72	(0.42–1.25)	0.246	—	—	—
Ethnicity						
Not Spanish or Hispanic or Latino	Reference	—	—	Reference	—	—
Spanish or Hispanic or Latino	0.96	(0.89–1.03)	0.207	0.91	(0.41–2.03)	0.819
Insurance status (2007+)						
Any Medicaid	Reference	—	—	Reference	—	—
Insurance status unknown	0.89	(0.79–0.99)	0.037	0.13	(0.02–0.72)	0.020
Insured/insured, NOS	0.90	(0.82–0.99)	0.032	0.10	(0.02–0.44)	0.002
Uninsured	0.87	(0.63–1.20)	0.398	1.46	(0.11–19.94)	0.776
Year of diagnosis						
2000–2003	Reference	—	—	Reference	—	—
2004–2007	1.07	(0.99–1.15)	0.087	0.46	(0.18–1.14)	0.092
2008–2011	0.96	(0.86–1.06)	0.387	0.65	(0.20–2.13)	0.479
2012–2016	0.95	(0.86–1.05)	0.345	0.90	(0.28–2.89)	0.859
Geographic location						
Northeast	Reference	—	—	Reference	—	—
South	1.25	(1.16–1.34)	<0.0001	0.39	(0.14–1.06)	0.064
North Central	1.14	(1.07–1.22)	<0.0001	0.41	(0.18–0.98)	0.046
West	1.09	(1.04–1.14)	0.001	0.38	(0.20–0.74)	0.004
Histologic type						
Glioblastoma, NOS	Reference	—	—	Reference	—	—
Giant cell glioblastoma	0.93	(0.76–1.13)	0.476	38.98	(3.64–417.45)	0.002
Gliosarcoma	0.99	(0.88–1.11)	0.874	1.19	(0.14–10.24)	0.872
Tumor size, categorical						
0–39 mm	Reference	—	—	Reference	—	—

CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified.

Continues

Table 5. Continued

	Supratentorial Glioblastoma			Cerebellar Glioblastoma		
Factor	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
>39 mm	1.12	(1.07–1.17)	<0.0001	0.53	(0.27–1.03)	0.061
Unknown	1.12	(1.06–1.19)	<0.0001	0.82	(0.41–1.65)	0.872
Extent of resection						
Biopsy/local excision	Reference	—	—	Reference	—	—
Subtotal resection	0.86	(0.82–0.90)	<0.0001	0.76	(0.45–1.29)	0.305
Gross total resection	0.65	(0.62–0.68)	<0.0001	0.53	(0.30–0.92)	0.023
Radiotherapy						
No/unknown	Reference	—	—	Reference	—	—
Yes	0.61	(0.58–0.64)	<0.0001	0.32	(0.17–0.60)	<0.0001
Chemotherapy						
No/unknown	Reference	—	—	Reference	—	—
Yes	0.58	(0.55–0.61)	<0.0001	0.67	(0.36–1.23)	0.196

CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified.

maximum survival benefits in elderly patients. However, additional studies at the single and multi-institutional level assessing patient-level prognostic factors and factors affecting OS are necessary to identify the best surgical candidates in this patient population who can undergo aggressive therapies with minimal morbidity.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Ankush Chandra: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Investigation, Software, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Victor Lopez-Rivera:** Software, Formal analysis, Data curation, Investigation, Writing - original draft, Writing - review & editing. **Antonio Dono:** Investigation, Writing - original draft, Writing - review & editing. **Michael G. Brandel:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Cole Lewis:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Kyle P. O'Connor:** Investigation, Writing - review & editing. **Sunil A. Sheth:** Visualization, Supervision, Writing - review & editing. **Leomar Y. Ballester:** Visualization, Supervision, Writing - review & editing. **Manish K. Aghi:** Conceptualization, Methodology, Validation, Formal analysis, Software, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Yoshua Esquenazi:** Conceptualization, Methodology, Validation, Formal analysis, Software, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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