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Lack of survival advantage among re-resected elderly glioblastoma patients: a SEER-Medicare study

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Abstract

Background. The survival benefit of re-resection for glioblastoma (GBM) remains controversial, owing to the immortal time bias inadequately considered in many studies where re-resection was treated as a fixed, rather than a time-dependent factor. Using the Surveillance, Epidemiology, and End Results-Medicare (SEER-Medicare) database, we assessed treatment patterns for older adults and evaluated the association between re-resection and overall survival (OS), accounting for the timing of re-resection.

Methods. This retrospective cohort study included elderly patients (age ≥66) in the SEER-Medicare linked database diagnosed with GBM between 2006 and 2015 who underwent initial resection. Time-dependent Cox regression was used to assess the association between re-resection and OS, controlling for age, gender, race, poverty level, geographic region, marital status, comorbidities, receipt of radiation + temozolomide, and surgical complications.

Results. Our analysis included 3604 patients with median age 74 (range: 66–96); 54% were men and 94% were white. After initial resection, 44% received radiation + temozolomide and these patients had a lower hazard of death (hazard ratio [HR]: 0.28, 95% confidence interval [CI]: 0.26–0.31, $P < .001$). In total, 9.5% ($n = 343$) underwent re-resection. In multivariable analyses, no survival benefit was seen for patients who underwent re-resection (HR: 1.12, 95% CI: 0.99–1.27, $P = .07$).

Conclusions. Re-resection rates were low among elderly GBM patients, and no survival advantage was observed for patients who underwent re-resection. However, patients who received standard of care at initial diagnosis had a lower risk of death. Older adults benefit from receiving radiation + temozolomide after initial resection, and future studies should assess the relationship between re-resection and OS taking the time of re-resection into account.

Key Points

- No survival advantage was found for SEER-Medicare re-resection GBM patients.
- Less than 50% received standard of care (SOC) at initial GBM diagnosis; those who received SOC had improved OS.
- Older patients benefit from SOC for GBM and should not be excluded from care.

Glioblastoma (GBM) is an aggressive primary central nervous system cancer with rising global incidence.[1,2] While survival from diagnosis has improved for GBM patients since the implementation of radiotherapy and temozolomide in 2005 as the initial standard of care,[3,4] GBM almost universally recurs and remains difficult to treat after recurrence. Systemic treatments that have improved survival in other cancers, such as immune checkpoint blockade, have failed to show a survival benefit for

Importance of the Study

Using appropriate statistical techniques, our study demonstrated a lack of survival benefit from re-resection in a nationally representative sample of elderly glioblastoma patients. Our findings parallel those of single-center retrospective studies accounting for the timing of re-resection and advance the literature on the association between re-resection and survival. Additionally, less than half of this elderly cohort received standard of care therapy; however, those who received standard of care had improved survival. These findings suggest that older adults are not receiving treatment at the same rates as younger patients and may benefit from receiving radiation + temozolomide after initial resection.

GBM patients.[5] Currently, no single standard of care exists for recurrent GBM; however, therapeutic approaches include repeat resection, repeat radiotherapy, systemic chemotherapy, and bevacizumab.

At recurrence, repeat resection is performed in some cases to reduce tumor burden. Re-resection can alleviate mass effect, reduce edema, and provide tumor for molecular profiling. While re-resection may improve quality of life[6] or ameliorate symptoms, evidence regarding the benefit of re-resection on survival has been conflicting. A recent meta-analysis noted that most studies do not account for the timing of re-resection when analyzing the association between re-resection and survival.[7] Whether a patient will undergo re-resection is unknown at initial surgery and this treatment decision occurs later in the disease course; therefore, re-resection status is a time-dependent factor, not a fixed factor. Treating time-dependent factors as fixed factors in the analysis will always result in biased estimation.[8] In our earlier work, we demonstrated that controlling for the timing of re-resection resulted in an attenuation of the associated benefit with overall survival (OS).[9]

Studies have shown that older patients with GBM undergo re-resection less frequently than younger patients.[10,11] In the United States, incidence of GBM increases with age, where individuals 75–84 years have the highest rates of GBM diagnosis, and the median age at diagnosis is 65 years.[2] Although GBM is more common in older adults, adults older than 70 were excluded in the initial clinical trial by Stupp et al.[4] where the current standard of care for initial treatment was established. Additionally, their exploratory subgroup analysis did not demonstrate evidence of survival benefit in those aged 60–70 years.[4,12] In a population-based analysis, older adults had lower odds of receiving standard of care for initial treatment.[13] However, recent retrospective studies have demonstrated older adults experience a significant survival benefit when given standard of care for initial treatment.[10–12,14] Undertreatment of older adults is not limited to initial treatment. A population-based study showed older adults receive bevacizumab, a common treatment at recurrence, at much lower rates relative to the broader GBM population, although the patients who received bevacizumab experienced significantly improved survival.[15]

As older adults are frequently excluded from clinical trials, registry data can provide key insights into treatment patterns and survival benefit in this age group. Population-based databases, such as the Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare claims, allow for a nationally representative cancer cohort of the older adult US population. Using SEER-Medicare, we report on the association between repeat resection and OS after the implementation of the *Stupp* protocol, accounting for the timing of re-resection in the analysis.

Materials and Methods

Cohort Selection

Our study included patients from the 2018 SEER-Medicare data release. We selected patients with a first primary diagnosis of GBM from January 2006 to December 2015 using the site code 31010 for brain, and histology codes 9440, 9442, and 9445, reflecting ICD-O-3 codes for grade IV gliomas from the SEER Patient Entitlement and Diagnosis Summary File (PEDSAF). Patients must also have had a resection at GBM diagnosis as indicated by one of the surgery or diagnosis codes from MEDPAR or NCH (detailed in Supplementary Table 1). Patients were followed up from initial resection until death, obtained through the national death index, or administrative follow-up defined as the last date of available claims in this release (December 31, 2016). Patients were excluded if they lacked Part A or B Medicare coverage, belonged to a health maintenance organization in the year prior to GBM diagnosis or through follow-up, were diagnosed with GBM at death, had no GBM diagnosis date, or were younger than 66 years old to allow for assessment of comorbidities in the year prior to GBM diagnosis. Patients were also excluded if they were not newly diagnosed, defined as initial resection more than 75 days after their initial GBM diagnosis date, or if they had chemotherapy or radiation prior to the first surgery, defined as chemotherapy or radiation claims more than 7 days before initial resection (Figure 1).

Measurements

We used codes detailed in Supplementary Table 1 to identify chemotherapy and radiation. Temozolomide use was identified using multiple sources: (1) NCH, (2) part D claims in PDESAF (Part D Claims File) for "temodar" or

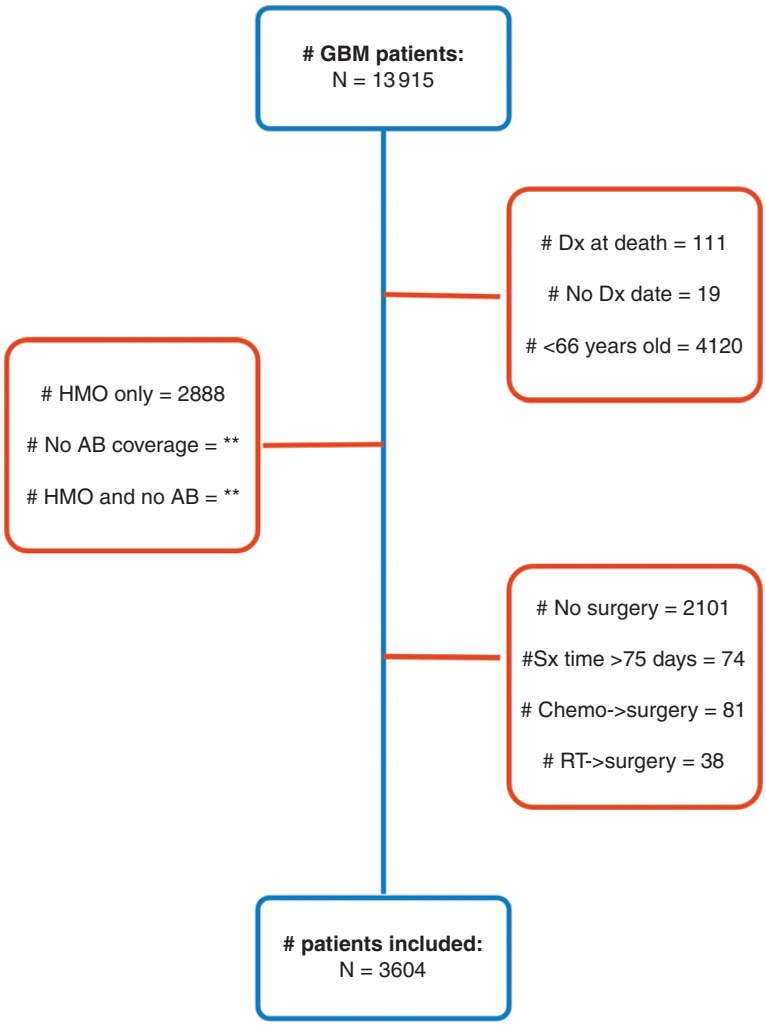

Figure 1. Flow chart of patient selection. Our final sample included $N = 3604$ from $N = 13\,915$ GBM patients from SEER-Medicare. The majority of patient exclusions were the result of insufficient Medicare coverage for claims identification ($N = 3770$) or patients younger than 66 years ($N = 4120$). **In accordance with SEER-Medicare data use agreement, cells with $N < 11$ were masked to prevent identification.

"temozolomide," and (3) DME claims using the national drug code directory (https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm) searched on April 9, 2020 for "temozolomide."

Patient demographics, including age at diagnosis, geographic region, race, sex, census tract poverty level, Charlson comorbidity index (CCI), and marital status, were extracted from SEER registry data. Census poverty level indicates the percentage of population at or below the federal poverty level in the patient's census tract of residence. We dichotomized census poverty into less than 10% below the poverty line versus at least 10% below the poverty line. Modified CCI (malignancies excluded) was evaluated using Medicare claims in the 12 months prior to GBM diagnosis.[16] The following surgical complications were identified within 30 days of initial surgery: deep vein thrombosis (DVT), pulmonary embolism, intracranial bleed/stroke, systemic infection, seizure, wound infection, and hemiparesis (codes detailed in Supplementary Table 2). Both ICD-9 and ICD-10 codes were used to identify relevant claims.

Statistical Methods

We assessed the association between clinical characteristics and time to re-resection using competing risks regression with Fine and Gray methods. In this analysis, time to re-resection was defined from the date of initial surgery to re-resection, and death was treated as a competing event. OS was estimated from the initial GBM surgery claim until death using Kaplan–Meier methods. Patients alive were censored at the last claims collection date. We also estimated OS from the date of re-resection in those who underwent a re-resection.

As patients who underwent re-resection had to survive long enough to receive a repeat resection, we used landmarked Kaplan–Meier methods to estimate and visualize survival distributions stratified by re-resection.

Median time to re-resection (7.7 months after initial surgery), the time at which half the patients underwent re-resection, was specified as the landmark time and survival was estimated from the landmark. Patients alive and who underwent a repeat resection by the landmark were included in the re-resection cohort, whereas if re-resection occurred after the landmark, they were included with the no re-resection cohort. As the specification of landmark times is subjective, we included alternative landmark time curves in supplementary material as sensitivity analyses. We also used the landmark method to provide estimates for patients who received radiation + temozolomide within 1 month of initial GBM surgery.

We used univariable and multivariable Cox regression to evaluate the relationship between clinical and treatment characteristics with OS. All variables were included in multivariable models regardless of univariable significance. We used complete case analysis (96% available) for the multivariable model. To account for the immortal time bias, re-resection, radiation + temozolomide, other treatment, and surgical complications were treated as time-dependent covariates. We also display the results from interaction analyses between re-resection and patient characteristics in a forest plot. Two-sided *P* values less than .05 were considered statistically significant. All analyses were performed with SAS 9.4 TS1 M6 (SAS Institute).

Table 1. Patient Characteristics

		N (%)
No. of patients		3604
Age at diagnosis, years	Median (range)	74 (66–96)
Gender	Male	1959 (54.4)
	Female	1645 (45.6)
Race	White	3369 (93.5)
	Black	125 (3.5)
	Other	**
	Unknown	**
Geographic region	West	1411 (39.2)
	Northeast	804 (22.3)
	South	776 (21.5)
	Midwest	**
	Unknown	**
Census poverty tract	Yes	1576 (43.7)
	No	2001 (55.5)
	Unknown	27 (0.7)
Marital status	Married	2350 (65.2)
	Unmarried	1147 (31.8)
	Unknown	107 (3)
CCI	Median (range, *N* = 3604)	0 (0–11)
	0	1855 (51.5)
	1	945 (26.2)
	2	406 (11.1)
	3+	398 (11)
Anatomical location	Temporal lobe	406 (11.1)
	Frontal lobe	942 (26.1)
	Parietal lobe	625 (17.3)
	Overlapping lesions	468 (13)
	Occipital lobe	196 (5.4)
	Brain NOS	196 (5.4)
	Other	65 (1.7)

**Due to the SEER-Medicare data use agreement, cells with *N* < 11 cannot be provided. "Other" anatomical location includes cerebellum, cerebrum, ventricle NOS, and brain stem. "Other" race includes Asian/Pacific Islander and Native American/Alaska Native. "Unmarried" marital status includes single, divorced, separated, unmarried/domestic partner.

Results

Patient Characteristics

After exclusions, 3604 patients were included in our study. Details of exclusions are outlined in Figure 1. Median age at diagnosis was 74 years (range: 66–96) and 54% were men (*n* = 1959). Most patients were white (94%, *n* = 3369) and 65% (*n* = 2350) were married. Over half (51%, *n* = 1855) had no prior comorbidities (CCI = 0), 26% (*n* = 945) had 1 comorbidity, 11% (*n* = 406) had 2 comorbidities, and 11% (*n* = 398) had at least 3 comorbidities. Tumors most commonly occurred in the temporal lobe (31%) and frontal lobe (26%; Table 1).

30-Day Complications After Initial Resection

Complications were common after initial resection with 44.9% (95% confidence interval [CI]: 43.3–46.5%) of patients experiencing one or more complications. Seizures (25.5%, 95% CI: 24.1–26.9%) and intracranial bleed/stroke (20.6%, 95% CI: 19.3–21.9%) occurred most frequently, followed by DVT (8.1% (95% CI: 7.2–9.9%)) and pulmonary embolism (3.3%, 95% CI: 2.8–4.0%). Overall, 30-day mortality was 8.2% (95% CI: 7.3–9.1%; Supplementary Table 3).

Treatment Patterns After Initial Resection

After initial resection, 44% (*n* = 1598) received radiation + temozolomide (median time after surgery: 0.6 months, interquartile range [IQR]: 0.4–0.9), 33% received some other combination of therapy (*n* = 1180; median time after surgery: 0.7 months, IQR: 0.5–1.0), and 23% (*n* = 826) received no additional therapy. Overall, 23% (*n* = 813) received bevacizumab during their treatment course at a median of 8.0 months (range: 0.5–93.5 months) from initial surgery. Only 343 patients (9.5%) underwent re-resection with a median time between initial and re-resection of 7.7 months (range: 1–86.5 months).

Factors Associated With Receipt of Repeat Resection

Patients who experienced a complication within 30 days of initial resection were less likely to undergo re-resection (hazard ratio [HR]: 0.75, 95% CI: 0.60–0.93, $P = .009$). Receipt of re-resection was also associated with several patient characteristics. Older patients (HR: 0.90, 95% CI: 0.88–0.92, $P < .001$) and those with more comorbidities were less likely (HR: 0.81, 95% CI: 0.73–0.91, $P < .001$) to undergo a re-resection. Men were more likely to undergo re-resection (HR: 1.38, 95% CI: 1.11–1.72, $P = .004$). Additionally, receipt of re-resection differed by geographic region ($P < .001$) where patients in the midwest (HR: 0.74, 95% CI: 0.52–1.04) and south (HR: 0.51, 95% CI: 0.35–0.73) were less likely to receive re-resection compared to those in the northeast, but no difference was found between patients in the west (HR: 1.02, 95% CI: 0.78–1.32) compared to northeast (Table 2).

Survival Estimates

Within the study period, 3450 individuals had died. For the 154 patients alive, median follow-up was 24 months. From the time of initial resection, median survival was 6.2 months (95% CI: 5.9–6.6 months). One and three-year OS estimates were 29.7% (95% CI: 28.2–31.2%) and 4.9% (95% CI: 4.2–5.7%), respectively. From the time of re-resection, median survival was 6.9 months (95% CI: 6.1–7.9) with 1- and 3-year survival estimates from re-resection of 26.4% (95% CI: 21.8–31.3%) and 5.8% (95% CI: 3.4–9.0%), respectively.

Associations Between Treatment and OS

In univariable analyses, no survival advantage was observed for patients who underwent a re-resection (HR: 1.22, 95% CI: 1.08–1.38, $P = .001$), which paralleled the findings in the landmarked Kaplan–Meier plots (Figure 2, Supplementary Figure 1). As shown in Figure 2, for patients who underwent a repeat resection by the landmark time ($n = 119$), the median OS was 6.7 months (95% CI: 5.3–9.1), compared to 7.9 months (95% CI: 7.3–8.4) for those who did not.

Patients who received radiation + temozolomide after surgery had a lower hazard of death (HR: 0.49, 95% CI: 0.46–0.53, $P < .001$). For patients who received radiation + temozolomide within 1 month of initial resection ($N = 1344$), median OS was 10.1 months (95% CI: 9.5–10.7) compared to 4.2 months (95% CI: 4.0–4.5) in patients who did not.

After adjusting for covariates in a multivariable analysis, no survival benefit was seen for patients who underwent re-resection compared to those who did not (HR: 1.12, 95% CI: 0.99–1.27, $P = .07$). However, patients who

Table 2. Factors Associated With Repeat Resection

		N (*E*)	HR (95% CI)	*P*
Age at diagnosis, years		3604 (343)	0.90 (0.88–0.92)	<.001
Gender	Male	1959 (212)	1.38 (1.11–1.72)	.004
	Female	1645 (131)	—	
Race	Other	104 (14)	1.44 (0.85–2.44)	.40
	Black	125 (12)	1.02 (0.57–1.81)	
	White	3369 (317)	—	
Geographic region	West	1411 (159)	1.02 (0.78–1.32)	<.001
	Midwest	605 (50)	0.74 (0.52–1.04)	
	South	776 (45)	0.51 (0.35–0.73)	
	Northeast	804 (89)	—	
Census poverty tract	Yes	1576 (131)	0.77 (0.62–0.96)	.021
	No	2001 (212)	—	
Marital status	Unmarried	1147 (69)	0.52 (0.40–0.68)	<.001
	Married	3604 (343)	0.81 (0.73–0.91)	<.001
	Widowed	2350 (264)	—	
CCI		3604 (343)	0.81 (0.73–0.91)	<.001
	2	406 (36)	0.75 (0.53–1.07)	<.001
	3+	398 (19)	0.39 (0.25–0.63)	
	1	945 (71)	0.63 (0.48–0.82)	
	0	1855 (217)	—	
Initial resection complication	Yes		0.75 (0.60–0.93)	**.009**
	No		—	

CCI, Charlson comorbidity index; N, number of patients within level; E, number of events. Bold *P*-values indicate statistical significance

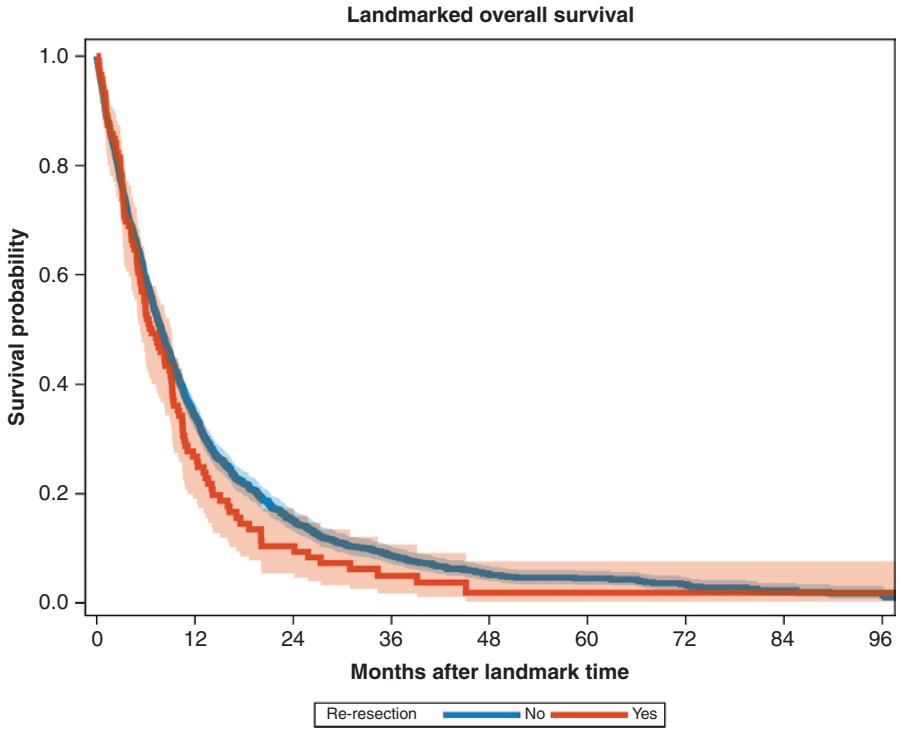

Figure 2. Landmarked Kaplan–Meier plot. Survival curves were estimated from 7.7 months after initial resection (landmark time), which was the median time between initial and re-resection (ie, the time at which 50% of patients had received re-resection). "Yes," shown in orange, indicates patients who underwent re-resection by the landmark time and "No," shown in blue, indicates patients who did not have a re-resection by the landmark time. Patients who died prior to the landmark time were excluded from the curves. Patients who underwent re-resection by 7.7 months had a median OS of 6.7 months (95% CI: 5.3–9.1) compared to a median of 7.9 months (95% CI: 7.3–8.4) in those who did not. No censoring marks or number at risk could be provided under the SEER-Medicare data use agreement.

received radiation + temozolomide had a significantly lower hazard of death (HR: 0.28, 95% CI: 0.26–0.31, $P < .001$; Table 3).

Association Between Demographics and OS

In multivariable analyses, we observed an increased risk of death with each year increase in age (HR: 1.04, 95% CI: 1.04–1.05, $P < .001$) and with increasing number of comorbidities (HR: 1.10, 95% CI: 1.08–1.13, $P < .001$). Patients from impoverished areas (HR: 1.12, 95% CI: 1.04–1.20, $P = .003$) and unmarried patients (HR: 1.16, 95% CI: 1.08–1.26, $P < .001$) had a higher hazard of death. Women had a lower hazard of death (HR: 0.91, 95% CI: 0.85–0.98, $P = .012$) compared to men (Table 3).

Interactions Between Demographics and Re-resection

No significant interaction was found between re-resection and gender, CCI, race, geographic region, or poverty tract ($P = .37$ to $>.95$). However, a significant interaction was found between re-resection and marital status ($P = .034$), where patients who were married and had re-resection had a higher hazard of death (HR: 1.34, 95% CI: 1.16–1.54), but no association between re-resection and OS was found for unmarried individuals (HR: 0.96, 95% CI: 0.75–1.24). A significant interaction was also found between re-resection and age ($P = .021$), where the association between re-resection and OS was stronger for younger patients than for older patients (Figure 3).

Discussion

In this SEER-Medicare population, we report a lack of survival benefit in patients who received a repeat resection when appropriately modeled as a time-dependent covariate in the analysis. The directionality of these results aligns with our earlier single-center analysis[9] and another recent single-center study[17] where the timing of re-resection was incorporated. While OS in this current study was lower than that of many single-center studies of GBM patients, our estimates were similar to those seen in studies specifically among older adults[18] and for the SEER-Medicare population.[19]

Importantly, fewer than 10% of patients underwent re-resection, fewer than 50% received RT + temozolomide after initial resection, and fewer than 25% received bevacizumab during their treatment course, consistent with known treatment patterns in the older adult

Table 3. Cox Regression Results for Overall Survival

		Univariable			Multivariable		
		N (*E*)	HR (95% CI)	*P*	*N* (*E*)	HR (95% CI)	*P*
Repeat resection[a]	Yes		1.22 (1.08–1.38)	**.001**		1.12 (0.99–1.27)	0.07
	No		—			—	
Age at diagnosis, years		3604 (3450)	1.05 (1.04–1.06)	**<.001**	3457 (3307)	1.04 (1.04–1.05)	**<.001**
Gender	Female	1645 (1571)	1.00 (0.93–1.07)	.94	1577 (1505)	0.91 (0.85–0.98)	**.012**
	Male	1959 (1879)	—		1880 (1802)	—	
Race	Black	125 (118)	0.93 (0.77–1.12)	.08	119 (113)	0.75 (0.62–0.90)	
	Other	104 (96)	0.80 (0.65 –0.98)		104 (96)	0.80 (0.65–0.99)	**.001**
	White	3369 (3231)	—		3234 (3098)	—	
Geographic region	South	776 (751)	1.25 (1.13–1.39)	**<.001**	739 (715)	1.33 (1.19–1.49)	**<.001**
	Midwest	605 (588)	1.21 (1.09–1.35)		581 (564)	1.28 (1.14–1.43)	
	West	1411 (1330)	1.01 (0.92–1.10)		1385 (1305)	1.03 (0.94–1.13)	
	Northeast	804 (773)	—		752 (723)	—	
Census poverty tract	Yes	1576 (1515)	1.20 (1.13–1.29)	**<.001**	1522 (1464)	1.12 (1.04–1.20)	**.003**
	No	2001 (1908)	—		1935 (1843)	—	
Marital status	Unmarried	1147 (1116)	1.31 (1.21–1.40)	**<.001**	1131 (1101)	1.16 (1.08–1.26)	**<.001**
	Married	2350 (2230)	—		2326 (2206)	—	
CCI		3604 (3450)	1.16 (1.13–1.19)	**<.001**		1.10 (1.08–1.13)	**<.001**
Stupp protocol[a]	Yes		0.49 (0.46–0.53)	**<.001**		0.28 (0.26–0.31)	**<.001**
	No		—			—	
other treatment[a]	Yes		1.21 (1.13–1.30)	**<.001**		0.44 (0.39–0.48)	**<.001**
	No		—			—	
Initial resection complication[a]	Yes		1.23 (1.15–1.31)	**<.001**		1.18 (1.10–1.26)	**<.001**
	No		—			—	

CCI, Charlson comorbidity index; N, number of patients within level; E, number of events.
[a]Repeat resection, adjuvant treatment, and complications after resection were treated as time-dependent covariates. Bold *P*-values indicate statistical significance.

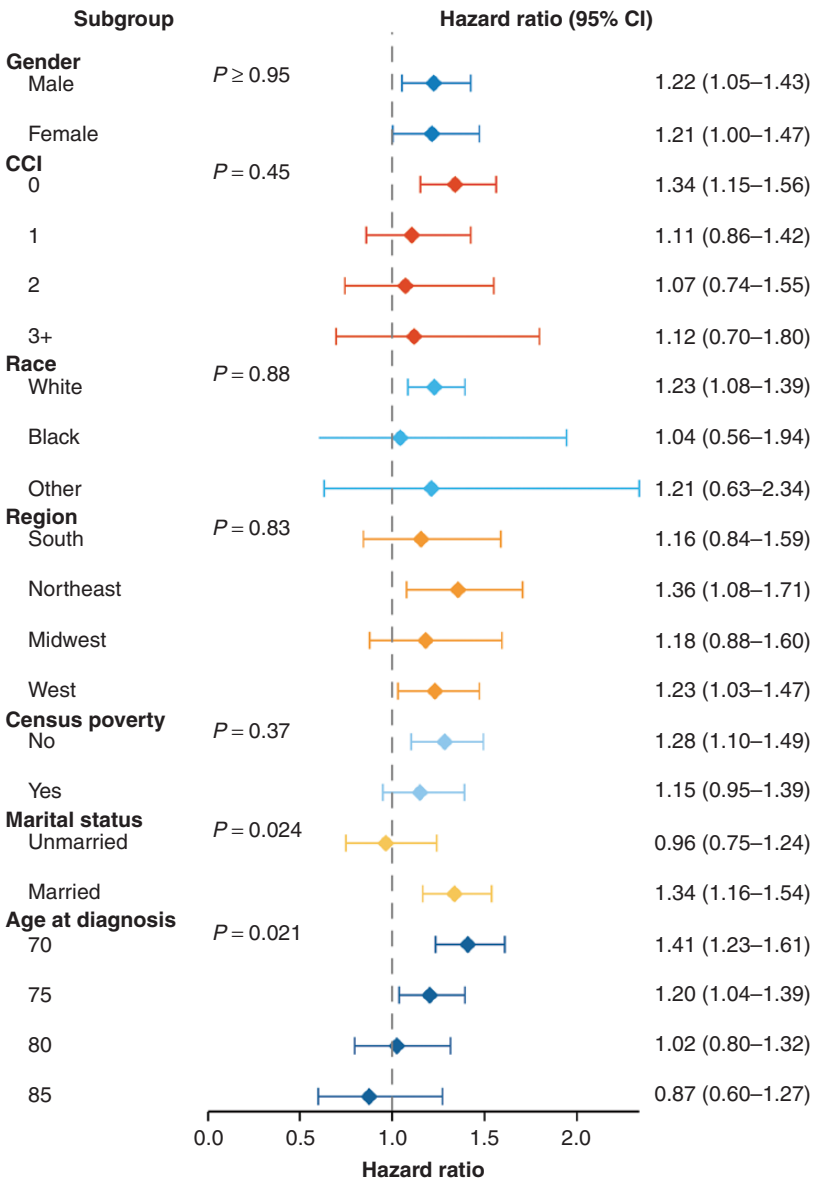

Figure 3. Forest plot of interaction effects. Hazard ratios are displayed from the interaction models between demographics and re-resection for the association with overall survival. The dashed line represents a hazard ratio of 1. Hazard ratios to the right (left) of the line indicate subgroups that had a higher (lower) hazard of death in patients who underwent re-resection compared to those who did not undergo re-resection. For the continuous factors, age, and CCI, the significance tests were derived from the interaction between the continuous variable and re-resection, but hazard ratios of discrete levels were presented for easier visualization.

population. However, in a retrospective cohort study, Lapointe et al.[10] demonstrated similar survival estimates for those at least 70 years compared to those 55–69 years when given the same treatment. Furthermore, in a randomized study, Perry et al.[20] demonstrated improved survival with the addition of temozolomide to short-course radiation for older GBM patients. Although the goal of our study was not to assess the benefit of all modes of treatment, we found that patients who received radiation + temozolomide had a lower risk of death. Our results indicate that standard of care therapy provides a survival benefit for older adults.

Given the well-known association between age and OS in GBM and the debilitating effects of disease progression, one might speculate that patients who underwent re-resection were healthier and more able to undergo additional treatment, which may contribute to a lower hazard of death. In fact, in our study, patients who were younger, from less impoverished areas, and with fewer comorbidities were more likely to receive repeat resection. Additionally, patients in our cohort had fewer comorbidities compared to those who did not undergo initial resection (no comorbidities: 51% vs 43%). While we controlled for comorbidities and other factors in our

multivariable analyses, we cannot fully account for underlying selection bias or underlying health status of patients.

In a SEER-Medicare analysis of GBM patients diagnosed from 1997 to 2009, Chen et al.[19] demonstrated a survival benefit after re-resection. However, in their analysis, re-resection was treated as a fixed, time-independent factor, similar to IDH1 or methylation status, which did not account for the immortal time bias.[21] In addition, their study included patients prior to the implementation of the *Stupp* protocol. A recent study by Nuñez et al.[22] attempted to control for both the timing of re-resection and the underlying selection bias in who receives re-resection. They matched 39 re-resected patients to 39 non-re-resected patients who had similar probabilities of receiving re-resection, and assessed the relationship between re-resection and OS using a time-dependent Cox model. They observed a lower hazard of death in patients who received re-resection (HR: 0.75, 95% CI: 0.62–0.85). While they accounted for the timing of re-resection, it is unclear if they accounted for the matched sampling design in their statistical model. Furthermore, the small sample size limits the reliability of the estimates. Nonetheless, their findings suggest that there may be a survival benefit from re-resection.

In addition to re-resection, we demonstrated notable associations between demographics and survival. Consistent with prior reports, men represented a larger proportion of GBM patients, but had worse survival compared to women.[23,24] Yu et al.[25] have suggested that androgens may promote GBM development and provide for less favorable tumor biology once diagnosed. We also observed differences based on marital status, where married individuals had improved survival. Our result aligns with those from Chang and Barker[26] for the pre-temozolomide era and by Wachtel and Yang[27] in the post-temozolomide era. Putz et al.[28] suggested that married individuals may be able to better tolerate treatment. Similarly, in our study, we found married individuals were more likely to undergo repeat resection.

Geographic differences in survival were also apparent, where patients from the south and midwest were less likely to receive re-resection and had worse survival compared to patients in the northeast; however, no difference was observed for patients in the west compared to patients in the northeast. Pan et al.[29] noted similar findings in their earlier study of GBM patients in the SEER-Medicare database. These findings may be a reflection of greater access to specialized care in these regions.[30] We also noted a significant interaction between age and re-resection, where the association was stronger for younger patients. While this may seem counterintuitive, we speculate that this may be due to selection bias, as older patients were less likely to undergo re-resection. Older patients who had re-resection may represent a highly selected group who were expected to tolerate a second craniotomy.

Limitations

The SEER-Medicare database covers approximately 30% of the US population, which allowed us to examine a large, representative sample of elderly GBM patients in the United States. On the other hand, we were unable to control for known prognostic markers, such as performance status, MGMT, IDH1, multifocality, and extent of initial or re-resection, as these factors are not currently available in the linked SEER-Medicare databases. Additionally, as no true graphical representation exists for time-dependent covariates, we used landmarked curves as an illustration of the relationship between re-resection and survival to supplement the HR estimates from the time-dependent Cox model. However, this visualization is not equivalent to the model estimation or statistical testing performed in this study. We also did not control for recurrence in our analyses, as recurrence data are unavailable in the linked SEER-Medicare databases. While it is possible that our analysis compared patients who did not recur to those that did, the aggressive nature of this disease and short survival observed make this comparison unlikely.

Conclusions

We found a lack of survival advantage for re-resected older adult patients with GBM treated during the radiation + temozolomide era. These results further demonstrate the importance of accounting for the timing of repeat resection when assessing its relationship with OS, as ignoring re-resection timing has led to biased conclusions in other studies. Future studies that account for re-resection timing along with all known prognostic factors are warranted. Additionally, we found a survival advantage when older adults with GBM received standard of care treatment. The feasibility of administering radiation + temozolomide to older adult patients deserves greater attention.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

elderly patients | glioblastoma | repeat resection | SEER-Medicare | time-dependent analysis

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