

# A Surveillance, Epidemiology and End Results-Medicare data analysis of elderly patients with glioblastoma multiforme: Treatment patterns, outcomes and cost

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**Abstract.** The Surveillance, Epidemiology and End Results (SEER) database was used to determine the treatment patterns, outcomes and cost of therapy in elderly patients with glioblastoma multiforme (GBM). The SEER-Medicare linked database was used to identify patients aged >66 years with GBM diagnosed between 1997 and 2009. The patients were stratified by initial treatment following diagnostic surgery (resection or biopsy) into 6 groups as follows: No treatment, standard radiation therapy (SRT) with and without concurrent temozolomide (TMZ), hypofractionated RT (HRT) with and without concurrent TMZ, or TMZ alone. The 3,759 patients identified had a median age of 74 years (range, 66-97 years). A total of ~48% of the patients received SRT without TMZ; ~10% received SRT with concurrent TMZ; ~29% received no treatment; ~10% received HRT without TMZ; ~1% received HRT with TMZ; and <1% received TMZ alone. Untreated patients had a median survival of 2 months (range, 0-89 months). Patients treated with SRT with and without concurrent TMZ had a median survival of 11 and 9 months, respectively (P=0.01). Patients treated with HRT with and without TMZ or TMZ alone had a median survivals of 3 months [adjusted hazard ratio (AHR)=0.48; 95% confidence interval (CI): 0.36-0.66], 4 months (AHR=0.55; 95% CI: 0.49-0.62) and 6 months (AHR=0.43; 95% CI: 0.29-0.62), respectively. The median post-surgery total treatment cost for patients receiving HRT with and without TMZ or TMZ alone was 63,915, 42,834 and 48,298 USD, respectively. Standard RT with concurrent TMZ was associated with improved survival, even in patients

aged >75 years. HRT with and without concurrent TMZ and TMZ alone improved survival compared to the no treatment group. Therefore, in certain cases, HRT or TMZ alone may be more cost-effective, with similar survival outcomes. The various treatment options highlight the need for geriatric assessment tools to aid in therapeutic decision making.

## Introduction

Glioblastoma multiforme (GBM) is an incurable primary brain cancer. The incidence of GBM increases with age, with the highest rates observed in individuals aged 75-84 years (1). Based on the landmark European Organization for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) randomized trial published in 2005 by Stupp *et al* (2), which demonstrated improved survival when temozolomide (TMZ) was added to radiotherapy (RT), the current standard of care for newly diagnosed GBM patients is 6 weeks of RT delivered in 1.8-2.0-Gy daily fractions to a total dose of 60 Gy, followed by adjuvant TMZ chemotherapy. However, the Stupp study excluded patients aged >70 years. Therefore, it has not been rigorously determined whether such patients benefit from this treatment, as was demonstrated for younger patients (3). The optimal treatment approach for elderly GBM patients has not yet been clearly established. In addition, due to factors such as poorer prognosis associated with older age and the presence of other comorbidities, elderly GBM patients may occasionally be treated with alternative therapies that may be better tolerated (4,5).

The alternative treatment for elderly GBM patients primarily includes hypofractionated RT (HRT), where larger fractions of radiation are administered over a shorter period of time compared with standard RT (6). In certain cases, concurrent TMZ has been added to HRT, based on the superior outcomes reported with the Stupp protocol (7,8), although it has not yet been established that combining HRT with concurrent TMZ is superior to HRT alone (9). More recently, TMZ was investigated as a single agent and, based on certain genetic factors in the tumor, it may also be an effective treatment option (10-13).

The number of studies investigating population-based treatment trends for elderly GBM patients is currently

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limited (14-16), whereas none have assessed survival outcomes by treatment method with the associated cost, which may significantly affect treatment recommendations. In order to determine treatment patterns, survival outcomes and cost associated with therapy for elderly GBM patients, we analyzed data from the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database in a contemporary cohort of elderly patients with GBM.

## Materials and methods

**SEER-Medicare.** In 2011, Medicare covered 40.4 million individuals aged  $\geq 65$  years (2012 Medicare Report); this is  $\sim 14\%$  of the total US population, which essentially includes all US citizens aged  $> 65$  years. The SEER-Medicare linked database contains information on Medicare beneficiaries with cancer. The SEER portion includes information pertaining to cancer, such as tumor details, first course of treatment and cause of death, along with patient demographics. The Medicare portion includes claims of individuals eligible to Medicare from enrollment until death. Each patient has a unique identifier that may be used to link the different sets. SEER-Medicare is available to researchers on a project basis for a fee.

In this study, we included a SEER-Medicare tailored cohort containing patients diagnosed with primary brain tumors from 1997 to 2010 and their Medicare claims. The Medicare part of our data includes the Medicare Provider Analysis and Review (Med PAR) file, the outpatient claims file, the Physician/Supplier Part B [National Claims History (NCH)] file, the Durable Medical Equipment (DME) file and the hospice file.

**Cohort selection.** From the SEER data, we extracted patients with histology codes 9440/3, 9441/3 and 9442/3, with concurrent topology codes C71.0-C71.4. The date of diagnosis was noted. As SEER only provides the month and year of diagnosis, the day of diagnosis was imputed to the 15th of the month. All the analyses were adjusted to account for this 15-day error. Patients who were diagnosed with other primary tumors within 1 year of diagnosis were excluded. In order to have a full year look-back for all, the cut-off age for inclusion was set to  $\geq 66$  years.

Only patients with confirmed surgical resection or biopsy were selected. At this end, patients who, according to the SEER data, did not undergo surgery, or for whom it was unknown whether surgery was performed, or the surgery data were missing, were excluded. In addition, patients for whom, according to the Medicare data, the surgery or biopsy was not found in the period from 15 days prior to the diagnosis date to 2 months after surgery, were also excluded.

Other inclusion/exclusion criteria included no Health Maintenance Organization (HMO) enrollment from the period from 1 month prior to diagnosis until death or December 31st, 2010; having both part A and B during the period from 1 month prior to diagnosis until death or December 31st, 2010; and having age as the sole reason for Medicare entitlement. The Medicare claims for the included patients were extracted.

**Patient characteristics and treatment variables.** Patient characteristics were mainly obtained from SEER. The age at

diagnosis and the race and gender of the patients were taken into consideration. All the included patients underwent surgery (biopsy or resection) within 2 months of the reported diagnosis date. Patients who did not undergo RT or chemotherapy within 90 days of surgery were considered to belong to the surgery alone group. If a patient received chemotherapy without RT within this period of 90 days after surgery, that patient was then considered to belong to the chemotherapy alone group. Similarly, the RT alone group was defined as undergoing RT without chemotherapy within 90 days after surgery. The HRT group was defined as having  $\leq 20$  claims of RT within 45 days after the first post-surgery RT and the standard RT (SRT) group comprised patients who had  $\geq 20$  RT sessions within 45 days after the first post-surgery radiation. There were 6 groups in total.

The Medicare Med PAR, outpatient, NCH and DME were used to search for claims of surgery, RT and chemotherapy. To search for surgery, we used the International Classification of Diseases, 9th Revision (ICD-9) codes 01.11-01.14 and 01.18 and Current Procedural Terminology (CPT)-4 61140 for biopsy; ICD-9 01.24, 01.25, 01.31, 01.32, 01.39, 01.51, 01.53 and 01.59 and CPT-4 61304 were used for resection. To check whether a patient had undergone RT, we used the CPT codes 77261-77799. In order to define the fractionation, we counted the number of RT sessions using two different methods and, for each patient, retained the one that yielded the highest value. The first method was to use the radiation delivery codes (CPT-4 codes 77401-77416, 77418, 0197T and G0174), which account for the treatment component. These delivery codes are billed for each fraction. The second method was to use the management code CPT 77427, which accounts for the physician examination and other services for each RT session. This management claim is billed for each 5 fractions. The chemotherapy considered was oral TMZ administration. Oral TMZ was searched for with the CPT code J8700 and the National Drug Code (NDC) numbers 54868-4141, 54868-5348, 54868-5350, 54868-5354, 54868-5980, 0085-1366, 0085-1381, 0085-1417, 0085-1425, 0085-1430, 0085-1519, 0085-3004, 0093-7599, 0093-7600, 0093-7601, 0093-7602, 0093-7638, 0093-7639, 47335-890, 47335-891, 47335-892, 47335-893, 47335-929, 47335-930, 0741-2641, 1741-2692, 0741-2693, 0741-2694, 0741-2695 and 0741-2696. TMZ was Food and Drug Administration-approved for use in 1999. To account for this fact, we looked at the data for the diagnosis years 1997-2009 and for the sub-sample of 2000-2009.

Medicare data were also used to evaluate comorbidities. For each patient, comorbidity was measured as the mean Charlson index score for all claims within 30 days of the diagnosis date (17). The Charlson index was computed using Deyo's adaptation to the ICD-9-CM codes (18).

**Cost data.** We only considered Medicare payments for the cost data analysis. We focused on the cost of treatment, which is the cost of the initial surgery, the cost of post-surgery RT during the entire time of survival and the cost of TMZ for this period. We also considered the total cost, which was the sum of the index surgery cost, plus all the post-surgery RT and TMZ. All the payments were inflated to 2014 USD using the medical component of the consumer price index accessed through the US bureau of Labor Statistics website ([www.bls.gov/cpi](http://www.bls.gov/cpi)).

**Statistical analysis.** The patient characteristics were compared across treatment groups using the Chi-square test for gender, race and age group at diagnosis, whether the patient succumbed to GBM and whether the patient succumbed to other causes. The costs of treatment were compared using the Wilcoxon Rank Sum test. Kaplan-Meier curves were used to estimate the survival time from diagnosis to either death or to the censoring date of December 31st, 2010. The unadjusted comparison of survival time was performed using the log-rank test. The proportional hazard models were used to compare the risk of death adjusting for age and comorbidities. The significance level was set at 0.05.

## Results

**Patients.** Using the search criteria, a total of 3,759 patients were identified. A total of 53.45% of the patients were male and 46.55% were female; 93.11% of the patients were Caucasian. The median age for all the patients was 74 years (range, 66-97 years). Approximately 48% of the patients (n=1,818) were treated using SRT without TMZ; ~10% (n=386) were treated with SRT plus concurrent TMZ; ~29% (n=1,094) received no treatment for their tumors following diagnostic surgery; ~10% (n=390) received HRT without TMZ; ~1% (n=43) had HRT with TMZ; and <1% (n=28) were treated with TMZ alone (Table I).

The median survival for all 3,759 patients was 6 months (range, 0-121 months). Those patients who received no treatment for their tumors following tissue diagnosis had a median survival of 2 months (range, 0-89 months). The median survival for all the treated patients was 8 months (range, 0-121 months) ( $P<0.0001$ ). Patients who were treated with SRT plus concurrent TMZ had a median survival of 11 months (range, 2-56 months) and those treated with SRT without TMZ had a median survival of 9 months (range, 1-121 months) ( $P=0.01$ ). The median survival of patients treated with HRT alone was 4 months (range, 0-33 months). Patients treated with HRT plus concurrent TMZ had a median survival of 3 months (range, 1-29 months). Those patients treated with TMZ alone had a median survival of 6 months (range, 1-24 months). There was no significant survival difference among the 3 cohorts of patients treated with HRT alone, HRT plus TMZ ( $P=0.4344$ ) or TMZ alone ( $P=0.3150$ ). However, survival in these 3 patient groups was statistically superior to that in the group of patients who received no treatment following surgical diagnosis ( $P<0.0001$ ). When comparing the combined cohorts of patients treated with HRT with or without TMZ (median survival, 4 months; range, 0-33 months) to those receiving SRT with or without TMZ (median survival, 9 months; range, 1-121 months), superior survival was exhibited by the SRT cohorts, even when adjusted for age and other comorbidities [adjusted hazard ratio (AHR)=0.531, 95% confidence interval (CI): 0.477-0.591,  $P<0.0001$ ] (Table II).

Patients were stratified by age into those aged 66-74 years and those aged  $\geq 75$  years. In the  $\geq 75$  cohort, 38.33% (693/1,808) of the patients were not treated following diagnostic surgery, whereas in the 66-74 cohort, only 20.55% (401/1,951) of the patients received no therapy. In the  $\geq 75$  group, the median overall survival for all the patients was 4 months, compared with 8 months in the younger cohort ( $P<0.0001$ ). A total of

69% of the patients in the younger cohort were treated with SRT with or without TMZ (1,351/1,951) and the median survival was 11 and 10 months, respectively ( $P<0.01$ ). In the older cohort, 47% of the patients (853/1,808) were treated with SRT with or without TMZ, with median survivals of 9 and 7 months, respectively ( $P=0.27$ ).

The younger patients treated with HRT with or without TMZ or TMZ alone totaled 10% (199/1,951) of the patients in this cohort, with median survivals of 5, 5 and 5 months, respectively. In the older cohort, a total of 14% were treated with HRT with or without TMZ or TMZ alone (262/1,808), with median survivals of 3, 4 and 6 months, respectively (Table III).

To assess temporal trends, the percentage of use by treatment type/year for the 6 different treatment groups was analyzed from 1998 to 2009 (Fig. 1). Over this time period, the percentage of patients foregoing any therapy following surgery remained approximately the same, ranging between 30 and 40%. From 2005 onwards, with the publication of the Stupp protocol, there was an increase in the use of SRT plus concurrent TMZ. Interestingly, prior to 2000, almost 50% of the patients were treated with HRT, as opposed to SRT. In 2000, this trend was reversed and by 2009, more elderly GBM patients were treated with SRT. The use of HRT had decreased to 5% by 2009. The use of TMZ alone (1-3%, 2007-2009) and HRT plus TMZ (1-6%, 2007-2009) was also low.

The median payer-reported treatment cost following diagnostic surgery for all the patients was 48,275 USD (range, 0-452,143 USD). Patients who did not receive RT or TMZ as initial treatment following diagnostic surgery had a median payer-reported cost of 33,443 USD (range, 0-263,292 USD). For those patients treated after surgery with SRT plus TMZ, the reported cost was 78,784 USD (range, 16,644-452,143 USD). The cost of SRT without TMZ was 55,228 USD (range, 0-383,114 USD). The median cost of HRT without TMZ was 42,834 USD (range, 852-230,331 USD). The cost of HRT plus TMZ was 63,915 USD (range, 13,646-132,550 USD) and the cost of TMZ alone was 48,298 USD (range, 3,772-195,836 USD) (Table I).

## Discussion

When analyzing the treatment trends for patients in this study, the majority of the patients (~60%), were treated using SRT with or without TMZ. However, in this cohort, the majority of the patients did not receive concurrent TMZ with SRT, due to the larger number of included patients who were treated prior to the publication of the Stupp protocol in 2005 (2). From 2005 onwards, the trend for SRT plus TMZ increased. A total of 29% of the patients received no therapy following diagnostic surgery, which is consistent with previous elderly GBM population-based studies in the USA and Europe (14,16,19). As of 2009, only a small percentage of patients included in this study were treated using HRT with or without TMZ or with TMZ alone; the use of HRT declined after 2000, for reasons that remain unclear.

The median overall survival for the entire cohort of patients was 6 months. Patients stratified into untreated vs. treated groups exhibited median survivals of 2 and 8 months, respectively. These outcomes are consistent with other published population-based studies and prognostic schemata (14,19,20).

Table I. Baseline characteristics and outcomes for all GBM patients diagnosed between 1997 and 2009.

Variables	Groups						P-value
	All patients (n=3,759)	Surgery, no RT, no TMZ (n=1,094)	Surgery, HRT, no TMZ (n=390)	Surgery, SRT, no TMZ (n=1,818)	Surgery, HRT, TMZ (n=43)	Surgery, SRT, TMZ (n=386)	Surgery, no RT, TMZ (n=28)
Female gender, n (%)	1,750 (46.55)	548 (50.09)	190 (48.72)	814 (44.77)	18 (41.86)	167 (43.26)	13 (46.43)
Race, n (%)							
Caucasian	3,500 (93.11)	1,000 (91.41)	361 (92.56)	1,699 (93.45)	43 (100.00)	371 (96.11)	26 (92.86)
African American	118 (3.14)	46 (4.20)	17 (4.36)	49 (2.70)		6 (1.55)	
Other	141 (3.75)	48 (4.39)	12 (3.08)	70 (3.85)		9 (2.33)	2 (7.14)
Age (years) at dx, n (%)							
66-69	818 (21.76)	144 (13.16)	60 (15.38)	486 (26.73)	7 (16.28)	115 (29.79)	6 (21.43)
70-74	1,133 (30.14)	257 (23.49)	106 (27.18)	614 (33.77)	12 (27.91)	136 (35.23)	8 (28.57)
75-79	1,038 (27.61)	333 (30.44)	125 (32.05)	469 (25.80)	17 (39.53)	87 (22.54)	7 (25.00)
80-84	546 (14.53)	230 (21.02)	69 (17.69)	196 (10.78)	5 (11.63)	41 (10.62)	5 (17.86)
>85	224 (5.96)	130 (11.88)	30 (7.69)	53 (2.92)	2 (4.65)	7 (1.81)	2 (7.14)
Charlson score							
Mean (SD)	0.020 (0.03)	0.03 (0.05)	0.02 (0.03)	0.02 (0.03)	0.02 (0.02)	0.01 (0.02)	0.02 (0.02)
Median (Q1-Q3)	0.01 (0.00-0.03)	0.02 (0.00-0.04)	0.01 (0.00-0.03)	0.01 (0.00-0.02)	0.01 (0.00-0.03)	0.00 (0.00-0.01)	0.02 (0.00-0.03)
Survival months estimate							
Median (range)	6 (0-121)	2 (0-89)	4 (0-33)	9 (1-121)	3 (1-29)	11 (2-56)	6 (1-24)
Post-dx post-surgery total treatment cost <sup>a</sup> , USD							
Mean (SD)	60,380 (46,379)	38,600 (27,403)	46,923 (23,095)	67,180 (43,430)	61,868 (27,036)	103,762 (74,680)	56,979 (42,889)
Median	48,275	33,443	42,834	55,228	63,915	78,784	48,298
(range)	(0-452,143)	(0-263,292)	(852-230,331)	(0-383,114)	(13,646-132,550)	(16,644-452,143)	(3,772-195,836)

<sup>a</sup>Medicare payment. GBM, glioblastoma multiforme; RT, radiation therapy; HRT, hypofractionated RT; SRT, standard RT; TMZ, temozolomide; dx, diagnosis; SD, standard deviation.



Table II. Adjusted comparison of GBM survival analysis among different treatment groups.

Treatment groups	Survival months estimate, median (range)	Adjusted analysis HR (95% CI)	P-value
Surgery alone (n=1,094)	2 (0-89)	Reference	
All other treatments (n=2,665)	8 (0-121)	0.345 (0.320-0.373)	<0.0001
HRT with or without TMZ (n=433)	4 (0-33)	Reference	
SRT with or without TMZ (n=2,204)	9 (1-121)	0.531 (0.477-0.591)	<0.0001
HRT without TMZ (n=390)	4 (0-33)	Reference	
HRT with TMZ (n=43)	3 (1-29)	0.880 (0.639-1.213)	0.4344
TMZ alone (n=28)	6 (1-24)	0.821 (0.558-1.207)	0.3150
SRT without TMZ (n=1,818)	9 (1-121)	Reference	
SRT with TMZ (n=386)	11 (2-56)	0.863 (0.770-0.967)	0.0111
Surgery, no RT, no TMZ (n=1,094)	2 (0-89)	Reference	
Surgery, HRT, no TMZ (n=390)	4 (0-33)	0.556 (0.495-0.625)	<0.0001
Surgery, SRT, no TMZ (n=1,818)	9 (1-121)	0.320 (0.295-0.347)	<0.0001
Surgery, HRT, TMZ (n=43)	3 (1-29)	0.484 (0.356-0.660)	<0.0001
Surgery, SRT, TMZ (n=386)	11 (2-56)	0.277 (0.244-0.313)	<0.0001
Surgery, no RT, TMZ (n=28)	6 (1-24)	0.434 (0.298-0.633)	<0.0001

GBM, glioblastoma multiforme; HR, hazard ratio (adjusted for age and Charlson comorbidity index); CI, Wald confidence interval; TMZ, temozolomide; RT, radiation therapy; HRT, hypofractionated RT; SRT, standard RT.

Table III. Comparison of survival months and non-treatment rate following diagnostic surgery across age groups.

Variables	Aged 66-74 years (n=1,951)	Aged ≥75 years (n=1,808)	P-value <sup>a</sup>
Survival months, median (range)			
All patients	8 (0-121)	4 (0-95)	<0.0001
Surgery, no RT, no TMZ	2 (0-61)	2 (0-89)	<0.0001 <sup>b</sup>
Surgery, HRT, no TMZ	5 (0-31)	4 (0-33)	0.0671
Surgery, SRT, no TMZ	10 (1-121)	7 (1-95)	<0.0001
Surgery, HRT, TMZ	5 (1-21)	3 (1-29)	0.8314
Surgery, SRT, TMZ	11 (2-56)	9 (2-31)	<0.0001
Surgery, no RT, TMZ	5 (1-24)	6 (1-24)	0.7289
Non-treatment rate following diagnostic surgery			
Number of non-treated patients (%)	401 (20.55)	693 (38.33)	<.0001

<sup>a</sup>For the survival analysis, this is the log-rank test comparing the overall survival times. For the non-treatment rate, this is the Chi-square P-value comparing the rates. <sup>b</sup>Although the two age groups have the same median survival, patients aged 66-74 years exhibited a higher overall survival. TMZ, temozolomide; RT, radiation therapy; HRT, hypofractionated RT; SRT, standard RT.

Since the publication of the Stupp protocol EORTC/NCIC randomized trial adding TMZ to RT, there has been no population-based study directly comparing the efficacy of SRT to that of SRT plus TMZ for elderly patients. In this analysis, treatment using SRT with concurrent TMZ correlated with an improved survival, which was also the trend for patients aged ≥75 years. This finding is supported by previously published studies reporting increased overall survival in elderly GBM patients since the TMZ era, as well as a recently published meta-analysis of non-randomized studies of elderly GBM

patients treated with RT and concurrent TMZ or RT alone, who also exhibited improved survival (21-23).

The groups treated using HRT with or without TMZ or TMZ alone did exhibit statistically significantly improved survival when compared to patients who received no therapy. There was no statistically significant survival advantage among these three treatment methods. However, when compared to patients treated using SRT with or without TMZ, even when adjusted for age and other comorbidities, patients treated using these regimens exhibited a poorer survival, although the

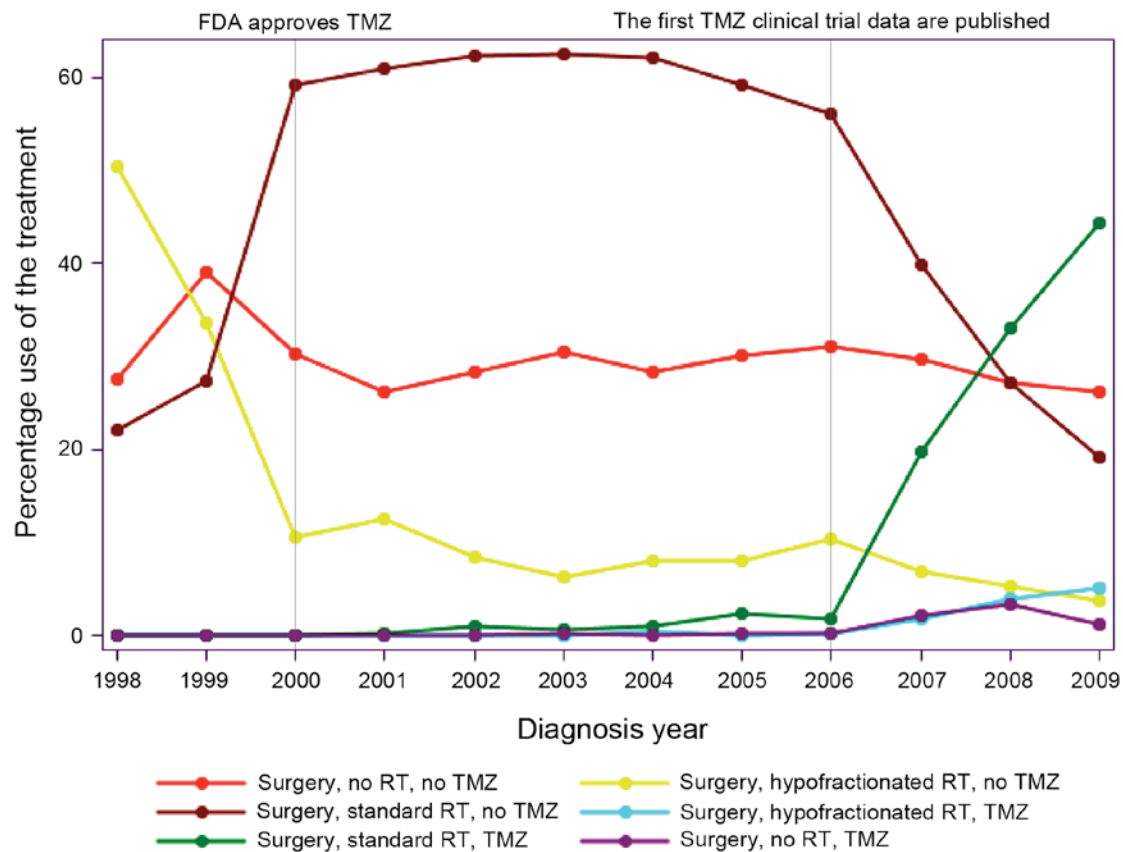


Figure 1. Rate of use by year of the defined treatment modalities. FDA, Food and Drug Administration; TMZ, temozolomide; RT, radiation therapy.

extent of surgery and functional status were not included in the analysis. This is in conflict with a prospective study published by Roa *et al* (24) in 2004, which demonstrated equivalent survival outcomes in elderly GBM patients randomized to receive a 3-week HRT course vs. the standard 6 weeks of RT. Interestingly, the survival times in that study (5.1 months for SRT and 5.6 months for HRT) were closer to the survival estimates of the patients in this analysis who were treated with alternatives to SRT. The relatively short survivals in the Roa study may be explained by the limited proportion of enrolled patients (<15%) who had undergone complete surgical resections, since the extent of surgery has been shown to positively affect survival (25). In addition, this trial was closed early due to slow accrual and was not sufficiently powered to conclude that the two treatments were truly statistically equivalent.

Further elucidating the role of alternative therapies, two important randomized phase III trials were published in 2012 that included comparisons of RT monotherapy vs. TMZ monotherapy in elderly GBM patients. The first trial was the German NOA-08, which enrolled high-grade glioma patients aged >65 years to receive SRT or TMZ (10). The median age was 72 years and 412 patients were enrolled. The median overall survival was 9.6 months for RT and 8.6 months for TMZ, with a P-value of 0.03, which was consistent with the non-inferiority of TMZ. The second study, the Nordic trial, randomized GBM patients onto 3 arms between TMZ, HRT and SRT (11). The median age was 70 years and 291 patients were enrolled. The median survival was 8.3 months in the TMZ group, 7.5 months in the HRT group and 6.0 months in

the SRT group. For patients aged >70 years, TMZ (HR=0.35;  $P<0.01$ ) and HRT (HR=0.59;  $P=0.02$ ) were associated with a significantly longer survival compared with SRT.

The two aforementioned clinical trials reported better survival outcomes for patients treated with HRT or TMZ compared with those observed in this study cohort. A possible explanation for this discrepancy is that, in this population-based retrospective analysis, patients treated with these abbreviated therapies possibly had worse prognostic factors (i.e., extent of surgery and performance status) compared with the patients enrolled in the German NOA-08 and Nordic clinical trials. To clarify, although the extent of surgery was beyond the scope of this analysis, in 2014 Noorbakhsh *et al* (25) published a SEER-based population study of elderly GBM patients, analyzing the extent of resection and the outcomes. They found that, of the 3,631 patients aged  $\geq 75$  years, only 24.2% had undergone complete resection, 24.1% had undergone partial resection, 17.2% local excision or biopsy, 32.7% had received no surgery and 1.8% was unknown. Moreover, the extent of resection correlated with survival. Patients aged  $\geq 75$  years who had no resection, partial resection or complete resection had median survivals of 3, 4 and 6 months, respectively. By comparison, in the Nordic trial, 67% of patients aged  $\geq 70$  years had undergone complete or partial resection and in the German NOA-08 trial, 58% of the patients treated with TMZ had undergone complete or partial resection. The patients in these trials also had good overall good performance status, with a median Karnofsky score of 80, and high performance scores are also known to be a treatment-independent positive

prognostic factor in brain tumor patients (20). Although our analysis could not include patient functional status, a common reason for treating elderly GBM patients with abbreviated therapies is poor function. Therefore, our population-based analysis may reflect a 'real-world' assessment as to the type of patient these alternative treatment methods are offered to, as opposed to patients who are enrolled in clinical trials.

Understanding that certain genetic markers may predict therapeutic response in addition to having prognostic value, the German and Nordic studies also investigated treatment response by methylation status of the promoter region of the O6-methylguanine methyltransferase (MGMT) gene. It was previously demonstrated that the expression of MGMT in the tumor may inhibit the response to TMZ and MGMT promoter methylation (which inhibits expression of MGMT) and is correlated with improved overall survival in patients treated with TMZ (26). The two studies found that patients with methylated tumors treated with TMZ had a significantly higher survival compared with those with unmethylated tumors, as well as with those who had methylated tumors but were treated using HRT and not TMZ. The authors concluded that MGMT methylation status should be routinely checked in elderly GBM patients in order to determine treatment with TMZ as a single agent vs. HRT.

The use of HRT with concurrent TMZ has been investigated in a few small trials and has shown possible benefit (7). In this analysis, there was no statistically significant difference in outcome compared with those patients who were treated with TMZ or HRT alone. There is an ongoing phase III randomized trial (NCIC CTG CE.6), where HRT is administered with and without TMZ in elderly patients with GBM, that should answer the question of whether TMZ added concurrently to HRT improves survival over either of these modalities alone (9).

When comparing standard treatment cost to alternatives, SRT and concurrent TMZ had a total median payer amount of 78,784 USD. The cost of HRT alone was 42,834 USD and that of TMZ alone 48,298 USD; in the alternative therapies, HRT with concurrent TMZ was the clear outlier at 63,915 USD.

In this retrospective study, elderly GBM patients appeared to benefit from standard as well as alternative treatment schemes, with the addition of TMZ to SRT appearing to improve survival. In this analysis, elderly GBM patients treated with alternative regimens did not fare as well as those treated with standard treatment protocols. However, in light of recent randomized prospective studies that demonstrated a benefit using HRT or TMZ alone, this discrepancy is likely due to patient selection bias. With regard to combination therapy, the results of NCIC CTG CE.6 will determine whether adding TMZ to HRT is superior to HRT alone. A positive outcome may justify the use of this more costly combination.

This study has used a national and comprehensive database, hence minimizing discrepancies and biases that are inherent to single-institution and single-provider studies. The data include cancer characteristics, as well as composite clinical and healthcare use information through claims for the United States elderly population. However, this study is not without limitations. Primarily, the limitations are those inherent to any retrospective analysis. Furthermore, important factors, such as functional status, extent of resection and quality of life, were not available. In addition, the extraction

of the cases was performed with the use of ICD-9-CM codes and NDC number, both of which carry a risk for miscoding. Our analysis only considered treatment initiated within the first 90 days of surgery; thus, potential secondary therapies were not included.

Future studies are required, that include more recent patient data, particularly in light of the 2012 German and Nordic trials, which may further alter practice patterns.

The availability of various treatment options also brings to light the need for geriatric assessment tools. Currently, physicians use best clinical judgment in making individualized treatment decisions and chronological age may not be the optimal marker for susceptibility to the potentially negative effects of therapy. Such tools may assist treating physicians in better managing this patient population.

## References

1. Dolecek TA, Propp JM, Stroup NE and Kruchko C: CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol* 14 (Suppl 5): v1-v49, 2012.
2. Stupp R, Mason WP, van den Bent MJ, *et al*; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987-996, 2005.
3. Brandes AA, Franceschi E, Toson A, Benevento F, Scopece L, Mazzocchi V, Bacci A, Agati R, Calbucci F and Ermani M: Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: Correlation with MGMT promoter methylation status. *Cancer* 115: 3512-3518, 2009.
4. Arvold ND and Reardon DA: Treatment options and outcomes for glioblastoma in the elderly patient. *Clin Interv Aging* 9: 357-367, 2014.
5. Combs SE, Wagner J, Bischof M, Welzel T, Wagner F, Debus J and Schulz-Ertner D: Postoperative treatment of primary glioblastoma multiforme with radiation and concomitant temozolomide in elderly patients. *Int J Radiat Oncol Biol Phys* 70: 987-992, 2008.
6. Minniti G and Enrici RM: Radiation therapy for older adults with glioblastoma: Radical treatment, palliative treatment, or no treatment at all? *J Neurooncol* 120: 225-233, 2014.
7. Minniti G, Lanzetta G, Scaringi C, Caporello P, Salvati M, Arcella A, De Sanctis V, Giangaspero F and Enrici RM: Phase II study of short-course radiotherapy plus concomitant and adjuvant temozolomide in elderly patients with glioblastoma. *Int J Radiat Oncol Biol Phys* 83: 93-99, 2012.
8. Cao JQ, Fisher BJ, Bauman GS, Megyesi JF, Watling CJ and Macdonald DR: Hypofractionated radiotherapy with or without concurrent temozolomide in elderly patients with glioblastoma multiforme: A review of ten-year single institutional experience. *J Neurooncol* 107: 395-405, 2012.
9. Perry JR, O'Callaghan CJ, Ding K, *et al*: A phase III randomized controlled trial of short-course radiotherapy with or without concomitant and adjuvant temozolomide in elderly patients with glioblastoma (NCIC CTG CE.6, EORTC 26062-22061, TROG 08.02, NCT00482677). *Neuro Oncol* 16 (Suppl 3): iii46, 2014.
10. Wick W, Platten M, Meisner C, *et al*; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society: Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. *Lancet Oncol* 13: 707-715, 2012.
11. Malmström A, Grönberg BH, Marosi C, *et al*; Nordic Clinical Brain Tumour Study Group (NCBTSG): Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. *Lancet Oncol* 13: 916-926, 2012.
12. Gállego Pérez-Larraya J, Ducray F, Chinot O, *et al*: Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: An ANOCEF phase II trial. *J Clin Oncol* 29: 3050-3055, 2011.

13. Yin AA, Cai S, Dong Y, Zhang LH, Liu BL, Cheng JX and Zhang X: A meta-analysis of temozolomide versus radiotherapy in elderly glioblastoma patients. *J Neurooncol* 116: 315-324, 2014.
14. Iwamoto FM, Reiner AS, Panageas KS, Elkin EB and Abrey LE: Patterns of care in elderly glioblastoma patients. *Ann Neurol* 64: 628-634, 2008.
15. Barnholtz-Sloan JS, Maldonado JL, Williams VL, Curry WT, Rodkey EA, Barker FG II and Sloan AE: Racial/ethnic differences in survival among elderly patients with a primary glioblastoma. *J Neurooncol* 85: 171-180, 2007.
16. Arrigo RT, Boakye M and Skirboll SL: Patterns of care and survival for glioblastoma patients in the Veterans population. *J Neurooncol* 106: 627-635, 2012.
17. Charlson ME, Pompei P, Ales KL and MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 40: 373-383, 1987.
18. Deyo RA, Cherkin DC and Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 45: 613-619, 1992.
19. Zouaoui S, Darlix A, Fabbro-Peray P, *et al*: Oncological patterns of care and outcomes for 265 elderly patients with newly diagnosed glioblastoma in France. *Neurosurg Rev* 37: 415-424, 2014.
20. Scott JG, Bauchet L, Fraum TJ, *et al*: Recursive partitioning analysis of prognostic factors for glioblastoma patients aged 70 years or older. *Cancer* 118: 5595-5600, 2012.
21. Darefsky AS, King JT Jr and Dubrow R: Adult glioblastoma multiforme survival in the temozolomide era: A population-based analysis of Surveillance, Epidemiology, and End Results registries. *Cancer* 118: 2163-2172, 2012.
22. Dubrow R, Darefsky AS, Jacobs DI, Park LS, Rose MG, Laurans MS and King JT Jr: Time trends in glioblastoma multiforme survival: The role of temozolomide. *Neuro Oncol* 15: 1750-1761, 2013.
23. Yin AA, Zhang LH, Cheng JX, Dong Y, Liu BL, Han N and Zhang X: Radiotherapy plus concurrent or sequential temozolomide for glioblastoma in the elderly: A meta-analysis. *PLoS One* 8: e74242, 2013.
24. Roa W, Brasher PM, Bauman G, *et al*: Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. *J Clin Oncol* 22: 1583-1588, 2004.
25. Noorbakhsh A, Tang JA, Marcus LP, McCutcheon B, Gonda DD, Schallhorn CS, Talamini MA, Chang DC, Carter BS and Chen CC: Gross-total resection outcomes in an elderly population with glioblastoma: A SEER-based analysis. *J Neurosurg* 120: 31-39, 2014.
26. Hegi ME, Diserens AC, Gorlia T, *et al*: MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 352: 997-1003, 2005.