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Glioblastoma in the Elderly:

The Memorial Sloan-Kettering Cancer Center Experience (1997–2007)

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Abstract

BACKGROUND—Glioblastoma (GBM) is the most common malignant primary brain tumor, and approximately 50% of cases occur in patients aged ≥ 65 years. However, to the authors' knowledge, there is no accepted standard treatment for elderly GBM patients, and specific prognostic factors in the elderly GBM population have not been systematically studied to date.

METHODS—The Memorial Sloan-Kettering Cancer Center institutional database was used to identify patients with histologically confirmed GBM who were aged ≥ 65 years at the time of diagnosis.

RESULTS—Three hundred ninety-four GBM patients with a median age of 71.9 years (59% of whom were men) were included. Approximately 18% of patients underwent biopsy, whereas 82% underwent tumor resection; 81% received radiotherapy (RT), and 43% received adjuvant chemotherapy. The median overall survival was 8.6 months; at the time of last follow-up, 90% of patients had died, and the median follow-up of the 39 surviving patients was 12 months. In a multivariate analysis, younger age, better Karnofsky performance status (KPS), single tumor, and surgical resection were found to be independent predictors of survival. Comparing 103 patients who received adjuvant chemotherapy with 48 who were only followed after RT, there was a 55% decrease in the risk of death (hazards ratio, 0.45; 95% confidence interval, 0.30–0.66 [$P < .0001$]) after adjusting for age, KPS, extent of surgical resection, and number of lesions.

CONCLUSIONS—Similar to studies in younger GBM patients, advancing age, KPS, and extent of tumor resection were found to be independent prognostic factors in the current study. Although survival is inferior in older GBM patients, age alone should not disqualify patients from aggressive therapy with surgical resection, RT, and chemotherapy.

Keywords

glioblastoma; elderly; prognosis; surgical resection; radiotherapy; temozolomide

Glioblastoma (GBM) is the most common malignant primary brain tumor, and approximately 50% of cases occur in patients aged ≥ 65 years.¹ Because the incidence of GBM increases with age, as the population in the seventh to ninth decades of life grows, the number of persons diagnosed with GBM is expected to increase. GBM diagnosis bestows a poor prognosis for patients in all age groups, but older patients have poorer survival rates than younger patients,² which could be related to age-dependent underlying molecular differences.³ Even though $<25\%$ of GBM patients aged ≥ 65 years survive 1 year after diagnosis, and only 4% of elderly patients survive 2 years after diagnosis,² to the best of our knowledge specific prognostic factors in the elderly GBM population have not been systematically studied.

Unfortunately, many randomized clinical trials have excluded elderly GBM patients. The landmark phase 3 trial demonstrating a survival benefit for concurrent radiotherapy (RT) and temozolomide followed by adjuvant chemotherapy did not include patients aged >70 years.⁴ Indeed, population-based studies have shown that elderly patients were less likely to receive surgical resection, RT, and adjuvant chemotherapy.^{5,6} A continuing dilemma for clinicians treating elderly GBM patients is the paucity of treatment data in this population.

The current study characterizes the patterns of care, survival, and prognostic factors of elderly GBM patients treated at the Memorial Sloan-Kettering Cancer Center (MSKCC) between 1997 and 2007.

MATERIALS AND METHODS

Study Design

The MSKCC institutional database was used to identify patients with GBM diagnosed between January 1, 1997, and December 31, 2007. Inclusion criteria included histologically confirmed GBM at MSKCC, and age ≥ 65 years at the time of diagnosis. Patients with a prior grade 1 to 3 glioma diagnosis were excluded (grading determined according to the World Health Organization grading system). The initial diagnosis was considered as the date of the surgical procedure that led to a definitive histopathologic diagnosis. Data were collected by means of chart review, and extent of tumor resection was evaluated by surgical reports and immediate postoperative brain magnetic resonance imaging. We examined the impact of demographic variables and comorbidities on the probability of undergoing a surgical resection, RT, and adjuvant chemotherapy. Overall survival was defined as the interval between initial GBM diagnosis to death or last follow-up. This study was reviewed and approved by the MSKCC Internal Review Board.

Statistical Analyses

Descriptive statistics were used to illustrate the baseline cohort characteristics and patterns of care. Demographic variables, Karnofsky performance status (KPS), comorbidities, and

tumor characteristics were analyzed by univariate analysis for prediction of treatment receipt. Factors with a P value $\leq .1$ in univariate logistic regression were entered into a multivariate logistic regression model to identify factors that were independently associated with receipt of therapy. Multivariate analyses were performed using the Cox proportional hazards regression model to identify variables independently predictive of survival outcomes. Factors with a P value $\leq .1$ in univariate analyses were entered as variables for multivariate analyses. Because RT and chemotherapy are given sequentially after biopsy or surgical resection, 2 additional Cox proportional hazards regression models were prepared whereby patients who were not alive or followed at 4 and 10 weeks after diagnosis, respectively, were excluded. Statistical significance was determined by a 2-sided P value $\leq .05$. All calculations were performed using SAS statistical software (version 9.1; SAS, Inc, Cary, NC).

RESULTS

Patient Characteristics

Three hundred ninety-four patients aged ≥ 65 years who were diagnosed with a GBM between 1997 and 2007 were included. The median age at diagnosis was 71.9 years; there was a predominance of men (59.4%), and the majority of patients were non-Hispanic, white, and married. The most common comorbidities were hypertension and cardiac disease. Eighty-seven patients had prior cancer, including 27 patients with prostate cancer, 18 with nonmelanoma skin cancer, 16 with breast cancer, and 9 with colon cancer. The most common symptoms or signs at the time of initial presentation were cognitive changes, language changes, and hemiparesis (Table 1).

Treatment

Seventy-three patients (18.5%) underwent biopsy, whereas 321 (81.5%) patients underwent tumor resection. A total of 318 patients (80.7%) received RT (27.2% with concurrent temozolomide and 51.5% received RT alone); 231 patients received the standard course of RT (with total dose of at least 5940 centigrays), 67 received shorter courses of RT, and 10 did not complete the planned RT treatment due to clinical deterioration. Adjuvant chemotherapy was given to 169 patients, the majority of whom received temozolomide or carmustine (Table 2); only 10 patients received adjuvant chemotherapy without prior RT. Most patients withdrew from upfront treatment due to radiographic disease progression (60%) or clinical deterioration (27%); only 5 patients ceased initial treatment primarily due to treatment toxicity, most commonly cytopenia or severe fatigue. A total of 163 patients received salvage treatment at the time of disease recurrence. Fifty-eight patients (14.7%) participated in therapeutic clinical trials.

Predictors of Treatment

The odds ratios of undergoing surgical resection, RT, and adjuvant chemotherapy as determined from multivariate logistic regression analyses are shown in Table 3. Increasing age decreased the probability of undergoing RT but not surgical resection or chemotherapy. Race, gender, and marital status were not found to be significant predictors of the receipt of any treatment. Comorbidities were not strong predictors of treatment receipt in the adjusted

regression models. A higher KPS score was found to be a significant predictor of receipt of both RT and adjuvant chemotherapy. Patients with > 1 lesion were less likely to undergo RT and adjuvant chemotherapy, whereas patients with bilateral disease were less likely to undergo surgical resection.

Survival Analyses

The median overall survival was 8.6 months (95% confidence interval [95% CI], 8 months–9.4 months). Approximately 90% of patients had died at the time of last follow-up, and the median follow-up of the 39 surviving patients was 12 months. In the multivariate analysis, younger age, better KPS, single tumor, and surgical resection were found to be independent predictors of survival (Table 4). Because the majority of patients underwent RT, this database has limited ability to interpret the survival benefit of RT. Because adjuvant chemotherapy is given sequentially after biopsy, surgical resection, and RT, we excluded patients who were not alive or followed for at least 10 weeks after diagnosis when evaluating the survival benefit of chemotherapy. Comparing 103 patients who received adjuvant chemotherapy with 48 who were only followed after RT, there was a 55% decrease in the risk of death (hazards ratio [HR], 0.45; 95% CI, 0.30–0.66 [$P < .0001$]) after adjusting for age, KPS, extent of surgical resection, and number of lesions. We could not identify a trend toward improved survival after temozolomide became available on the market (1999) or after the introduction of concomitant RT and temozolomide (2005) into clinical practice (Table 4).

DISCUSSION

The results of this large retrospective study demonstrate that more aggressive treatments such as surgical resection and adjuvant chemotherapy provide a survival benefit for patients aged ≥ 65 years with newly diagnosed GBM. Although maximal safe surgical resection has become the standard procedure for both diagnosis and tumor debulking of gliomas before RT and chemotherapy in younger patients,⁷ the evidence of a survival benefit for elderly GBM patients is sparse. It is often believed that elderly patients take longer to recover from aggressive neurosurgical procedures and are at higher risk for postoperative complications.⁸ One small randomized trial of 23 patients aged >65 years with malignant gliomas indicated that surgical resection was associated with longer survival compared with biopsy.⁹ A retrospective study compared 88 patients aged >65 years with GBM who underwent biopsy with 40 patients who underwent surgical resection and demonstrated a modest improvement in survival in the group who underwent resection; however, no statistical analyses were performed to determine whether surgical resection was an independent predictor of survival.¹⁰ In addition, decisions regarding surgical resection are influenced heavily by tumor location and the presence of multifocal or bilateral disease.

Based on the results of a randomized trial, there is strong evidence that RT prolongs survival compared with supportive care alone without compromising quality of life in elderly patients with GBM.¹¹ Nevertheless, to our knowledge, the exact dose and schedule of RT is undefined. Alternative RT schedules and doses have been developed, because the standard RT of 60 grays (Gy) over a period of 6 weeks is often considered inconvenient for elderly

GBM patients with an expected short survival. In addition, older individuals are at an increased risk of radiation-induced neurotoxicity, which occurs more frequently with higher radiation doses. In the randomized trial of elderly GBM patients aged ≥ 70 years, a total dose of 50 Gy was delivered over approximately 5 weeks.¹¹ Another randomized trial of patients with GBM who were aged ≥ 60 years compared standard RT (60 Gy over 6 weeks) with an abbreviated course (40 Gy over 15 fractions) and found no difference in survival; however, this study was relatively small and not powered to detect significant survival differences between the 2 RT regimens.¹² In the current study, standard RT doses were used in the majority of patients, especially in those with a good KPS, whereas abbreviated RT courses were given for patients with worse KPS.

To our knowledge, the role of adjuvant chemotherapy remains unclear for elderly GBM patients. A large meta-analysis demonstrated that the benefit of adjuvant chemotherapy was less significant in older patients.¹³ Moreover, the pivotal clinical trial that established the current standard treatment for patients with newly diagnosed GBM (RT with concurrent temozolomide followed by adjuvant temozolomide) excluded patients aged >70 years and indicated no benefit for patients aged >65 years.⁴ In contrast, small prospective studies specifically designed for older GBM patients have shown the feasibility of adjuvant chemotherapy in patients with good performance status and a possible survival benefit compared with historical controls.^{14,15} Data from the current study also suggest that adjuvant chemotherapy given after RT prolongs survival independent of other important prognostic factors. Likely due to limited sample size, we did not observe a survival benefit after the introduction of temozolomide or the use of concurrent RT and temozolomide. Small studies of GBM patients aged ≥ 70 years treated with temozolomide alone and deferred RT demonstrated good tolerability and a median survival of 6 months.^{16,17} This regimen could be an alternative to standard upfront RT, and although few of our patients were treated with this regimen, further studies are needed before the widespread use of this approach.

Although increased age is among the most significant factors associated with poor prognosis in patients with GBM, to our knowledge, prognostic factors specific to the elderly GBM population have been studied only in small case series.^{18–20} The risk-stratification scheme using recursive partitioning analysis from 1578 patients entered in 3 Radiation Therapy Oncology Group malignant glioma trials did not include patients aged >70 years.²¹ Another recursive partitioning analysis of prognostic factors for GBM including 832 patients of all ages demonstrated that patients aged >65 years had the worst prognosis, independent of the extent of surgical resection or performance status.²² Our data regarding elderly patients with GBM indicated that, similar to studies in younger patients,²¹ advancing age, KPS, and extent of tumor resection were independent prognostic factors.

The median survival in the cohort in the current study was 8.6 months, which compares favorably with a 4-month survival of elderly GBM patients from a large population-based study in the United States.⁶ Although the selection of patients likely accounted for a significant amount of this survival benefit, higher rates of surgical resection (82% vs 61%), RT (81% vs 65%), and adjuvant chemotherapy (43% vs 10%) may also have contributed to the better survival rate.⁶ There is evidence to suggest that GBM patients treated at academic

institutions are more likely to undergo aggressive treatments compared with those treated at community centers, but this also could reflect a referral pattern bias.²³ We found that increasing age, poor KPS, bilateral disease, and multiple tumors influenced receipt of treatment in this population. Although patients often had comorbidities, these did not appear to be strongly predictive of the receipt of therapy. This finding could be explained by our inability to retrospectively evaluate less quantifiable measurements of general health status as perceived by the patient and the treating physician that likely determined treatment decisions.

The current study has several limitations, including the inherent bias associated with the retrospective analysis of clinical data. Other potentially important variables, such as quality-of-life measurements and detailed treatment toxicity, were not available. Finally, the current study is limited to the patients of a single tertiary institution and is open to potential referral and treatment practice biases. Thus, the applicability of these results may be limited for institutions with substantially different patient populations or treatment opportunities. Nonetheless, we believe this study improves on the available literature because of its relatively large cohort size. Moreover, this study examined patterns of care, prognostic factors, and survival outcomes of current treatment practices that specifically apply to the elderly GBM population.

Although overall survival is inferior in older GBM patients, age alone should not disqualify patients from aggressive standard therapy with surgical resection, 60 Gy of RT with concurrent temozolomide, and adjuvant chemotherapy, until further information from randomized trials is available.²⁴ For example, the European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada has an open phase 3 clinical trial investigating RT alone versus RT plus temozolomide for elderly GBM patients.²⁵ Approximately 15% of the patients in the current study were enrolled in therapeutic clinical trials, mostly for recurrent GBM, which is higher than the national clinical trial enrollment averages for cancer patients of all ages; clinical trials tailored toward older GBM patients would most likely accrue successfully and also meet the desire of these patients to be treated with investigational therapies. Because the survival of elderly GBM patients is short, even with current aggressive treatments, more effective therapies that improve survival and quality of life are required.

Acknowledgments

Conflict of Interest Disclosures

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Table 1.

Patient Demographics, Comorbidities, and Signs/Symptoms at the Time of Presentation

Characteristic	No. of Patients	%
Age at diagnosis, y		
65–69	153	38.8
70–74	120	30.5
75–79	83	21.1
80	38	9.6
Gender		
Men	234	59.4
Women	160	40.6
Race		
Non-Hispanic white	316	80.2
Non-Hispanic black	10	2.5
Other	68	17.3
Marital status		
Married	283	71.8
Unmarried	109	27.7
Unknown	2	0.5
Comorbidities		
Hypertension	193	49.0
Cardiac disease	91	23.1
Diabetes mellitus	54	13.7
Prior cancer	87	22.1
COPD	9	2.3
KPS at presentation		
70	299	75.9
<70	95	24.1
Symptoms/signs		
Cognitive changes	166	42.1
Language changes	121	30.7
Hemiparesis	95	24.1
Headache	89	22.6
Seizure	79	20.1
Gait	63	16.0
Visual symptoms	53	13.5
Falls	25	6.4
Cranial neuropathy	17	4.3
Sensory	19	4.8
Increased ICP	6	1.5
No. of lesions		
1	352	89.3

Characteristic	No. of Patients	%
2	42	10.7
Hemisphere		
Right	185	47
Left	177	44.9
Bilateral	31	7.9
Other	1	0.3

COPD indicates chronic obstructive pulmonary disease; KPS, Karnofsky performance scale; ICP, intracranial pressure.

Table 2.

Patterns of Treatment for Elderly Patients With Glioblastoma

Treatment	No.	%
Surgical procedure		
Biopsy only	73	18.5
Partial resection	212	53.8
Gross total resection	109	27.7
Radiotherapy		
RT with temozolomide	107	27.2
RT with other agent	8	2.0
RT alone	203	51.5
None	52	13.2
Missing	24	6.1
Adjuvant chemotherapy		
Temozolomide	127	32.2
Carmustine	33	8.4
Other	9	2.3
None	182	46.2
Missing	43	10.9
Treatment at disease recurrence/progression		
Yes	163	41.4
No	130	33.0
Missing	101	25.6
Therapeutic clinical trial participant		
Yes	58	14.7
No	336	85.3

RT indicates radiotherapy.

Table 3.
Predictors of Receipt of Resection, Radiotherapy, and Adjuvant Chemotherapy Among Elderly Patients With Glioblastoma

Variable	Resection *			Radiotherapy			Adjuvant Chemotherapy		
	Unadjusted OR (95% CI)	P	Adjusted [†] OR (95% CI)	P	Unadjusted OR (95% CI)	P	Adjusted [†] OR (95% CI)	P	
Age categories, y									
65–69	1.0	.07	1.0	.10	1.0	.005	1.0	.01	
70–74	0.6 (0.3–1.1)		0.7 (0.4–1.5)		0.7 (0.3–1.6)		0.7 (0.3–1.6)		
75–79	0.4 (0.2–0.8)		0.4 (0.2–0.9)		0.3 (0.1–0.6)		0.3 (0.1–0.6)		
80	0.5 (0.2–1.1)		0.5 (0.2–1.2)		0.3 (0.1–0.8)		0.3 (0.1–0.9)		
Gender									
Men	1.0	.38			1.0	.91		.79	
Women	0.8 (0.5–1.3)				1.0 (0.5–1.8)			1.1 (0.7–1.6)	
Race									
Non-Hispanic white	1.0	.66			1.0			.97	
Non-Hispanic black	2.2 (0.3–17.3)				No estimate	.85		1.1 (0.3–4.4)	
Other									
Marital status	1.2 (0.6–2.5)				0.8 (0.4–1.7)			0.9 (0.5–1.6)	
Married	1.0	.74			1.0	.26		1.0	
Unmarried	0.8 (0.5–1.4)				0.7 (0.4–1.4)			0.9 (0.6–1.5)	
Unknown	No estimate				0.1 (0.0–2.4)			1.0 (0.1–17.0)	
Hypertension									
No	1.0	.65			1.0	.16		.02	
Yes	1.1 (0.7–1.9)				0.7 (0.4–1.2)			1.0	
Cardiac disease									
No	1.0	.03	1.0	.09	1.0	.71	1.0	.38	
Yes	0.5 (0.3–0.9)		0.6 (0.3–1.1)		0.9 (0.4–1.7)		0.8 (0.5–1.3)		
Diabetes mellitus									
No	1.0	.14			1.0	.007	1.0	.02	
Yes	0.6 (0.3–1.2)				0.4 (0.2–0.8)		0.4 (0.2–0.9)	.74	
Prior cancer									

Variable	Resection*			Radiotherapy			Adjuvant Chemotherapy		
	Unadjusted OR (95% CI)	P	Adjusted [†] OR (95% CI)	P	Unadjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P	Adjusted [†] OR (95% CI)
No	1.0	.23			1.0	.85	1.0	.37	
Yes	0.7 (0.4–1.2)				1.1 (0.5–2.2)		0.8 (0.5–1.3)		
COPD									
No	1.0	.06	1.0	.07	1.0	.48	1.0	.38	
Yes	0.3 (0.1–1.0)		0.3 (0.1–1.1)		0.6 (0.1–2.8)		0.5 (0.1–2.2)		
KPS									
<70	1.0	.05	1.0	.38	1.0	.0005	1.0	.0006	1.0
70	1.7 (1.0–3.0)		1.3 (0.7–2.5)		3.0 (1.6–5.5)		2.5 (1.5–4.2)		2.3 (1.4–3.9)
No. of lesions									
1	1.0	.01	1.0	.21	1.0	.004	1.0	.007	1.0
>2	0.4 (0.2–0.8)		0.6 (0.3–1.3)		0.3 (0.2–0.7)		0.4 (0.2–0.8)		0.4 (0.2–0.8)
Hemisphere									
Right	1.0	<.0001	1.0	.0002	1.0	.70	1.0	.27	
Left	0.8 (0.5–1.5)		0.8 (0.4–1.4)		1.0 (0.5–1.9)		1.0 (0.6–1.5)		
Bilateral	0.1 (0.05–0.3)		0.1 (0.05–0.3)		0.6 (0.2–1.5)		0.4 (0.2–1.0)		

OR indicates odds ratio; 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; KPS, Karnofsky performance scale.

* Defined as partial or gross total resection versus biopsy only.

[†] Adjusted for other variables in multivariate logistic model. Variables were entered into the multivariate model if univariately significant (at $\alpha < 0.1$ level).

Predictors of Overall Survival for Elderly Glioblastoma Cohort Treated Between 1997 and 2007

Table 4.

Variable	Unadjusted HR (95% CI)	P	Adjusted* HR (95% CI)	P
Age categories, y				
65–69	1.0	<.0001	1.0	<.0001
70–74	1.3 (1.0–1.7)		1.3 (1.0–1.7)	
75–79	2.0 (1.5–2.6)		2.0 (1.5–2.7)	
80	2.3 (1.6–3.3)		1.8 (1.2–2.7)	
KPS				
<70	1.0	<.0001	1.0	<.0001
70	0.5 (0.4–0.7)		0.6 (0.5–0.8)	
No. of lesions				
1	1.0	<.0001	1.0	.007
2	2.1 (1.5–2.9)		1.7 (1.2–2.5)	
Resection				
Biopsy only	1.0	<.0001	1.0	.0003
Partial resection	0.6 (0.4–0.8)		0.7 (0.5–0.9)	
Gross total resection	0.4 (0.3–0.5)		0.5 (0.4–0.7)	
Diabetes mellitus				
No	1.0	.02	1.0	.12
Yes	1.5 (1.1–2.0)		1.3 (0.9–1.8)	
Hemisphere				
Right	1.0	<.0001	1.0	.21
Left	0.8 (0.6–1.0)		0.9 (0.7–1.1)	
Bilateral	1.9 (1.3–2.9)		1.2 (0.8–1.9)	
Hypertension				
No	1.0	.03	1.0	.77
Yes	1.3 (1.0–1.6)		1.0 (0.8–1.3)	
Prior cancer				
No	1.0	.04	1.0	.91
Yes	1.3 (1.1–1.7)		1.0 (0.8–1.3)	

Variable	Unadjusted HR (95% CI)	P	Adjusted* HR (95% CI)	P
Race				
Non-Hispanic white	1.0	.27		
Non-Hispanic black	0.8 (0.4–1.6)			
Other	0.8 (0.6–1.1)			
Gender				
Men	1.0	.72		
Women	1.0 (0.8–1.2)			
Year of diagnosis				
1997–1998	1.0	.89		
1999–2004	1.0 (0.7–1.5)			
2005–2007	1.0 (0.7–1.6)			
Marital status				
Married	1.0	.84		
Unmarried	1.0 (0.8–1.2)			
Unknown	1.8 (0.2–12.6)			
Cardiac disease				
No	1.0	.60		
Yes	1.1 (0.8–1.4)			
COPD				
No	1.0	.52		
Yes	1.3 (0.6–2.5)			

HR indicates hazards ratio; 95% CI, 95% confidence interval; KPS, Karnofsky performance scale; COPD, chronic obstructive pulmonary disease.

* Adjusted for other variables in a multivariate logistic model. Variables were entered into the multivariate model if univariately significant (at $\alpha < .1$ level).