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Aggressive treatment is appropriate for glioblastoma multiforme patients 70 years old or older: a retrospective review of 206 cases*

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Elderly patients have largely been excluded from randomized trials for glioblastoma multiforme (GBM). We reviewed the results of treatment approaches, which included surgery, chemotherapy, and radiation in this group of patients. Patients were treated during the period 1979–2007 and were 70 years of age and older with histologically confirmed GBM. Overall survival (OS) was the primary endpoint of this retrospective study. Two hundred six patients 70 years of age and older were identified. Median age was 75 years (range 70–90). Median OS time was 4.5 months. Univariate analysis showed that OS was significantly impacted by KPS score (1.8 months for KPS $\leq$50 to 17.2 months for KPS $\geq$90, $P < .001$), age at diagnosis (5.1 months for age 70–79 versus 3.1 months for age $\geq$80, $P < .001$), and extent of disease (worse for bilateral disease [$P = .003$], multifocal disease [$P = .005$], and multicentric disease [$P = .02$]). On multivariate analysis, higher KPS score ($P = .006$), surgical resection (any surgery beyond biopsy) ($P < .001$), radiation therapy ($P < .001$), and chemotherapy ($P < .001$) were all found to be independently associated with improved OS. In this study of newly diagnosed glioblastoma patients over the age of 70 years, aggressive treatment with radiation, chemotherapy, and surgery is associated with OS.

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Glioblastoma multiforme (GBM) is the most commonly diagnosed primary CNS neoplasm, accounting for more than half of all adult primary brain tumors diagnosed annually in the United States.[1] Despite significant research and advances, GBM remains the cause of significant morbidity and certain mortality. The incidence of GBM is highest in patients 65–84 years of age,[2] yet we know the least about this age group's prognosis, as they have been largely excluded from prospective randomized trials and therefore from prognosis algorithms.[3,4] The current standard of care is based on evidence supporting a survival benefit associated with gross total or near total surgical resection[5] and adjuvant radiotherapy after surgery.[6–8] In the elderly, radiation delivered in various fractionation schedules provides a significant survival benefit over supportive care alone.[9] Most recently, the European Organisation for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC) CE3 randomized, phase III trial by Stupp et al. demonstrated that the addition of temozolomide to radiation therapy increases survival in patients with GBM under the age of 70 years.[10,11] For patients 70 years old and older, however, there have been no large-scale, prospective, randomized trials, with the exception of the work of Keime-Guibert et al. delineating "modest improvements in survival without reducing quality of life" with the addition of radiotherapy to the treatment of GBM.[9] In addition to that work, a number of small, prospective studies have shown the benefit of chemotherapy,[12–15] radiation therapy,[16–18] and maximal safe resection[19] in patients 70 years old and older.

In stark contrast to the results of these studies, several recent population-based studies have shown that elderly GBM patients are far less likely than younger ones to receive radiation, chemotherapy, or surgery.[20,21] Until the results of the Radiation Therapy Oncology Group (RTOG) 0525 trial (a prospective, randomized trial for GBM that does not exclude patients 70 years old and older) are published, we must continue to make treatment decisions using the limited data in the current literature. Our study adds to the body of evidence by reporting our institution's experience using radiation therapy, chemotherapy, and surgery to treat GBM in patients at least 70 years old and represents the largest study to date of patients in this age group.

Patients and Methods

By querying an institutional brain tumor database approved by an institutional review board, we identified 282 patients at least 70 years old with a clinical diagnosis of glioma, all of whom had been treated solely at the Cleveland Clinic during the period from May 1979 to September 2007. Out of this group we excluded 72 patients whose clinical diagnosis could not be confirmed pathologically because of an unclear tumor histology and 4 patients who did not have survival information in the database, leaving 206 patients 70 years of age and older with newly diagnosed, histologically proven GBM. No other inclusion or exclusion criteria were applied.

Treatments

All patients had a pathologically confirmed diagnosis of GBM. Date of diagnosis was considered to be the date of biopsy or surgery. As the study period spans 28 years and standards of care changed significantly over that time, we defined all fractionation schedules as simply "radiotherapy," all chemotherapeutic, immunologic, or biologic interventions as "chemotherapy," and all surgical interventions beyond biopsy as "surgery." The extent of surgical resection was defined by each surgeon, and that determination was based on a combination of intra- and post-operative imaging and pathology. Patients who received "no treatment" had biopsy only along with best supportive care.

Statistical analysis

Overall survival (OS) time was the primary endpoint of this retrospective study and was measured from the date of initial diagnosis of GBM. Univariate and multivariate analyses were performed to assess the differences in OS between patients with various characteristics and undergoing different treatments (see below). The log-rank test and stratified Cox proportional hazards model were used to statistically analyze the data. Multivariate models employed stepwise variable selection, with $P = .05$ as the criterion for entry and retention, in order to identify factors that were independently prognostic for OS. In addition, since there was an association between OS time and time of diagnosis, all models were stratified by diagnosis time period.

Factors considered in the univariate and multivariate analyses included patient age, gender, and KPS score at diagnosis; maximum tumor diameter; tumor bilaterality, multifocality, and multicentricity (presence versus absence); extent of surgery (gross total resection [GTR] versus subtotal resection [STR]); type of radiation therapy (external beam [EBRT] versus stereotactic radiosurgery [SRS]); chemotherapy (presence versus absence) and each specific combination of regimen/agents; and date of diagnosis. To simplify the data, we used a recursive partitioning algorithm in an attempt to identify cut points that would help categorize patients according to their age at diagnosis and the date of diagnosis. The cut points identified were 80 years of age (categories were <80 and ≥ 80 years) and diagnosis year equal to 1997 (categories were <1997 and ≥ 1997). All tests of statistical significance were 2-sided and all analyses were performed using SAS version 9.1 (SAS Inc.).

Results

A full listing of patient and treatment characteristics at the time of diagnosis can be found in Table 1. The mean age was 76.1 years (SD 4.6 years; range, 70–90), and the gender distribution was slightly skewed in favor of males (55% vs. 45%). Most patients received 30 fractions of 200-cGy partial brain EBRT (total dose range, 300–7000 cGy; median, 5970 cGy). Forty-one patients (33%) did not receive a full course (at least 50 Gy), as they were unable to complete their regimens for various reasons (not captured in the database), 6 received SRS in addition to EBRT, and 1 patient received intensity-modulated radiotherapy. Chemotherapeutic regimens varied widely over the period covered by the study. Among the 42 patients (20%) who did receive chemotherapy, the most common agent was temozolomide (67%), followed by carmustine (10%) and carboplatin (7%). A number of other regimens/agents were used, but none of them in more than 2 patients (5%); a complete list of chemotherapeutics is in Table 1. Surgically, all patients received at least biopsy, and 23 (11%) received GTR, while 70 (34%) received STR. Median OS for all patients was 4.5 months (Table 1 and Fig. 1A), which is similar to that in other published studies of patients in this age group.[20,21]

Treatment selection was also analyzed and found to be significantly correlated with age ($P < .001$; the oldest patients more commonly received no treatment), the presence of multifocal disease ($P = .02$; patients with multifocal disease tended not to receive surgery), and KPS ($P < .001$; patients with the highest KPS scores tended to receive chemotherapy).

Univariate analysis for OS is shown in Table 2. With the exception of gender, tumor diameter, and extent of surgical resection, all the factors in Table 2

Table 1. Patient and treatment characteristics

Factor	*N* (%)
Age (years)	
Mean ± SD	76.1 ± 4.6
Median	75
Range	70–90
Gender	
Male	114 (55)
Female	92 (45)
KPS at diagnosis	
90–100[1]	20 (10)
80	34 (17)
70	51 (25)
60	47 (23)
50	24 (12)
30–40[1]	6 (3)
Unknown	24 (12)
Tumor location	
Infratentorial	3 (1)
Supratentorial	201 (98)
Unknown	2 (1)
Maximum tumor	
Diameter (cm)[2]	
Mean ± SD	4.2 ± 1.5
Median	4.0
Range	0.6–9.6
Bilateral disease	
No	182 (88)
Yes	21 (10)
Unknown	3 (1)
Multicentric disease	
No	153 (74)
Yes	17 (8)
Unknown	36 (17)
Multifocal disease	
No	177 (86)
Yes	28 (14)
Unknown	1 (<1)
Overall treatment	
None	62 (30)
Surgery only	19 (9)
EBRT only	37 (18)
SRS only	1 (<1)
Surgery + RT[3]	45 (22)
Chemo + RT[4]	13 (6)
Surgery + Chemo + RT[5]	29 (14)
Surgery (other than biopsy)	
No	113 (55)
Yes	93 (45)
GTR	23 (25%)
STR	70 (75%)
Chemotherapy	
No	164 (80)
Yes	42 (20)
Concurrent[6]	22 (52)
Adjuvant	8 (19)
Concurrent + Adj.	12 (29)
Temozolomide	28 (67)
Carmustine	4 (10)
Carboplatin	3 (7)
IL-13	2 (5)
Isotretinoin	2 (5)
Cilengitide	2 (5)
Adoptive immunotherapy	1 (2)
Lomustine	1 (2)
Polifeprosan	1 (2)
Propylthiouracil	1 (2)
Tamoxifen	1 (2)
Erlotinib	1 (2)
EBRT	
No	83 (40)
Yes	123 (60)
Whole brain	21 (17)
Partial	72 (59)
Unknown	30 (24)
Total dose (cGy)[7]	
Mean ± SD	5028.9 ± 1559.1
Median	5970
Range	300–7000
Most common	6000 ($n = 42\%$)
No. fractions[8]	
Median	30
Range	1–60
Most common	30 ($n = 40\%$)
Dose/fraction[9]	
Median	200
Range	150–600
Most common	200 ($n = 57\%$)
SRS	
No	200 (97)
Yes	6 (3)
Gamma knife	5 (83)
Linac	1 (17)
Dose (cGy)[10]	1500
IMRT	
No	205 (99)
Yes	1 (<1)

Abbreviations: SD, standard deviation; EBRT, external-beam radiation therapy; SRS, stereotactic radiosurgery; RT, radiation therapy; GTR, gross total resection; STR, subtotal resection; Adj., adjuvant; Linac, linear accelerator; IMRT, intensity-modulated radiation therapy.
[1]KPS 100: $n = 1$; 40: $n = 5$.
[2]Missing for 22 patients.
[3]EBRT + SRS in 3 patients.
[4]EBRT + SRS in 2 patients.
[5]IMRT in 1 patient.
[6]Concurrent with other treatment; no patient received chemotherapy only.
[7]Missing for 5 patients.
[8]Missing for 7 patients.
[9]Missing for 10 patients.
[10]Missing for 1 patient.

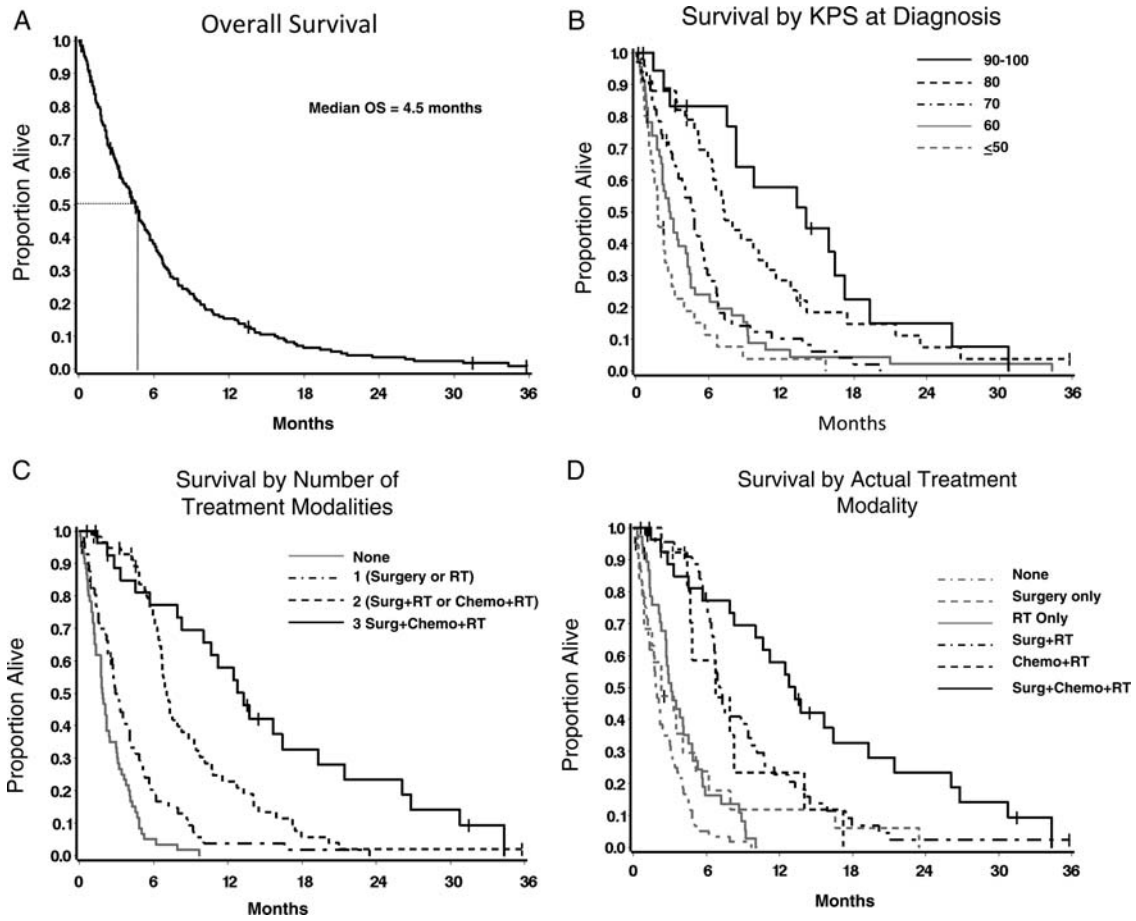

Fig. 1. (A) OS for all patients. (B) OS by KPS score at time of diagnosis. (C) OS stratified by number of treatment modalities. RT, radiation therapy; Surg, surgery; Chemo, chemotherapy. (D) OS by actual combination of treatment modalities. RT, radiation therapy; Surg, surgery; Chemo, chemotherapy.

were found to significantly affect OS time, including age, extent of disease, KPS score, treatment modality, and time period of diagnosis. Older age at diagnosis, worse KPS, greater extent of disease (bilateral, multifocal, and multicentric), not receiving each modality of therapy, and being diagnosed before 1997 were all associated with a shorter OS. On multivariate analysis, which was stratified by diagnosis period, lower KPS score (hazard ratio [HR] 1.24; 95% confidence interval [CI] 1.06–1.44; $P = .006$), lack of surgical resection (HR 3.09; 95% CI 2.09–4.56; $P < .001$), lack of radiation therapy (HR 2.60; 95% CI 1.57–4.31; $P < .001$), and lack of chemotherapy (HR 2.20; 95% CI 1.52–3.17; $P < .001$) were independently associated with decreased OS (Table 3). As shown in Fig. 1B, prognosis improved as KPS score increased: median OS was 1.8 months for patients with KPS ≤ 50; 2.8 months for patients with KPS = 60; 4.8 months for patients with KPS = 70; 7.3 months for patients with KPS = 80; and 17.2 months for patients with KPS = 90 or 100. Figure 1C plots OS by the number of treatment modalities used, independent of KPS. Figure 1D plots OS by the actual combination of modalities used, independent of KPS.

Discussion

Treatment of GBM in the elderly population, defined here as age 70 years and older, has largely been excluded from evaluation in large, phase III, randomized, controlled clinical trials.[10] These patients' treatment, therefore, largely has been left up to individual and institutional preferences and has been guided by smaller, nonrandomized trials, with small improvements accruing over time as investigators adopted/tried various combinations of treatment modalities, ranging from treatment with single modalities to aggressive treatment with combination surgery and chemoradiation.

Radiation was shown to be of value by Mohan et al., who retrospectively studied 102 patients 70 years and older and found that those treated optimally (that is, with GTR and definitive radiation) had significantly longer OS (7.4 months) than other patients (2.4 months) regardless of KPS. Mohan et al. also reported a significant relationship between recursive partitioning analysis (RPA) class and OS, showing decreased survival for patients in RPA classes IV, V, and VI, who had OS times of 9.2 months, 6.6 months, and 2.4 months, respectively.[17] In a multicenter randomized prospective

Table 2. Univariate analysis of overall survival from diagnosis

		3-Month		Median Survival Time	
Factor	**N**	**No. Deaths**	**Survival**	**(months)**	***P*[1]**
Overall	206	191	63%	4.5	—
Age at diagnosis					
<80	157	145	66%	5.1	
≥80	49	46	53%	3.1	<.001
Uncoded age	—	—	—	—	<.001[2]
Gender					
Male	114	108	58%	4.1	
Female	92	83	69%	4.9	.54
KPS score at diagnosis					
90–100	20	15	83%	17.2	
80	34	30	88%	7.3	
70	51	50	69%	4.8	
60	47	46	48%	2.8	
≤50	30	28	26%	1.8	<.001[3]
Maximum tumor					
Diameter (cm)	—	—	—	—	.75[2]
Bilateral disease					
No	182	170	65%	4.8	
Yes	21	18	43%	2.8	.003
Multicentric disease					
No	153	140	59%	3.8	
Yes	17	15	38%	2.2	.02
Multifocal disease					
No	177	164	62%	4.8	
Yes	28	26	68%	3.4	.005
Treatment modality					
Surgery (other than biopsy)					
No	113	106	46%	2.8	
Yes	93	85	83%	7.3	<.001
Extent of surgical					
Resection					
GTR	23	23	96%	10.7	
STR	70	64	79%	6.9	.24
Treatment modality					
RT (EBRT, SRS, IMRT)					
No	81	78	37%	1.9	
Yes	125	113	80%	6.7	<.001
Extent of EBRT					
Partial	72	62	87%	7.9	
Whole brain	21	21	67%	4.1	<.001
Treatment modality					
Chemotherapy					
No	164	159	56%	3.5	
Yes	42	32	90%	11.2	<.001
Actual treatment					
None	62	60	33%	1.9	
Surgery only	19	18	47%	2.3	
RT only[4]	38	37	51%	3.1	
Surgery + RT[5]	45	44	96%	7.2	
Chemo + RT[6]	13	9	92%	6.7	

Continued

Table 2. *Continued*

Factor	N	3-Month No. Deaths	3-Month Survival	Median Survival Time (months)	P^1
Surgery + Chemo + RT[7]	29	23	89%	13.3	<.001
Year of diagnosis					
<1997	42	42	55%	3.5	
≥1997	164	149	65%	4.7	.003

Abbreviations: EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery; RT, radiation therapy; GTR, gross total resection; STR, subtotal resection; IMRT, intensity-modulated radiation therapy; Chemo (including biologics and immunotherapy); Surgery (GTR and STR).
[1]Log-rank test, except as noted.
[2]From proportional hazards model.
[3]Trend test.
[4]SRS for 1 patient.
[5]EBRT + SRS in 3 patients.
[6]EBRT + SRS in 2 patients.
[7]IMRT in 1 patient.

trial of 85 patients age 70 and older, Keime-Guibert and colleagues[9] showed an improvement in OS from 4.2 months for best supportive care to 7.3 months with the addition of 50 Gy in 1.8-Gy fractions. Hypofractionated radiation therapy was reported on by Chang and associates in a retrospective study[16] in which 59 patients with GBM with a median age of 65 years were given 50 Gy in 2.5-Gy fractions. They reported survival similar to those reported in the RTOG RPA classification study[3] and concluded that their hypofractionated regimen was not inferior to standard regimens. Hypofractionation was also shown prospectively to be of equal benefit when compared with standard adjuvant EBRT by Roa et al.,[18] who randomized 100 patients aged 60 years or older to either standard radiation therapy (60 Gy in 30 fractions) or a shorter course (40 Gy in 15 fractions). They found no statistical difference in OS and found a benefit of the short course in the form of a reduced need for corticosteroids. Further, a recent study of the 2836 patients with glioblastoma over the age of 70 years from the Surveillance Epidemiology and End Results database showed a significant cause-specific benefit to the receipt of EBRT (HR 0.43 for death; 95% CI 0.38–0.49).[22]

Our study strongly agrees with the literature on the use of radiation therapy. On univariate analysis, the use of radiation therapy was shown to increase OS from 1.9 months to 6.7 months ($P < .001$), and this was confirmed on multivariate analysis, where not receiving radiation therapy carried an HR for death of 2.60 ($P < .001$).

The addition of chemotherapy to regimens including radiation and surgery was shown to be beneficial by Brandes and associates,[14] who randomized 79 patients over the age of 65 to surgery plus radiation (group A); surgery, radiation, and chemotherapy in the form of procarbazine, lomustine, and vincristine (group B); and surgery, radiation, and temozolomide (group C). Group C did better than groups A and B in this trial, for both time to progression and OS. Although the trial could not differentiate statistically between the 2 chemotherapy regimens, it showed that the addition of chemotherapy to surgery and radiation confers significant benefit in this age group. Brandes and associates[13] also recently reported on a prospective study of 58 patients 65 years of age or older who were treated with standard-of-care radiotherapy (60 Gy in 30 fractions) plus concomitant temozolomide followed by 12 maintenance temozolomide cycles. They reported a median OS time of 13.7 months and a significant improvement in survival for patients whose tumors had O^6-methylguanine-methyltransferase (MGMT) methylation. Combs and associates[15] also reported on the safety and efficacy of temozolomide in a study of 43 patients aged 65 years and older. They found that the addition of concomitant temozolomide to standard-of-care surgery and radiotherapy was well tolerated and conferred a survival advantage when compared with other reported studies without temozolomide. They reported a significant benefit to OS for all the patients studied when compared with published data for RPA class-matched controls ($P = .004$) and limited toxicity; they also reestablished the survival benefit conferred by maximal resection ($P = .002$).

On the use of chemotherapy, our study is in strong concordance with the above literature. While we did not attempt to parse the differences between chemotherapeutic regimens, the addition of chemotherapy was found, on univariate analysis, to carry a significantly better prognosis of 11.2 months (vs. 3.5 months for

Table 3. Multivariate analysis of factors influencing overall survival

Factor	Hazard Ratio	95% Confidence Interval	P
KPS (≤50 vs 60 vs 70 vs 80 vs 90–100)	1.24	1.06–1.44	.006
Surgery (no vs yes)	3.09	2.09–4.56	<.001
Radiotherapy (no vs yes)	2.60	1.57–4.31	<.001
Chemotherapy (no vs yes)	2.20	1.52–3.17	<.001

those patients not receiving chemotherapy; $P < .001$). This was confirmed on multivariate analysis as well, where not receiving chemotherapy carried HR for death of 2.20 ($P < .001$). Interestingly, on univariate analysis, being diagnosed before 1997 carried a significantly worse prognosis. This cutoff date of 1997 was identified using a recursive partitioning approach and was, after the fact, identified as the time at which the institution under study began routinely offering chemotherapy to this group of patients (only 3 patients received chemotherapy before this date), which again argues for the efficacy of chemotherapy. For this reason, and to allow for other possibly inherent time-related effects, the multivariate analyses were stratified by diagnosis period.

Maximal surgical resection is widely accepted as the standard primary diagnostic and therapeutic modality for GBM for patients who can tolerate it.[23] The literature is somewhat more equivocal with regard to the elderly. A recent randomized trial of 30 patients over the age of 65 done in Finland by Vuorinen et al.[19] showed a significant survival benefit for patients receiving maximal resection (median OS = 171 days vs. 85 days in the biopsy-alone group; $P = .035$). These authors tempered their recommendations, however, by reporting a nonstatistically significant difference in time to deterioration ($P = .057$). Our study showed a strong OS benefit attributable to resection (7.3 months vs. 2.8 months; $P < .001$) in univariate analysis, and the result was corroborated in multivariate analysis, with patients receiving biopsy alone having an HR for death of 3.09 ($P < .001$). We were unable to show a difference between the effects of GTR and STR in our analysis; patients undergoing GTR had an OS of 10.7 months versus 6.9 months for those undergoing STR ($P = .24$).

Aggressive treatment in the elderly has been studied by a number of groups. This has largely been done retrospectively and has used a number of different definitions of both "aggressive" and "elderly."[15,17,24,25] Patwardhan et al. studied 30 patients aged 59 and older who received therapy for GBM and found a significant benefit to OS with combination therapy including surgery, chemotherapy, and radiation therapy, irrespective of KPS (OS = 13.2 months with combination therapy).[24] Piccirilli et al.[25] reported on 22 patients over the age of 80 with KPS greater than 60. In their study, they compared patients receiving combined surgery and chemoradiation with those receiving chemotherapy and/or radiation without resection and found a large difference in OS (16.7 months vs. 5.8 months). A secondary finding was a significant correlation between MGMT promoter methylation status and OS (17.9 months for patients with methylated promoters vs. 7.7 months for those with unmethylated promotors).[25] Additionally, Iwamoto et al. reported on a large retrospective study from Memorial Sloan-Kettering Cancer Center for patients aged 65 years and older that showed a strong benefit from aggressive treatment including chemotherapy; although their study also showed a trend toward benefit with radiation therapy, it was not sufficiently powered to show a significant effect for this modality.[26]

Our study of 206 patients aged 70 years and older revealed that radiation therapy, chemotherapy, and surgery all significantly improved OS, independent of other factors. With the addition of each treatment modality (individually discussed above), patients saw an increase in OS, regardless of the modality added, culminating in the greatest benefit to our patients when all 3 modalities were used (OS = 13.3 months; Fig. 1D).

While the literature more strongly supports aggressive treatment in this group of patients, 2 recent large epidemiological reviews demonstrate that undertreatment is still the norm.[20,21] While these two studies focused on patients with different age cutoffs (one defined "elderly" as 60 years and up and the other as 65 years and up), their results are strikingly similar to ours. In contrast to these studies, Iwamoto et al. described the experience at Memorial Sloan-Kettering, demonstrating a trend at that institution to treat elderly patients more aggressively over time,[26] and the OS rate at the time of publication of that article was almost twice that in studies such as this one that reported less aggressive treatment (8.6 months vs. 4.5 months). While the Iwamoto et al.[26] study defined patients over 65 as elderly, it highlights a trend toward longer survival in elderly patients who have received more aggressive treatment. While our institution has been moving toward more aggressive treatment in this patient population, our data show that those with worse KPS ($P < .001$) and multifocal disease ($P = .02$) often receive submaximal therapy.

Although we cannot advocate specific treatment methodologies based on the data reported here, it is clear that aggressive treatment with chemotherapeutic agents, radiation, and surgery is appropriate in selected patients 70 years and older who have primary GBM. For chemotherapy regimens, the current standard of care for adult patients is concurrent and adjuvant temozolomide,[10,11] and the current literature strongly supports the efficacy and tolerability of this agent in the elderly as well.[10,11,13,15] Our study included a wide range of radiotherapy schedules and methodologies, and there is strong evidence in the recent literature for the noninferiority and efficacy of hypofractionated schedules in elderly patients.[9,18,27,28] On the surgical side, maximal resection remains the standard for all age groups.[5,23] Based on these rationales and our data, we recommend maximal surgical resection, concurrent and adjuvant temozolomide, and EBRT in either a standard or a hypofractionated scheme for elderly patients with primary GBM.

As this was a retrospective study, we were unable to control treatment specifics and were forced to consider each chemotherapeutic, radiotherapeutic, and surgical intervention as equivalent. Our results clearly show that each intervention significantly added to patients' OS time, though we are not able to suggest whether one type of chemotherapy or one radiation scheme was better than another. Additionally, we did not collect

any quality-of-life data and so we are able to comment only on how these treatments affected the quantity of life of these patients. Over the course of the 28 years covered by this study, there have been many advances in radiotherapy planning and treatment delivery, imaging for presurgical planning and postsurgical assessment, and novel chemotherapeutics with superior efficacy and toxicity profiles. This taken into consideration, the assumptions we made equating all modalities likely makes for inaccurate predictions, but despite that, the predictions likely do not overestimate the benefit of current therapy.

An additional caveat is that while aggressive treatment was found to be beneficial independent of all other factors, KPS was found to be significantly different between treatment groups, with only the patients with the highest KPS tending to receive the full complement of radiation, surgery, and chemotherapy. Regardless of this unintended treatment selection bias, each additional level of treatment maintained its benefits in multivariate analysis. This analysis highlights the difficulties inherent in retrospective studies, especially when the diagnosis is rare, and points out the need for prospective, protocol-driven trials to answer the important questions surrounding the care of patients 70 years and older with GBM.

Two newly reported phase III trials of therapies for GBM in the elderly had conflicting results, and neither tested combined-modality therapy. These two trials, reported at the annual meeting of the American Society of Clinical Oncology in 2010, were both conducted in Europe. The NOA-08 trial[29] accrued 412 patients over the age of 65 years from May 2005 to November 2009 in Germany and Switzerland. The investigators endeavored to prove equivalence between single-agent temozolomide and involved-field radiation therapy, both in the adjuvant setting. They concluded that EBRT could not be forgone in favor of single-agent temozolomide but did not test or comment on the efficacy of combined chemoradiation. Another European trial, reported by Malmstrom et al.,[30] compared 3 separate treatment modalities, again in the adjuvant setting. These investigators randomized 291 patients over the age of 60 years to either "standard radiation therapy," defined as 60 Gy in 2-Gy fractions; hypofractionated radiation therapy, defined as 34 Gy in 3.4-Gy fractions; or 6 cycles of temozolomide (200 mg/m^2 on days 1–5 every 28 days). They found no difference in survival among the 3 arms and concluded strongly that standard radiation therapy should no longer be offered. While these 2 results are intriguing, they are limited in that neither trial evaluated combined-modality therapy and in that the trials themselves are difficult to compare, as the patient age groups are different.

The National Cancer Institute of Canada in collaboration with the EORTC is currently sponsoring a phase III trial of short-course radiation therapy with and without temozolomide in patients over the age of 65 years, but there are currently no national trials open in the United States specifically for patients in this age group.

In conclusion, these data represent the largest single-institution study of patients 70 years of age and older with GBM and add to the growing body of evidence that supports the use of aggressive treatment to prolong OS for elderly patients with primary GBM. While we await prospective confirmation to provide definitive answers for this age group, our data suggest that the aggressive treatment of this population, in appropriately selected patients, increases OS.

Conflict of interest statement. **J.G. Scott**, none; **J.H. Suh**, Schering Plough, speakers bureau/honoraria; **P. Elson**, none; **G.H. Barnett**, Elekta, speakers bureau/honoraria, Consultant: Monteris medical; **M.A. Vogelbaum**, Honoraria or Consulting: Schering Plough, AstraZeneca, BrainLAB; **D.M. Peereboom**, Honoraria: Schering Plough; **G.H.J. Stevens**, Speaker: UCB PHARMA; **H. Elinzano**, none; **S.T. Chao**, none.

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