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The efficacy of carmustine wafers for older patients with glioblastoma multiforme: prolonging survival

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Abstract

Objective—Peak incidence of glioblastoma multiforme (GBM) occurs in individuals aged 65 years and older. The goal was to evaluate the efficacy of carmustine wafers in prolonging survival for older GBM patients.

Methods—One hundred and thirty-three consecutive patients aged 65 years and older who underwent surgery for an intracranial primary (*de novo*) GBM from 1997–2007 were retrospectively reviewed. Among these 133 patients, 45 patients with carmustine wafer implantation were matched with 45 patients without implantation. These groups were matched for factors consistently shown to be associated with survival (age, Karnofsky performance scale, extent of resection, radiation therapy, and temozolomide). Survival was expressed as estimated Kaplan–Meier plots, and log-rank analysis was used to compare survival curves. Variables with $P<0.05$ were considered statistically significant.

Results—The mean (±standard deviation) age of the cohort was 73±5 years, and the median survival of the entire cohort was 5.9 months. Among patients with and without carmustine wafers, there were no significant differences in pre- and peri-operative variables. However, patients with carmustine wafers demonstrated prolonged survival as compared to patients without wafers. The median survival for patients with carmustine wafers was 8.7 months, while median survival for patients without wafers was 5.5 months ($P=0.007$). Likewise, in subgroup analysis, patients older than 70 years ($P=0.0003$) and 75 years ($P=0.04$) who had carmustine wafers had significantly longer survival than matched patients without wafers.

Discussion—Older patients with GBM may benefit from carmustine wafers. The survival for older patients who received carmustine wafers is significantly longer than matched patients who did not receive carmustine wafers.

Keywords

Carmustine wafers; Elderly; GBM; Gliadel; Glioblastoma; Survival

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Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor, with ~10 000 newly diagnosed cases every year in the USA.[1] The majority of these patients are older, with the peak incidence of this disease occurring in individuals aged 65 years and older.[2] This subset of the population is increasing more than any other age group in the USA, and has at least partly contributed to the increasing incidence of patients with GBM.[3] Despite modern advances in surgery and adjuvant chemotherapy, the median survival among patients with malignant gliomas remains dismal, with older patients having poorer survival.[2] Studies devoted to older patients with GBM are few and limited, where most studies are limited to younger patients.[4–7]

Carmustine or Gliadel wafers are biodegradable polymers containing 3.85% carmustine (1,3-bis[2-chlor-oethyl]-1-nitroso-urea).[8–10] Placement of these wafers in the resection cavity at the time of surgery for patients with primary or recurrent GBM has been shown to improve median survival by 2–4 months.[8–10] However, the safety and efficacy of this approach has only been demonstrated among a pooled group of patients of all ages. It remains largely unknown whether the application of these wafers confers the same survival benefit for older patients, who typically have more complicated medical co-morbidities and worse clinical outcome than younger patients. Adequate characterization of the efficacy of carmustine wafers among older patients is becoming increasingly important as the US population ages and the incidence of older patients with GBMs increases.[3]

The goal of this study is to characterize the efficacy of carmustine wafers among patients aged 65 years and older using retrospective data over a 10-year period at our institution. A better understanding of the efficacy of local delivery of chemotherapeutic agents within this age group may provide insight into optimizing treatment for older patients with GBM.

Methods

Patient selection

One hundred and thirty-three consecutive patients older than 65 years of age who underwent surgery for an intracranial primary (*de novo*) GBM between 1997 and 2007 were retrospectively reviewed. Patients at least 65 years old with a tissue-proven diagnosis of a primary supratentorial GBM (World Health Organization Grade IV) were included in the study. The pathology was determined by a neuro-pathologist in all cases. Patients with prior resections or needle biopsies, previous adjuvant therapy (chemotherapy or radiation therapy), and/or infratentorial gliomas were excluded from the analysis. Because carmustine wafers were not typically implanted when tumors were multifocal, extended across the corpus callosum, or required large opening of the ventricle, tumors with these characteristics were also excluded. Patients with incomplete medical records lacking presenting symptoms, pre- and post-operative magnetic resonance imaging (MRI), and adjuvant therapies were also excluded from the analysis. Additionally, patients who were not confirmed as having died were also excluded. Likewise, patients who died from other non-brain tumor causes were excluded.

Recorded variables

The clinical, operative, and hospital course records of all patients who met the inclusion and exclusion criteria were reviewed. The information collected from clinical notes included patient demographics, presenting symptoms, neuro-imaging characteristics, peri-operative course, and adjuvant therapy. The Karnofsky performance scale (KPS) index was used to classify patients' pre-operative functional status,[11] and was assigned by a reviewer blinded to patient outcomes at the clinic visit prior to surgery. A language deficit was defined as any combination of receptive and/or expressive aphasia. A motor deficit was defined as decreased strength, and a sensory deficit was decreased sensation to light touch.

Images by MRI were obtained and reviewed for each patient. The characteristics that were recorded included the lesion's size (largest diameter based on T1-weighted contrast images), specific lobe involvement, and involvement of eloquent cortex. Eloquent cortex included motor/sensory cortex, language cortex, and/or basal ganglia/internal capsule. Extent of resection was classified from dictations of MRIs obtained <48 hours after surgical resection as either gross total resection (GTR) or subtotal resection (STR) by an independent neuro-radiologist blinded to patient outcomes. STR and GTR were defined as having residual and no residual enhancement, respectively. This was done by comparing pre- and postoperative MRIs.

The date of death was recorded for all patients, where survival data were obtained from the social security index database.[12] Peri-operative death was defined as death within 30 days of surgery. Patients whose deaths were unconfirmed were classified as lost to follow-up and were excluded from the analysis.

Peri-operative treatment

The general aim of each surgery was to achieve GTR of the tumor when possible. The extent of resection was generally limited by involvement of eloquent brain. Motor- and somatosensory-evoked potentials were routinely used in the majority of cases, while surgical navigation (computed tomography and/or MRI wand) was used in all cases after 2001. The use of motor mapping or electrocorticography largely depended upon surgeon preference.

The use of carmustine wafers was determined by both the surgeon as well as the patient. These carmustine wafers were typically not implanted when tumors were multifocal, extended across the corpus callosum, or required large opening of the ventricle. The particular use of adjuvant radiation and chemotherapy was determined by the surgeon, radiation oncologist, medical oncologist, and the patients themselves. All patients typically receive post-operative radiation therapy.

Statistical analysis

In order to compare the efficacy of carmustine wafer implantation, a case–control study was performed.[13] Fifty-seven of 133 reviewed patients had carmustine wafer implantation. Forty-five patients with carmustine wafer implantation were matched with 45 patients without carmustine wafer implantation. The groups were matched for factors consistently shown to be associated with survival, which included age (±3 years), KPS index (±0),

eloquent cortex involvement (yes/no), extent of resection (GTR/STR), post-operative radiation (yes/no), and postoperative temozolomide chemotherapy (yes/no).[8,14]

Survival as a function of time after surgical resection was expressed as estimated Kaplan–Meier plots. Parametric data were expressed as mean ± standard deviation (SD). Non-parametric data were expressed as median [interquartile range (IQR)]. Percentages were compared via chi-squared test. Continuous variables were compared via Student's t-test or Mann–Whitney *U* test where appropriate. Survival between patients with and without carmustine wafer implantation was compared via log-rank analysis. Values with $P<0.05$ in these analyses were considered statistically significant.

Results

Patient population

Among patients older than 65 years who underwent non-biopsy surgical resection, 45 patients with carmustine wafer implantation were matched with 45 patients without carmustine wafer implantation (Table 1). These groups were matched for factors consistently shown to be associated with survival. These factors were age, KPS, extent of resection, post-operative radiation therapy, and post-operative temozolomide chemotherapy.[8,14] For the entire group, the mean±SD age was 73±5 years and 51 (57%) were male. At presentation, median (IQR) KPS was 80 (80–80). Fourteen (16%) patients presented with seizures, 24 (27%) with headaches, 30 (33%) with motor deficits, 3 (3%) with sensory deficits, 14 (16%) with language deficits, 9 (10%) with gait deficits, and 29 (32%) with mental status changes. The average tumor size was 4.3±1.5 cm, and involved the frontal lobe in 33 (37%), temporal lobe in 29 (32%), parietal lobe in 22 (24%), and occipital lobe in 6 (7%). Eighteen (20%) patients had tumors that involved eloquent cortex, where 4 (4%), 5 (6%), and 9 (10%) involved the motor/sensory, language, and basal ganglia/internal capsule, respectively. There were no significant differences in the pre-operative characteristics between patients who received and did not receive carmustine wafers (Table 1).

Peri-operative characteristics and long-term outcome

Gross total resection was achieved in 76 (84%) patients. Peri-operatively, eight (9%) patients incurred a motor deficit and five (6%) a language deficit. Nine (10%) patients developed a deep vein thrombosis or pulmonary embolism, three (3%) a surgical site infection, and zero (0%) meningitis. Among patients who received carmustine wafers, 1 (1%) patient developed increased cerebral edema with headaches, 0 (0%) developed increased seizures, and 1 (1%) complained of increased fatigue/weakness. Zero (0%) patients died in the peri-operative period. At last follow-up, temozolomide was used in 12 (13%) patients and radiation therapy in 80 (89%) patients. All patients who underwent temozolomide had concurrent radiation therapy according to the Stupp protocol.[15] There were no significant differences in the peri-operative characteristics between patients who received and did not receive carmustine wafers including surgical site infection, cerebral edema, and increased seizures. No patients required repeat surgeries for removal of the wafers (Table 2).

At last follow-up, all patients (100%) had died. The median (IQR) survival of the entire cohort was 5.9 months, where the 3-, 6-, 9-, and 12-month survival rates were 77, 48, 33, and 18%, respectively (Fig. 1).

Patients with and without carmustine wafers

Despite similarities in pre-operative clinical status and treatment regimens (Tables 1 and 2), patients who had carmustine wafers implanted at the time of surgery demonstrated prolonged survival as compared to patients without carmustine wafer implantation (Fig. 2). The median survival for patients with carmustine wafer implantation was 8.7 months, while the median survival for patients without carmustine wafer implantation was 5.5 months (P=0.007). The 3-, 6-, 9-, and 12-month survival rates for patients with carmustine wafers were 89, 62, 47, and 33% as compared to 71, 40, 24, and 9% for patients without carmustine wafers. This was significantly different in log-rank analysis (P=0.007).

Additionally, subgroup analysis was performed on patients older than 70 and 75 years of age. As with patients older than 65 years, patients older than 70 years with carmustine wafer implantation had significantly longer survival times as compared to matched patients without carmustine wafer implantation (Fig. 3A). The median survival for patients older than 70 years with carmustine wafers was 9.1 months, while the median survival for patients older than 70 years without carmustine wafers was 4.8 months (P=0.0003). The 3-, 6-, 9-, and 12-month survival rates for patients with carmustine wafers were 89, 61, 50, and 36% as compared to 64, 36, 18, and 3% for patients without carmustine wafers. This was significantly different in log-rank analysis (P=0.0003). Likewise, patients older than 75 years with carmustine wafer implantation had significantly longer survival times as compared to patients without carmustine wafer implantation (Fig. 3B). The median survival for patients older than 75 years with carmustine wafers was 6.0 months, while the median survival for matched patients older than 75 years without carmustine wafers was 4.7 months (P=0.04). The 3-, 6-, 9-, and 12-month survival rates for patients with carmustine wafers were 88, 47, 41, and 24% as compared to 65, 35, 18, and 6% for patients without carmustine wafers. This was significantly different in log-rank analysis (P=0.04). There were too few patients older than 80 years to perform log-rank analysis with sufficient statistical power.

Discussion

Several clinical studies have demonstrated that carmustine wafers can prolong survival for patients with malignant gliomas.[8,16–18] These studies, however, have typically involved patients of all ages, but primarily patients younger than 65 years of age.[16] Studies on older patients with GBM are few and limited even though older patients represent a large proportion of patients with GBM.[19] In our case– control series of 90 patients older than 65 years of age with primary GBM, the use of carmustine wafers was associated with an increase in median survival of 3.2 months. Among patients older than 70 years of age, this survival advantage was even more pronounced with an increase in median survival by 4.3 months. Furthermore, patients who received carmustine wafers did not have any significant increase in side effects or peri-operative morbidity and mortality. Our retrospective data

analysis indicates that the use of carmustine wafers may be safe and effective in prolonging survival among older patients with primary GBMs.

Some reports may indicate that older patients are often excluded from clinical trials and rarely offered aggressive therapies for their disease.[19–21] This apprehension in enrolling older patients in clinical trials has been reinforced by several published reports which show that older patients typically exhibit reduced survival.[7,14,22,23] In fact, the typical survival for patients older than 65 years of age is 4–6 months as compared to 1 year for the general population.[24–26] This poorer survival among these patients with GBM may be due to several reasons. Older patients may harbor tumors which have accumulated more mutations.[27–29] This increase in mutations may create tumors that behave more aggressively or are more resistant to adjuvant therapies including radiation and chemotherapy.[27–29] Older patients also have an increased number of medical co-morbidities along with poor physiological reserves. This may make it difficult for these patients to tolerate various treatments.[24–26] Additionally, older patients are relatively immunosuppressed, which may make them more susceptible to concomitant infections as well as weakened tumor suppression.[21] These features have limited the enrollment of older patients in major clinical trials, and limited an understanding of the utility of novel therapies for older patients with GBM.

Carmustine wafers have been shown to be efficacious in prolonging survival primarily for younger patients with either recurrent or primary GBM.[8,16–18] We showed in a phase 3 trial that carmustine wafers can increase median survival from 5.5 to 7.4 months for patients with recurrent GBM.[8] The average age of this trial, however, was 48 years.[8] Likewise, in a recent 10-year retrospective study, we demonstrated that the combination of carmustine wafers, radiation, and temozolomide chemotherapy can increase median survival for patients with recurrent GBM to 11.3 months.[30] The average age in this study was 51 years.[30] Additionally, Valtonen *et al*. showed in a randomized, placebo-controlled study that the use of carmustine wafers increased median survival from 10.0 to 14.5 months for patients with primary GBM.[9] The average age of this study was 53 years, and actually excluded patients older than 65 years of age.[9] Similarly, Westphal *et al*. showed in a larger study that carmustine wafers increased median survival from 11.6 to 13.8 months for patients with primary GBM, but excluded patients older than 65 years of age.[10] Therefore, the safety and efficacy of carmustine wafers for older patients with GBM remain poorly understood.

The present study provides several useful insights for older patients with GBM. First, the use of carmustine wafers in these patients does not increase peri-operative morbidity and mortality. Only one patient developed significant cerebral edema which caused headaches, but did not require removal of the wafers. Another patient developed fatigue and weakness. There was also no increase in surgical site infection or seizures in patients with carmustine wafers. Second, the use of carmustine wafers is nearly as efficacious in prolonging survival for older patients with GBM as it is with younger patients with GBM. Westphal *et al*. and Valtonen *et al*. demonstrated an increase survival benefit of 2.2 and 4.5 months for patients younger than 65 years with primary GBM, respectively.[9,10] Our study demonstrated an increased survival of 3.2 months. Finally, studies on older patients with GBM are few and limited. The present study is the first study to assess the efficacy of carmustine wafers in this population of patients with GBM.

This study, however, has some limitations. First, this is a case–control study and does not have the statistical power and relevance as a randomized, placebo-controlled study. Second, this study may not be applicable to patients with recurrent or infratentorial GBM as well as patients unable to tolerate surgery since all the patients in this study underwent surgery for a primary, supratentorial GBM. Furthermore, the use of carmustine wafers may have been biased to healthier patients and lesions that might lend themselves to more aggressive local treatment. However, we tried to control for this by matching patients with similar KPS and imaging characteristics. Additionally, this study is inherently limited by its retrospective design, and, as a result, it is not appropriate to infer direct causal relationships. However, we tried to create a uniform population of patients undergoing surgery for primary GBM by using strict inclusion/exclusion criteria. We only included patients aged >65 years at time of surgery and only those who underwent surgical resection of supratentorial lesions. Furthermore, we controlled for factors known to be associated with survival (age, KPS, extent of resection, radiation, and temozolo-mide) and only included patients with long-term follow-up. With the use of these strict statistical controls and a relatively precise outcome measure, we believe that our findings offer useful insights for the management of older patients with GBM. However, prospective studies are needed to provide better data to guide clinical decision-making.

Conclusion

Although the peak incidence of GBM occurs in individuals aged 65 years and older, the utility of carmustine wafers in this population of patients remains poorly understood. The present case-control study shows that carmustine wafers can prolong survival by 3.2 months, which is similar for younger patients with GBM in previous studies. Furthermore, the use of carmustine wafers was not associated with any increase in peri-operative morbidity or mortality. The use of carmustine wafers may be therefore be safe and efficacious in patients older than 65 years of age.

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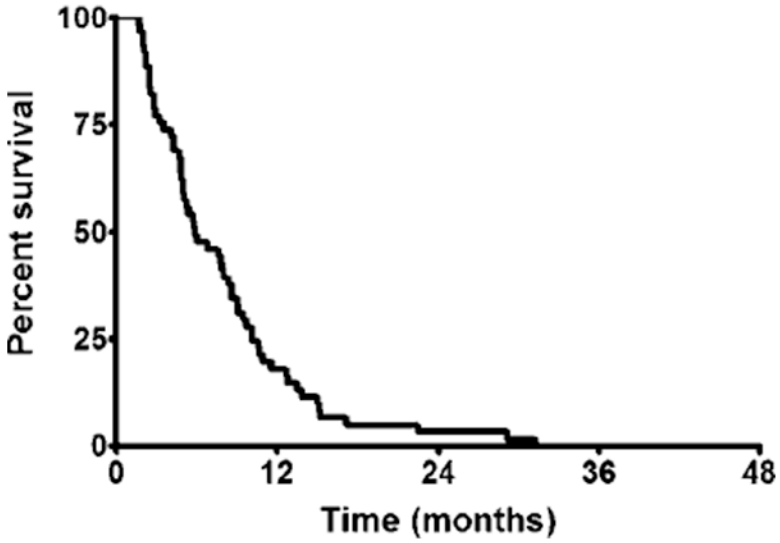

Figure 1. Kaplan–Meier plots of survival for all patients older than 65 years of age with glioblastoma multiforme (GBM) in this study

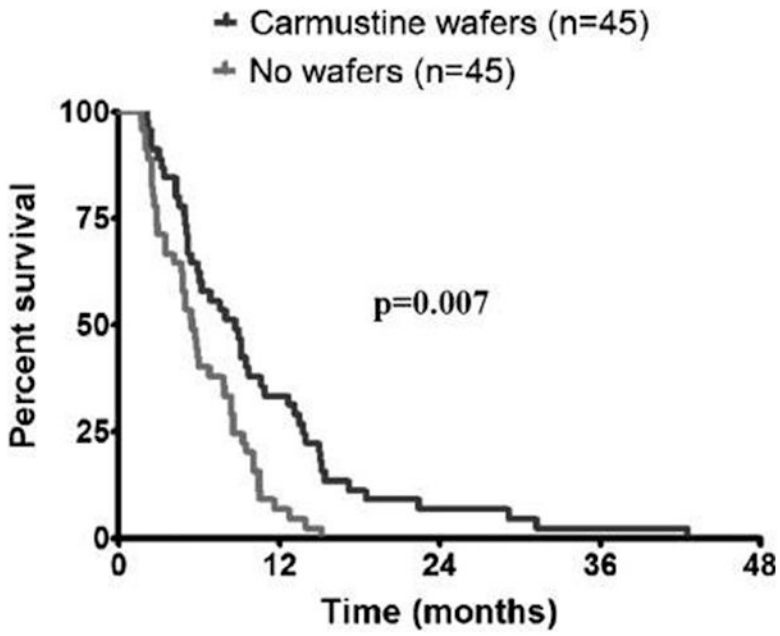

Figure 2.

Kaplan–Meier plots of survival for patients older than 65 years of age with glioblastoma multiforme (GBM) who did and did not have carmustine wafer implantation. The groups were matched for age, Karnofsky performance score (KPS), extent of resection, post-operative radiation, and postoperative temozolomide chemotherapy.

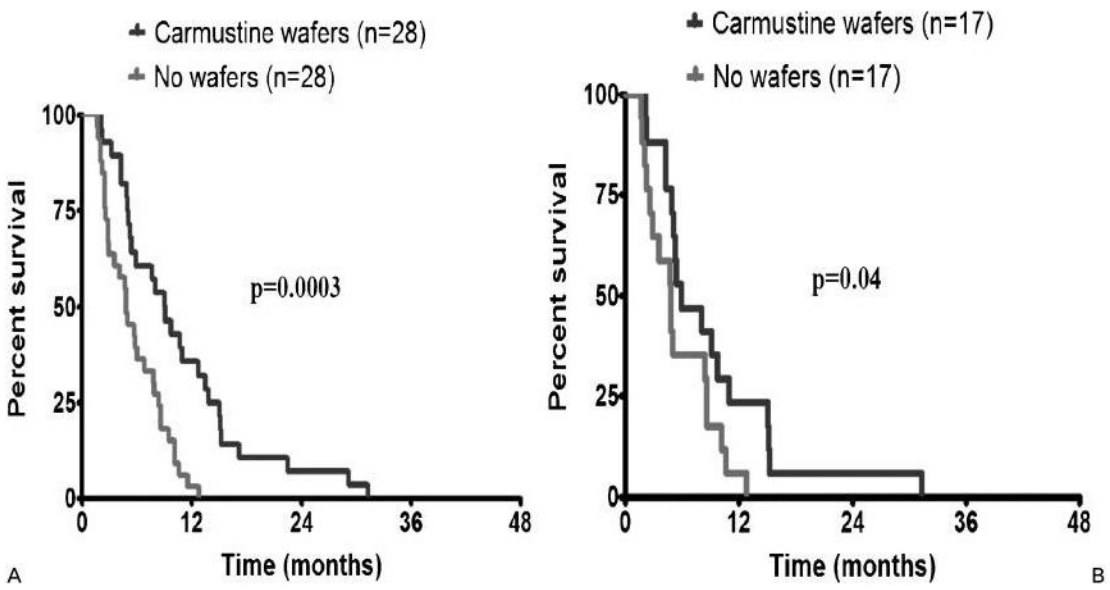

Figure 3.

Kaplan–Meier plots of survival for patients older than (A) 70 years and (B) 75 years with glioblastoma multiforme (GBM) who did and did not have carmustine wafer implantation. The groups were matched for age, Karnofsky performance score (KPS), extent of resection, post-operative radiation, and post-operative temozolomide chemotherapy.

Table 1

Summary of clinical, radiological, and treatment characteristics of 90 patients older than 65 years of age with primary glioblastoma multiforme (GBM)*

Study population			
	Wafers	No wafers	
Characteristics	No. (%)	No. (%)	*P* value
Gender			
Male	26 (58%)	25 (56%)	0.99
Age† (years)	72.8 ± 5.0	72.2 ± 5.3	0.62
65–70	16 (36%)	15 (33%)	0.99
71–75	13 (29%)	14 (31%)	0.99
76–80	12 (27%)	12 (27%)	0.99
>80	4 (9%)	4 (9%)	0.99
Presenting symptoms			
KPS‡	80 (80–80)	80 (80–80)	0.99
Symptom duration† (months)	1 (0.5–2.0)	1 (0.5–1.5)	0.90
Pre-operative symptoms			
Seizures	6 (13%)	8 (18%)	0.77
Headaches/nausea/vomiting	15 (33%)	9 (20%)	0.22
Motor deficit	16 (36%)	14 (31%)	0.82
Sensory deficit	1 (2%)	2 (4%)	0.99
Language deficit	6 (13%)	8 (18%)	0.77
Visual deficit	11 (24%)	6 (13%)	0.27
Gait deficit	4 (9%)	5 (11%)	0.99
Confusion/memory loss	16 (36%)	13 (29%)	0.64
Radiographics			
Tumor size† (cm)	4.6±1.4	4.1 ± 1.5	0.15
Location			
Frontal	17 (38%)	16 (36%)	0.99
Temporal	11 (24%)	18 (40%)	0.16
Parietal	13 (29%)	9 (20%)	0.45
Occipital	4 (9%)	2 (4%)	0.68
Hemorrhagic	6 (13%)	5 (11%)	0.99
Eloquent cortex	9 (20%)	9 (20%)	0.99
Motor/sensory cortex	2 (4%)	2 (4%)	0.99
Language cortex	3 (7%)	2 (4%)	0.99
Basal ganglia/internal capsule	4 (9%)	5 (11%)	0.99

Note:

*Forty-five patients who underwent surgical resection of GBM and placement of carmustine wafers were matched with 45 patients who underwent surgical resection of GBM and no carmustine wafer implantation. The groups were matched for age, Karnofsky performance score (KPS), extent of

resection, post-operative radiation, and post-operative temozolomide chemotherapy. Clinical and treatment variables were similar between patients with and without carmustine wafer implantation.

† Mean ± standard deviation.

‡ Median (interquartile range).

Table 2

Incidence of peri-operative morbidity and overall survival in 90 patients older than 65 years of age undergoing resection of glioblastoma multiforme (GBM)*

Peri- and post-operative outcomes			
	Wafers	No wafers	
Characteristics	**No. (%)**	**No. (%)**	***P* value**
Surgical variables			
Gross total resection	38 (84%)	38 (84%)	0.99
Subtotal resection	7 (16%)	7 (16%)	0.99
Peri-operative morbidity			
New motor deficit	3 (7%)	5 (11%)	0.71
New language deficit	3 (7%)	2 (4%)	0.99
Deep vein thrombus/pulmonary embolus	3 (7%)	6 (13%)	0.48
Surgical site infection	2 (4%)	1 (2%)	0.99
Meningitis	0 (0%)	0 (0%)	0.99
Cerebral edema	1 (2%)	0 (0%)	0.99
Increased seizures	0 (0%)	0 (0%)	0.99
Fatigue/weakness	1 (2%)	0 (0%)	0.99
Mortality	0 (0%)	0 (0%)	0.99
Adjuvant therapy			
Carmustine wafers	45 (100%)	0 (0%)	<0.0001
Temozolomide	6 (13%)	6 (13%)	0.99
Radiation therapy	40 (89%)	40 (89%)	0.99
Survival			
Died at last follow-up	45 (100%)	45 (100%)	0.99
Median survival (months)	8.7	5.5	0.007
3-month survival rate	89%	71%	
6-month survival rate	62%	40%	
9-month survival rate	47%	24%	
12-month survival rate	33%	9%	

Note:

* Forty-five patients who underwent surgical resection of GBM and placement of carmustine wafers were matched with 45 patients who underwent surgical resection of GBM and no carmustine wafer implantation. The groups were matched for age, Karnofsky performance score (KPS), extent of resection, post-operative radiation, and post-operative temozolomide chemotherapy. With the exception to survival, clinical and treatment variables were similar between patients with and without carmustine wafer implantation.