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Supratentorial Glioblastoma Multiforme: The Role of Surgical Resection Versus Biopsy Among Older Patients

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Abstract

Background—The peak incidence of glioblastoma multiforme (GBM) occurs in those aged 65 years and older. However, studies on this patient group remain limited. The goal of this study is to evaluate the efficacy of surgery versus biopsy for older patients with these lesions.

Methods—133 and 72 consecutive patients aged 65 years and older who underwent surgery and needle biopsy for intracranial primary (de novo) GBM between 1997 and 2007 were retrospectively reviewed. Among these patients, 40 who underwent surgical resection were matched with 40 who underwent needle biopsy alone for factors consistently shown to be associated with survival [age, Karnofsky Performance Scale (KPS) indexing, eloquent involvement, radiation, temozolomide]. Survival was expressed as estimated Kaplan–Meier plots, and log-rank analysis was used to compare survival curves.

Results—Mean ± standard deviation age was 73 ± 5 years, and median survival was 4.9 months. There were no significant differences in perioperative outcomes among patients who underwent surgical resection versus needle biopsy. Patients who underwent resection had median survival of 5.7 months as compared with 4.0 months for patients who underwent needle biopsy ($P = 0.02$). Likewise, for patients aged 70 years and older, median survival was 4.5 months for 26 patients who underwent surgical resection as compared with 3.0 months for 26 patients who underwent needle biopsy ($P = 0.03$).

Conclusion—This study demonstrates that older patients tolerate aggressive surgery without increased surgery-related morbidity and have prolonged survival as compared with similar patients undergoing needle biopsy. These findings may help guide treatment decisions for patients, their families, and their physicians.

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults.[1] Incidence of this malignant tumor increases with increasing age, with median age at diagnosis of 64 years.[2] Despite the increasing number of older patients with GBM, the optimal treatment strategy for older patients remains poorly defined.[3,4] Treatment can vary from observation to radical resection, but the effectiveness of different types of surgical intervention remains poorly understood in this population of patients.[3,4]

The prognostic factors for patients with GBM are well known. These factors include age, preoperative neurological function, extent of resection, and eloquent location.[5–9] These factors, especially age, typically dictate the aggressiveness of the treatment strategy. Even though it is believed that extent of resection may be associated with prolonged survival, aggressive surgery is rarely pursued in older patients.[3,4,10,11] Older patients are often assumed to have poor prognosis because of their increased age and number of medical comorbidities, poor physiological reserves, and inability to tolerate surgery.[3,4] As a result, these patients often undergo needle biopsy for diagnosis, followed by adjuvant therapy.[3] Therefore, the benefit of aggressive resection in older patients remains poorly understood.

The goal of this retrospective study is to compare outcomes among patients who underwent aggressive surgical resection versus needle biopsy to better understand the efficacy of aggressive therapy versus needle biopsy for older patients with GBM.

Methods

Patient Selection

All patients aged >65 years who underwent surgery (surgical resection or needle biopsy) for intracranial primary GBM from 1997 to 2007 were identified by review of all consecutive cases performed at a single institution. Pathology was determined by a neuropathologist in all cases and was based on World Health Organization (WHO) criteria. Patients with prior resections or needle biopsies, previous adjuvant therapy, tumors crossing the corpus callosum, and/or infratentorial gliomas were excluded. Patients with incomplete medical records lacking presenting symptoms, pre- and postoperative magnetic resonance imaging (MRI), and adjuvant therapies were also excluded. Patients who were considered not healthy enough to tolerate surgical resection as well as those who underwent carmustine wafer implantation were excluded, since wafers are only implanted in patients who undergo resection. Additionally, patients who were not confirmed as having died were also excluded.

Recorded Variables

The clinical, operative, and hospital course records of all patients who met the inclusion and exclusion criteria were abstracted. Information collected from clinical notes included patient demographics, presenting symptoms, medical comorbidities, neuroimaging characteristics, perioperative course, and postoperative adjuvant therapy. The Karnofsky Performance Scale (KPS) index was used to classify preoperative functional status.[12] KPS index was assigned by a reviewer blinded to patient outcomes based upon review of the clinic note prior to surgery. MRI images were obtained and reviewed for each patient. Recorded characteristics included lesion size (largest diameter based on T1-contrast-weighted images), specific lobe involvement, and involvement of eloquent cortex. Eloquent cortex included motor/sensory cortex, language cortex, and/or basal ganglia/internal capsule.[9] Degree of resection was retrospectively classified from dictations of MRIs obtained <48 h after surgical resection by a blinded reviewer as: gross total resection (GTR) (>99%) if no residual enhancement was noted on postoperative MRI, near total resection (NTR) (>95%) if only rim enhancement of the resection cavity was noted on postoperative MRI, or subtotal resection (STR) (>90%) if residual nodular enhancement was noted on postoperative MRI.[13]

Date of death was recorded based on the Social Security index database.[14] Perioperative death was defined as death within 30 days of surgery.

Perioperative Treatment

The decision to pursue surgical resection versus needle biopsy was determined by a multidisciplinary team including the surgeon, radiation oncologist, medical oncologist, and the patient. For patients undergoing surgical resection, the general aim was to achieve GTR when possible. GTR was typically not achieved when the tumor involved eloquent brain. For needle biopsies, the general aim was to obtain tissue for diagnosis. Tissue was typically obtained from the contrast-enhanced portion of the tumor. Motor and somatosensory evoked potentials were routinely used in the majority of cases when tumors were near eloquent motor areas, and surgical navigation [computed tomography (CT) and/or MRI wand] was used in all cases after 2001. Use of motor mapping or elecrocorticography largely depended upon the preference of the surgeon and the location of the tumor. Use of adjuvant radiation and chemotherapy was also based upon recommendations from a multidisciplinary team. Following surgery, all patients received physical and occupational therapy. The decision to refer patients to rehabilitation was based upon recommendations of physical and occupational therapists.

Statistical Analysis

To compare the efficacy of surgical resection versus needle biopsy, a case–control study was performed.[15] During the review period, 133 and 72 patients underwent surgical resection and biopsy of primary GBM, respectively. Forty patients who underwent surgical resection were matched with 40 patients who underwent needle biopsy. The groups were matched by a reviewer blinded to patient outcomes for factors consistently shown to be associated with survival, including age (± 3 years), KPS (± 0), eloquent involvement (yes/no), radiation (yes/no), and temozolomide (yes/no).[5,8,9]

Survival as a function of time after surgical resection or biopsy was expressed as estimated Kaplan–Meier plots. Parametric data were expressed as mean ± standard deviation (SD). Nonparametric data were expressed as median [interquartile range (IQR)]. Percentages were compared via chi-squared test. Continuous variables were compared via Student *t*-test or Mann–Whitney *U* test where appropriate. Survival between patients who underwent surgical resection and needle biopsy was compared via log-rank analysis. Values with $P < 0.05$ in these analyses were considered statistically significant.

Results

Patient Population

Forty older patients who underwent needle biopsy were matched with 40 patients who underwent surgical resection (Table 1). For all 80 patients, mean ± SD age was 73 ± 5 years. At presentation, median (IQR) KPS was 80 (80–80). Seventeen (21%) patients presented with seizures, 11 (14%) with headaches, 33 (41%) with motor deficits, 10 (13%) with sensory deficits, 21 (26%) with language deficits, 11 (14%) with gait deficits, and 26 (33%) with mental status changes. Average tumor size was 4.0 ± 1.5 cm, involving the frontal lobe in 35 (44%), temporal lobe in 28 (35%), parietal lobe in 14 (18%), and occipital lobe in 3 (4%). The characteristics of the patients in each group are presented in Table 1. There were no significant differences in the preoperative characteristics between patients who underwent needle biopsy versus surgical resection.

Perioperative Characteristics and Long-Term Outcomes

Among the 40 older patients who underwent surgical resection, GTR was achieved in 15 (38%) patients, NTR in 25 (62%), and STR in 0 (0%) patients. All of the patients who underwent surgical resection had >95% of their tumor resected. Perioperatively, seven (9%) patients incurred a motor deficit and two (3%) a language deficit. Twenty-eight (35%) required inpatient rehabilitation, and median (IQR) hospital length of stay was 5 (2.8–8) days. At last follow-up, temozolomide was used in 8 (10%) patients and radiation therapy in 64 (80%) patients. There were no significant differences in perioperative characteristics between patients who underwent needle biopsy and surgical resection (Table 2). At last follow-up, all patients (100%) had died. Median (IQR) survival (40 biopsy, 40 surgical resection) of all patients in this study was 4.9 (2.9–10.4) months (Fig. 1).

Patients Who Underwent Needle Biopsy versus Surgical Resection

Despite similarities in preoperative clinical status and treatment regimens (Tables 1 and 2), patients who underwent surgical resection demonstrated prolonged survival as compared with patients who only underwent needle biopsy (Fig. 2). Median survival for patients who underwent surgical resection was 5.7 months, while median survival for patients who underwent needle biopsy was 4.0 months ($P = 0.02$). This was significantly different on log-rank analysis ($P = 0.02$).

Additionally, a subgroup analysis was performed on patients aged 70 years and older. As shown in Fig. 3, similar to the overall analysis, the group who underwent surgical resection had significantly longer survival times as compared with those who underwent needle biopsy (median survival 4.5 months versus 4.0 months, $P = 0.03$). These differences were significantly different on log-rank analysis ($P = 0.03$). There were not enough patients to compare the efficacy of surgical resection versus needle biopsy for patients older than 75 years of age. Among those patients who underwent surgical resection, 15 and 25 patients who had GTR and NTR of their tumor had median survival times of 5.8 and 5.4 months, respectively ($P = 0.79$).

Discussion

In this GBM study, 40 older patients who underwent aggressive surgical resection were matched with 40 older patients who underwent needle biopsy. These two cohorts were matched for factors consistently shown to be associated with survival, including age, KPS index, eloquent involvement, radiation, and temozolomide.[5,8,9] Importantly, patients who underwent surgical resection had median survival of 5.7 months, while patients who underwent needle biopsy without resection had median survival of 4.0 months. Likewise, when looking at individuals over the age of 70 years, patients who underwent surgical resection had median survival of 4.5 months, while individuals who underwent needle biopsy had median survival of 3.0 months. Although modest in absolute terms, older patients did have significantly prolonged survival with aggressive resection as compared with needle biopsy, without an increase in surgical morbidity or mortality. These findings can inform discussions with patients about potential risks and benefits from surgery, and should prove helpful to patients, families, and their physicians who are called upon to help in these difficult decisions.

GBM are characterized by their invasive and infiltrative nature, making curative resection difficult.[16] In fact, in the 1930 s, Walter Dandy performed hemispherectomies to attempt to achieve curative resection, but survival remained less than 2 years.[17] In recent years, with the advent of new surgical technologies, there has been renewed interest in understanding the effects of extensive resection on survival for patients with GBM.[18–22] These previous studies, however, are primarily limited to younger patients.[18–22] Lacroix et al. performed a multivariate analysis on 416 patients with GBM (mean age 53 years) and found that patients who underwent >98% resection had improved survival over patients who underwent less extensive resection.[10] Similarly, Laws and colleagues compared the effects of surgery versus biopsy for patients (mean age 54 years; 20% under 40 years) with malignant astrocytomas (GBM and ana-plastic astrocytomas) and found that surgery was associated with prolonged survival over biopsy.[23] Neither study included enough older patients to define the risks and benefits in those aged over 65 years. Besides age, previous outcome studies have been limited by not controlling for pre- and postoperative confounding variables, including pathology, adjuvant treatment, and follow-up time.[18–21] As a result, the effects of extensive resection for older patients with GBM have remained poorly understood.

Older patients with GBM are rarely offered aggressive surgery.[3,4] This is presumably due to the assumption that older patients have poor survival.[24–26] Median survival for most older patients with GBM is approximately 4 months as compared with 14 months for the general population.[24–26] Older patients tend to have an increased number of medical comorbidities, which presumably makes it difficult for older patients to tolerate surgical resection because of their reduced physiological reserves.[27–29] In the postoperative period, older patients are relatively immunosuppressed as compared with younger individuals, which may make them more susceptible to concomitant infections and prolonged hospital courses.[30] These features have all been used as arguments for not offering older patients aggressive therapies for their disease.[3,30,31] These patients instead are offered needle biopsy for diagnosis with or without subsequent adjuvant therapy.[3,4]

This study demonstrates that older patients undergoing aggressive resection have similar surgery-related morbidity to older patients undergoing needle biopsy. The incidence of perioperative morbidity among older patients undergoing surgical resection is also similar to the complication rates seen in younger patients undergoing surgical resection in previous studies.[6,22,32] While the majority of older patients undergo needle biopsy for diagnosis, older patients may be able to tolerate aggressive surgery without significantly added inherent risks of surgery.[3,4] Interestingly, the number of patients requiring rehabilitation placement was similar between the two cohorts. Not surprisingly, median length of hospital stay was longer for those patients undergoing surgical resection than for those undergoing needle biopsy, which trended towards but did not reach statistical significance.

This study also found that older patients undergoing surgery have increased survival times as compared with those undergoing needle biopsy. Patients who underwent surgery experienced an approximate 2-month increase in survival, or a 40% increase in survival time. This is substantial given that the survival time for older patients is approximately 4 months in previous studies.[24–26] While survival may seem dismal regardless of surgery or biopsy, older patients can benefit from surgery. Surgical resection, besides prolonged survival, may also provide additional benefits beyond needle biopsy, including decreasing mass effect, allowing for improved efficacy of radiation and chemotherapy, and possibility of implanting carmustine wafers or brachytherapy.[5,33,34] Especially with advances in surgical technology including navigational systems, motor and language mapping, and radiology techniques including diffusion-tensor-imaging-based fiber tracking, older patients may benefit from aggressive surgical resection as seen in younger patients without an increase in surgery-related morbidity.[35,36] The 3-day increase in median hospital stay for older patients undergoing surgical resection appears to be justified by the increase in survival time.

This study demonstrates that older patients tolerate aggressive resection without increased morbidity and have prolonged survival, but it does have limitations. This was a retrospective case–control analysis, not a prospective randomized trial. However, we tried to create a uniform population of older patients undergoing surgery for primary GBM by using strict inclusion/exclusion criteria. We included only patients aged >65 years at time of surgery and only those who underwent surgical resection or biopsy of supratentorial lesions. Furthermore, we controlled for factors known to be associated with survival (age, KPS, tumor location, radiation, and temozolomide) 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. Second, the decision to pursue aggressive surgery may have been biased to healthier patients with better preoperative neurological function or tumor location. However, this bias was mitigated by matching KPS index and tumor location. Because this was a retrospective study, data indicative of quality of life and differences in quality of life between patients undergoing surgical resection versus needle biopsy were not ascertainable, and future prospective studies should consider data collection in this regard. Furthermore, this study did not use volumetric analysis of tumor, which may be a more accurate means of analyzing tumor sizes. The patients in this study also had aggressive (estimated to be >95%) resection of their tumors, and the findings of this study may therefore not apply to patients who underwent STR (<95%) of their tumor. Ultimately, larger, prospective studies are needed to confirm the role of aggressive surgery and extent of resection for older patients with GBM.

Conclusions

Incidence of GBM in older patients is expected to increase in coming decades, reflecting national and world demographics. Currently, older patients are typically not offered aggressive surgery for their tumors because of their poor prognosis, and concomitant age-related morbidity. This case–control study demonstrates that older patients undergoing aggressive resection did not have an increase in surgical morbidity, and had prolonged survival as compared with matched older patients undergoing needle biopsy. Older patients, as with younger patients, may therefore benefit from aggressive surgical resection, and aggressive resection should be considered for older patients who present with GBM.

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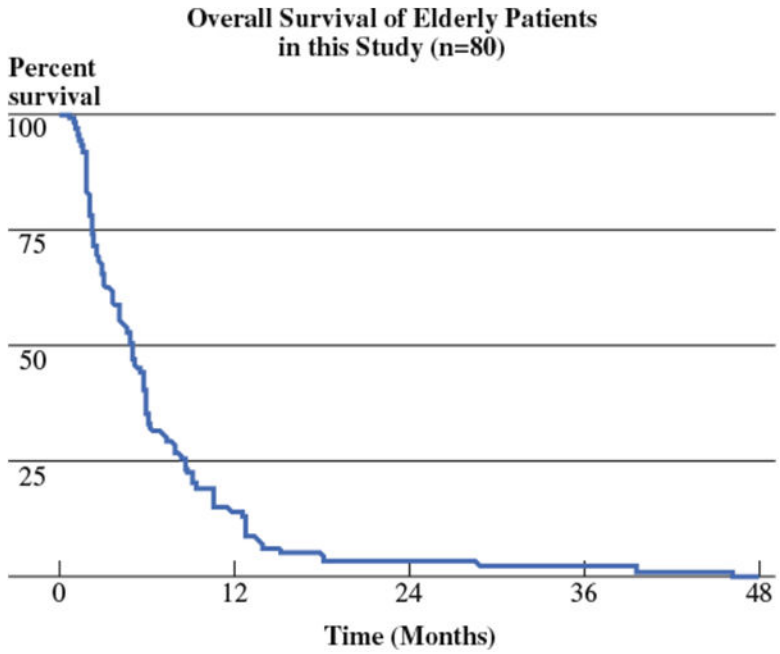

Fig. 1.
Kaplan–Meier plots of survival for older patients (aged 65 years and older) with glioblastoma multiforme (GBM) who underwent surgical resection or needle biopsy. Median survival was 4.9 months, and 3-, 6-, 9-, and 12-month survival rates were 63%, 33%, 21%, and 14%, respectively

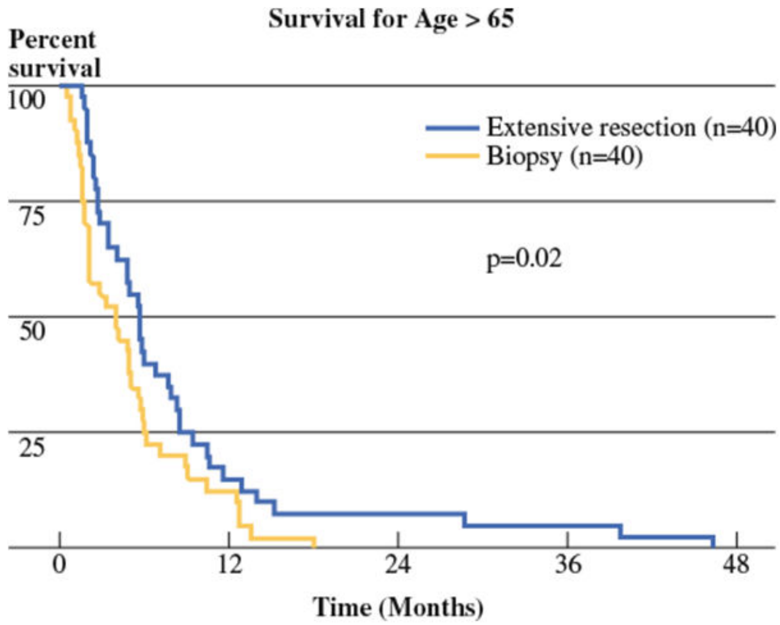

Fig. 2.

Kaplan–Meier plots of survival for older patients (aged 65 years and older) who underwent surgical resection versus biopsy of a primary glioblastoma multiforme (GBM). Median survival was significantly longer for patients who underwent aggressive resection as compared with patients who underwent biopsy (5.7 versus 4.0 months, respectively, P = 0.02). The groups were matched for age, Karnofsky performance score (KPS index), eloquent location, postoperative radiation, and postoperative temozolomide chemotherapy

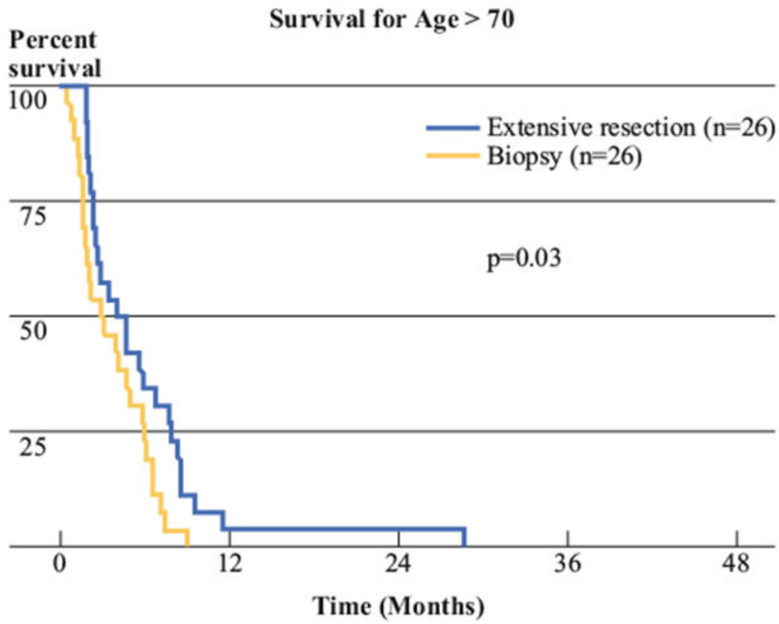

Fig. 3.

Kaplan–Meier plots of survival for older patients (aged 70 years and older) who underwent surgical resection versus biopsy of a primary glioblastoma multiforme (GBM). Median survival was significantly longer for patients who underwent surgical resection as compared with needle biopsy (4.5 versus 3.0 months, respectively, *P* = 0.03). The groups were matched for age, Karnofsky performance score (KPS), eloquent location, postoperative radiation, and postoperative temozolomide chemotherapy

Table 1

Study population

Characteristics	Resection number (%)	Biopsy number (%)	*P*-value
Gender			
Male	20 (50%)	20 (50%)	0.99
Age (years)[a]	72.8 ± 4.8	72.9 ± 5.1	0.74
Presenting symptoms			
KPS index[b]	80 (70–80)	80 (70–80)	0.32
Symptom duration (months)[a]	1 (0.5–1.5)	1.4 (0.9–3.0)	0.19
Preoperative symptoms			
Seizures	6 (15%)	11 (28%)	0.27
Headaches/nausea/vomiting	5 (13%)	6 (15%)	0.99
Motor deficit	15 (38%)	18 (45%)	0.65
Sensory deficit	3 (8%)	7 (18%)	0.32
Language deficit	9 (23%)	12 (27%)	0.61
Visual deficit	4 (10%)	3 (7%)	0.99
Gait deficit	5 (13%)	6 (13%)	0.99
Confusion/memory loss	12 (30%)	14 (35%)	0.81
Radiographics			
Tumor size (cm)[a]	4.0 ± 1.6	4.0 ± 1.4	0.84
Location			
Frontal	16 (40%)	19 (48%)	0.65
Temporal	14 (35%)	14 (35%)	0.99
Parietal	8 (20%)	6 (15%)	0.77
Occipital	2 (5%)	1 (3%)	0.99
Hemorrhagic	4 (10%)	3 (7%)	0.99
Cortical	14 (31%)	11 (28%)	0.63
Subcortical	33 (73%)	30 (75%)	0.59
Eloquent cortex	11 (28%)	11 (28%)	0.99
Motor/sensory cortex	4 (10%)	5 (13%)	0.99
Language cortex	4 (10%)	4 (10%)	0.99
Basal ganglia/internal capsule	3 (7%)	2 (5%)	0.99
Adjuvant therapy			
Carmustine wafers	0 (0%)	0 (0%)	0.99
Temozolomide	4 (10%)	4 (10%)	0.99
Radiation therapy	32 (80%)	32 (80%)	0.99

Characteristics of patients aged 65 years and older with primary glioblastoma multiforme (GBM) who underwent surgical resection or biopsy. Forty patients who underwent surgical resection were matched with 40 older patients who underwent needle biopsy of GBM. The groups were matched for age, Karnofsky performance score (KPS), eloquent location, postoperative radiation, and postoperative temozolomide chemotherapy. Clinical and treatment variables were similar between patients who underwent surgical resection and patients who underwent needle biopsy.

[a] Mean ± standard deviation.

[b] Median (interquartile range)

Table 2

Peri- and postoperative outcomes

Characteristics	Resection number (%)	Biopsy number (%)	*P*-Value
Perioperative outcomes			
New motor deficit	5 (11%)	2 (5%)	0.43
New language deficit	1 (3%)	1 (3%)	0.99
Surgical-site infection	1 (3%)	1 (3%)	0.99
Meningitis	0 (0%)	0 (0%)	0.99
Mortality	0 (0%)	1 (3%)	0.99
Discharge			
Discharge to home	25 (63%)	27 (68%)	0.81
Discharge to rehabilitation	15 (37%)	13 (32%)	0.81
Hospital stay (days)[a]	6 (4–8.3)	3 (1–6.5)	0.08
Survival			
Died at last follow-up	40 (100%)	40 (100%)	0.99
Median survival (months)	5.7	4.0	**0.02**
3-Month survival rate	70%	53%	
6-Month survival rate	40%	25%	
9-Month survival rate	25%	18%	
12-Month survival rate	15%	12%	

Incidence of 30-day perioperative morbidity and overall survival in adults aged 65 years and older undergoing resection or biopsy of glioblastoma multiforme (GBM). Forty patients who underwent surgical resection were matched with 40 patients who underwent surgical biopsy. The groups were matched for age, Karnofsky performance score (KPS index), tumor size, postoperative radiation, and postoperative temozolomide chemotherapy. Incidence of perioperative morbidity did not differ between the two cohorts. However, older patients who underwent resection experienced prolonged survival as compared with patients who underwent biopsy.

[a]Median (interquartile range)