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Multiple craniotomies in the management of multifocal and multicentric glioblastoma

Clinical article

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Object. Multiple craniotomies have been performed for resection of multiple brain metastases in the same surgical session with satisfactory outcomes, but the role of this procedure in the management of multifocal and multicentric glioblastomas is undetermined, although it is not the standard approach at most centers.

Methods. The authors performed a retrospective analysis of data prospectively collected between 1993 and 2008 in 20 patients with multifocal or multicentric glioblastomas (Group A) who underwent resection of all lesions via multiple craniotomies during a single surgical session. Twenty patients who underwent resection of solitary glioblastoma (Group B) were selected to match Group A with respect to the preoperative Karnofsky Performance Scale (KPS) score, tumor functional grade, extent of resection, age at time of surgery, and year of surgery. Clinical and neurosurgical outcomes were evaluated.

Results. In Group A, the median age was 52 years (range 32–78 years); 70% of patients were male; the median preoperative KPS score was 80 (range 50–100); and 9 patients had multicentric glioblastomas and 11 had multifocal glioblastomas. Aggressive resection of all lesions in Group A was achieved via multiple craniotomies in the same session, with a median extent of resection of 100%. Groups A and B were comparable with respect to all the matching variables as well as the amount of tumor necrosis, number of cysts, and the use of intraoperative navigation. The overall median survival duration was 9.7 months in Group A and 10.5 months in Group B ($p = 0.34$). Group A and Group B (single craniotomy) had complication rates of 30% and 35% and 30-day mortality rates of 5% (1 patient) and 0%, respectively.

Conclusions. Aggressive resection of all lesions in selected patients with multifocal or multicentric glioblastomas resulted in a survival duration comparable with that of patients undergoing surgery for a single lesion, without an associated increase in postoperative morbidity. This finding may indicate that conventional wisdom of a minimal role for surgical treatment in glioblastoma should at least be questioned. *(DOI: 10.3171/2010.6.JNS091326)*

Key Words • **multifocal tumor** • **multicentric tumor** • **glioblastoma** • **resection** • **craniotomy** • **survival** • **outcome**

High-grade gliomas, also called malignant gliomas, are the most common primary brain tumors in the adult population. Their incidence is 5–10 per 100,000 people annually. The median survival time is about 10–12 months in patients with glioblastoma.[10,18,22,29,31,32] The term glioblastoma multiforme was introduced by Mallory in 1914 and is still applied to the most malignant of intracranial glial tumors.[22]

Although solitary lesions are typical for glioblastoma, multiple synchronous gliomatous foci may be found at diagnosis, with a reported incidence of 0.5–20%.[20,25,31,43] Multiple synchronous gliomas can be categorized as either multifocal or multicentric.

Although the concept of gliomas arising as multicentric or multifocal entities is controversial, several authors have tried to differentiate them based on pathological and radiological characteristics.[1,8,28,31,34,37,43] Multiple gliomas can be categorized as multifocal, if there is a pattern of dissemination along an established route, spreading through commissural pathways, CSF channels, or through local extension by satellite formations. This pattern of dissemination can be demonstrated by contiguous areas of T2-weighted signal on MR images of the brain.[8] True multicentric gliomas, however, are widely

Abbreviation used in this paper: KPS = Karnofsky Performance Scale.

separated lesions that cannot be attributed to one of the aforementioned pathways.

There is still no entirely satisfactory hypothesis regarding the pathogenesis of multifocal or multicentric gliomas. The hypothesis most cited is that of Willis,[42] who contended that the evolution of multiple gliomas is a 2-step process. In the first stage, a large area of brain parenchyma undergoes neoplastic transformation. During the second phase, various rates of tumor proliferation within the larger field give rise to separate lesions. Eventually the separate tumor foci fuse together, forming a single lesion without evidence of previous multicentricity. Zülch[44] suggested that the multicentric lesions are metastases from a primary focus via "some pathway as yet unknown to us." Kyritsis et al.[11,13] reported that multifocal gliomas are more frequent in patients with secondary malignancies or a family history of cancer and that, in such cases, they are associated with a greater frequency of germline *P53* mutation.

Multiple intracranial lesions seen on CT and MR imaging represent a diagnostic dilemma in that multiple ring-enhancing lesions usually are diagnosed as metastatic entities or brain abcesses.[8,12,26,28] No definitive characteristics seen on brain MR images can differentiate multifocal or multicentric gliomas from metastatic lesions. In some cases, irregularity of the boundaries of at least one of the lesions, cortical localization, and evidence of meningeal, intraventricular, or subependymal dissemination can suggest the diagnosis of multifocal or multicentric glioma.[12,23]

Recently, it was reported that the use of diffusion tensor imaging,[40,41] PET,[10] and perfusion weighted and spectroscopic MR imaging[17] may aid in differentiating glioblastoma from brain metastatic lesions. This may facilitate the detection of multifocal and multicentric gliomas.

Previously, an unfavorable prognosis has been reported for multifocal or multicentric glioblastomas, with median patient survival estimates of 6–8 months after different treatment modalities.[1,12,31] Although the association of the extent of resection and survival duration in patients with glioblastoma has been well described,[4,6,14,15,21,33,38] the role of surgical intervention in patients with multifocal or multicentric gliomas remains controversial. Some authors recommend aggressive surgical treatment, mostly resection of one tumor focus,[27,31] for longer and better survival, whereas others, such as Chadduck and colleagues,[7] believe that biopsy alone is preferable and can be followed by radio- and chemotherapy. The use of multiple craniotomies during a single operation has been reported by Bindal et al.[3] for resection of multiple brain metastases, with no associated increase in risk of mortality or complications per surgery compared with those of patients receiving a single craniotomy. Pathak et al.[24] described a patient in whom a multicentric oligodendroglioma was resected via 2 craniotomies in the same session, and no neurological deficits were reported during a 4-year follow-up. We report a series of patients treated at the M. D. Anderson Cancer Center. Twenty patients underwent aggressive resection of multifocal and multicentric glioblastomas via multiple craniotomies in the same session.

Methods

Patient Population

We conducted a retrospective analysis of data prospectively collected in 20 patients with multifocal or multicentric glioblastomas (Group A), who each underwent resection of all lesions via multiple craniotomies in a single session; the procedures were performed between June 1993 and July 2008. These 20 cases will be referred to as the study group. (We did not include in the study patients with multifocal glioblastomas who were treated via a single craniotomy.) The study group was further divided into 2 subgroups based on MR imaging–documented tumor characteristics: in Group A_1 (multicentric lesions [9 patients]) there were widely separated lesions having no connection when visualized on FLAIR MR sequences and no identified route of dissemination; in Group A_2 (multifocal lesions [11 patients]) there were multiple separate lesions seen to be connected on FLAIR sequences and/or there was evidence of leptomeningeal, subependymal, or CSF dissemination. Tumor status was classified as new, residual, or recurrent.

Patients in the study group were matched in a 1:1 ratio with patients who underwent surgery for the removal of a solitary glioblastoma (control patient, Group B). From approximately 6000 patients, 20 controls were selected who best matched the 20 patients in the study group with respect to characteristics known to be prognostic indicators for survival in those undergoing surgery for glioblastoma,[14,18,33] including preoperative KPS score, age at surgery, year of surgery, tumor functional grade, and extent of tumor resection. As described by Sawaya et al.,[30] tumor functional grade assigns a functional grade to a tumor based on its proximity to brain regions controlling eloquent functions. For multiple lesions, the functional grade of each lesion was identified, and the highest grade was used as a matching factor. Similarly, in patients with multiple tumors, the overall extent of resection of the tumors was used in the matching process. Because the study interval was 15 years, individuals in the study group and controls were matched according to the year of surgery to eliminate the possible impact on survival of any change in the mode of management of glioblastoma with time.

Tumor Management

In all patients the diagnosis was established using Gd-enhanced MR imaging. Patients underwent resection of all lesions in the same session via 2 craniotomies. The intent was to resect all lesions that had exhibited contrast enhancement on MR images. In study and control patients, standard procedures were used for microneurosurgical tumor resection and for intraoperative frozen-section histopathological analysis. Tumors were resected either circumferentially or intralesionally (piecemeal). A definitive pathological diagnosis of the lesions could only be confirmed postoperatively. Postoperatively, all patients underwent Gd-enhanced MR imaging to determine the extent of tumor resection and to exclude the presence of hematoma. Tumor volumes were calculated with the aid of commercially available computer software (Vitrea 3.5).

Follow-Up Review

The patients' postoperative KPS scores were reviewed and compared with preoperative KPS scores.

Surgical complications were defined as those occurring within 30 days of the operation. Complications were divided into 3 categories (neurological, regional, and systemic), with major and minor subclassifications that have been previously described.[30] Briefly, a complication was considered neurological if it directly produced a neurological deficit. Regional complications were those occurring within the cranium and were primarily related to the wound or the brain surface but did not directly result in a neurological deficit. Systemic complications were general medical conditions occurring at locations distant from the brain. Complications were regarded as major if they were life threatening, required aggressive or invasive treatment, or prolonged the postoperative hospital stay. Operative mortality was defined as a death from any cause occurring within 30 days of the operation. Patients were monitored until death, loss to follow-up, or the end date of the study. Brain Gd-enhanced MR imaging was performed every 2–3 months during follow-up or sooner if the patient exhibited any neurological deterioration.

Statistical Analysis

Frequencies and descriptive statistics of the various entities studied were obtained. Continuous and ordinal variables were tested using the Student t-test or a nonparametric test, as appropriate.

The logistic regression model was used to determine factors associated with surgical complications. Odds ratios and their 95% CIs were obtained. Kaplan-Meier estimates of survival were obtained, and differences in the survival curves among various subgroups were compared using a log-rank test. We used the Cox proportional hazards method to identify factors associated with survival. Crude hazard ratios and hazard ratios adjusted for the various covariates, as well as the 95% CIs, were obtained. A p value of ≤ 0.05 was considered statistically significant. All tests were 2 tailed. The Statistical Package for the Social Sciences (version 16.0) was used for the analyses.

Results

Clinical and Imaging Characteristics

The characteristics of patient groups are shown in Table 1. Group A included 14 men and 6 women, with a median age of 52 years (range 32–78 years). The preoperative KPS scores ranged from 50 to 100 (median 80). A motor deficit was evident in 35% of the patients. Speech, memory, and visual deficits each occurred in 30% of the patients. At the time of diagnosis, 85% of the patients were fully conscious, whereas 15% had altered mental status.

Eighteen patients (90%) harbored 2 MR imaging–documented synchronous cerebral lesions, whereas 2 patients had 3 lesions. In 75% of cases, the multifocal or multicentric glioblastomas were in the same hemisphere, and 45% of them were located on the right side. In 5 patients, tumors were bilateral. Forty percent of patients had 1 or more focus located in cortex controlling eloquent functions (functional Grade III).

Eleven patients (55%) presented with newly diagnosed lesions, and a solitary glioblastoma had been diagnosed previously in 9 patients (45%), 8 of whom had undergone prior resection. Eight patients underwent radiation therapy and 6 underwent chemotherapy.

The matching factors in the study group (Group A) and the control group (Group B) were statistically compared and found to be homogeneously distributed (preoperative KPS score [$p = 1.0$]; age at surgery [$p = 0.95$]; year of surgery [$p = 0.76$]; the overall extent of resection [$p = 0.145$]; and the highest tumor functional grade [$p = 1.0$]).

There was a nearly statistically significant difference between the study patients (Group A) and the controls (Group B) with respect to distribution of the sexes ($p = 0.056$). However, there was no significant difference between patients in the groups with respect to any of the following characteristics: mental status at presentation, preoperative symptoms, tumor location (right or left side), tumor status (as detailed in Table 1), previous treatment, tumor cysts (present or absent), tumor hemorrhage, use of intraoperative navigation during resection, or the method of tumor resection.

Surgical Management

All patients in Group A underwent resection of all lesions in the same session via 2 separate craniotomies (Fig. 1). Intraoperative navigation was used in 70% of cases. Circumferential resection was performed in 10 patients (50%), whereas resection was piecemeal in 50%. The median extent of lesion resection was 100%. Eighteen patients had a glioblastoma, 1 had a glioblastoma and anaplastic oligodendroglioma, and 1 had a glioblastoma and radiation necrosis.

All patients in Group B underwent resection of the solitary lesion via a single craniotomy. Intraoperative neuronavigation was used in 70% of cases. Circumferential tumor resection was performed in 12 patients (60%), whereas tumor resection was piecemeal in 40%. The median extent of lesion resection was 100%. All patients had a glioblastoma.

Forty-five percent of patients in Group A underwent postoperative radiotherapy. Postoperative radiotherapy was conducted in 55% of Group B patients. Other patients in both groups received radiotherapy after their initial resection except for 3 patients who were lost to follow-up. Postoperative chemotherapy was given to 90% of patients in Group B and to 45% of those in Group A. There was no significant difference in the proportions of patients in the study group and control group who received either postoperative radiotherapy ($p = 0.75$) or postoperative chemotherapy ($p = 0.13$). Because postoperative administration of temozolomide chemotherapy did not become the standard of care in glioblastoma treatment until late in our study's 15-year period, Groups A and B could not be matched for temozolomide treatment. Nevertheless, nearly equal numbers of patients in each group were treated postoperatively with temozolomide: 8 patients in Group A and 7 patients in Group B.

TABLE 1: Clinical characteristics of 20 patients with multicentric and multifocal glioblastomas and matched controls

Characteristic	No. of Patients (%)*			
	Group A	Subgroup A_1: Multicentric	Subgroup A_2: Multifocal	Group B: Controls
no. of patients	20	9 of 20	11 of 20	20
age in yrs†				
median	52	48	53	52
range	32–78	32–71	46–78	31–75
preop KPS score†				
median	80	80	80	80
range	50–100	50–90	50–100	50–100
% of total tumor resected†				
median	100	100	100	100
range	75–100	75–100	94–100	80–100
sex				
male	14 (70)	7	7	7 (35)
female	6 (30)	2	4	13 (65)
symptoms‡				
headache	4 (20)	1	3	8 (40)
speech deficit	6 (30)	4	2	6 (30)
motor deficit	7 (35)	4	3	11 (55)
unstable gait	3 (15)	1	2	2 (10)
seizures	2 (10)	2	—	4 (20)
cranial nerve deficit	3 (15)	1	2	—
memory deficit	6 (30)	3	3	3 (15)
altered mental status	3 (15)	1	2	3 (15)
sensory deficit	3 (15)	1	2	1 (5)
visual deficit	6 (30)	3	3	4 (20)
no. of tumors				
1	—	—	—	20 (100)
2	18 (90)	9	9	—
3	2 (10)	—	2	—
tumor location				
all rt side	9 (45)	2	7	9 (45)
all lt side	6 (30)	3	3	11 (55)
rt & lt sides	5 (25)	4	1	—
tumor status				
all new	11 (55)	5	6	9 (45)
new & recurrent	9 (45)	4	5	—
all recurrent	—	—	—	10 (50)
all residual	—	—	—	1 (5)
previous treatment¶				
resection	8 (40)	4	4	11 (55)
radiotherapy	8 (40)	3	5	10 (50)
chemotherapy	6 (30)	3	3	8 (40)
highest tumor functional grade†				
I or II	12 (60)	5	7	12 (60)
III	8 (40)	4	4	8 (40)
tumor hemorrhage	5 (25)	5	—	2 (10)
necrosis	20 (100)	9	11	20 (100)
cysts	3 (15)	1	2	4 (20)

(continued)

TABLE 1: Clinical characteristics of 20 patients with multicentric and multifocal glioblastomas and matched controls *(continued)*

Characteristic	No. of Patients (%)*			
	Group A	Subgroup A_1: Multicentric	Subgroup A_2: Multifocal	Group B: Controls
no. of craniotomies				
1	—	—	—	20 (100)
2	20 (100)	9	11	—
use of intraoperative navigation	14 (70)	7	7	14 (70)
method of resection				
circumferential	10 (50)	5	5	12 (60)
intralesional (piecemeal)	10 (50)	4	6	8 (40)
adjuvant radiation therapy	9 (45)	5	4	11 (55)
adjuvant chemotherapy	9 (45)	5	4	18 (90)

* Unless otherwise noted. Percentages may not add up to 100 owing to rounding.
† Matching factor between Groups A and B.
‡ Patients may have had more than 1 symptom.
¶ Patients may have received more than 1 modality of treatment.

Surgical complications are listed in Table 2. The overall complication rates for Groups A and B were 30% and 35%, respectively. In Group A, 5 patients (25%) who underwent multiple craniotomies experienced neurological complications, and 2 of these (10%) were major complications. The most common neurological complication was motor deficit (2 cases). One patient improved to the point of functional independence, but mild weakness was still noted. The other patient showed no improvement.

In Group B, 6 patients (30%) who underwent a single craniotomy suffered major neurological complications. The 2 most common neurological complications were motor deficit (4 cases) and speech deficit (4 cases). Within 30 days, the patients with motor deficits had improved and were functionally independent, and all patients with speech deficits (4 patients) had improved significantly.

Two patients (10%) in Group A suffered regional complications that were not major. Seizures occurred in 2 patients and were controlled by antiseizure medications. No patients in Group B experienced regional complications.

One patient in Group A suffered major systemic complications in the form of pneumonia and urine retention. Two patients in Group B suffered systemic complications, 1 of which was major.

The median postoperative KPS score was 80 in both the study group and the control group. Fourteen of the 20 patients in Group A (70%) retained their preoperative KPS score after surgery. In this group, the postoperative KPS score was worse in 3 patients (15%) and improved in 3 (15%). In Group B, 13 patients (65%) retained their preoperative KPS score postoperatively. Here, the postoperative KPS score was worse in 3 patients (15%) and improved in 4 cases (20%).

The surgical mortality in Group A was 5% (1 patient), whereas there was no surgical mortality in Group B. The cause of death for this 1 patient was unknown, and no autopsy was performed. There was no statistically sig-

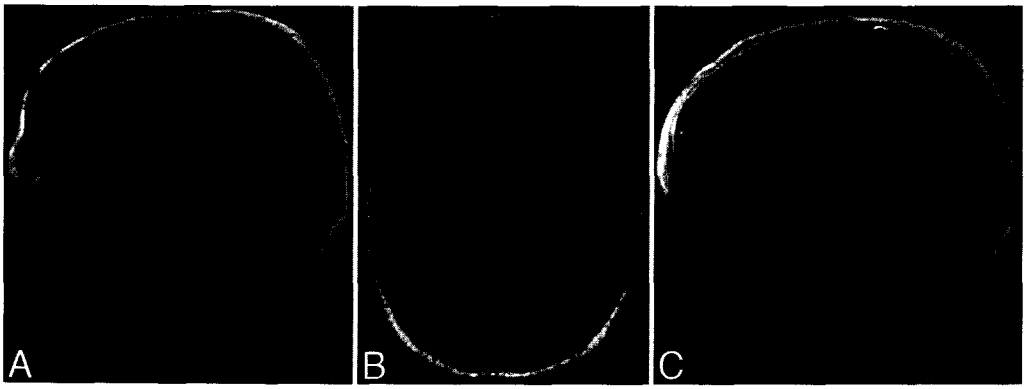

Fig. 1. Sagittal contrast-enhanced T1-weighted MR images of the brain in a patient with multicentric glioblastoma, showing right frontal and right parietal ring-enhancing lesions before **(A)** and after **(C)** resection. Gross-total resection was achieved via 2 craniotomies in the same surgical session with the aid of cortical mapping and intraoperative MR imaging. A preoperative axial FLAIR image of these same lesions **(B)** shows no connections between them.

TABLE 2: Complications and mortality according to patient group*

Category	No. of Patients (%)		p Value
	Multiple Craniotomies (Group A)	Single Craniotomy (Group B)	
overall complications	6 (30)	7 (35)	1.0
overall major complications	2 (10)	7 (35)	0.13
neurological complications†	5 (25)	6 (30)	1.0
major neurological complications	2 (10)	6 (30)	0.24
regional complications†	2 (10)	—	0.49
major regional complications	—	—	NA
systemic complications†	1 (5)	2 (10)	1.0
major systemic complications	1 (5)	1 (5)	1.0
mortality	1 (5)	—	1.0

* NA = not applicable.

† More than 1 complication occurred per patient.

nificant difference in surgical mortality between Groups A and B (p = 1.00).

Two patients were alive in both groups at the end of the study. The median follow-up duration in Group A was 5.3 months, whereas in Group B it was 8.9 months.

Patient Survival

The overall median survival time after surgery for patients in Group A was 9.7 months (95% CI 5.2–25.8 months) and in Group B was 10.5 months (95% CI 7.5–30.7 months). There was no statistically significant difference in survival between Groups A and B (p = 0.34) (Fig. 2). The study group was subdivided into patients with either multicentric glioblastoma (Group A_1) or multifocal glioblastoma (Group A_2) in the analysis of survival. The overall median survival duration of patients in Group A_1 was 12.9 months (95% CI 0.0–54.0 months), whereas that of patients in Group A_2 was 9.6 months (95% CI 5.2–15.2 months) (Fig. 3). Survival among patients presenting with new lesions at diagnosis was also assessed. The median survival time was 12.9 months (95% CI 5.0–18.5 months) for Group A_1, 9.6 months (95% CI 7.5–10.6) for Group A_2, and 14.6 months (95% CI 10.2–18.8) for Group B (Fig. 4). There was a statistically significant difference between Groups A_2 (multifocal lesions) and B (solitary lesion) (p = 0.014).

Discussion

Multicentric gliomas, although relatively uncommon, must be carefully considered in the differential diagnosis of multiple cerebral lesions.[43] Treating patients with multifocal or multicentric glioblastomas has traditionally been a serious challenge for both the neurosurgeon and the radiation oncologist,[31] especially in the absence

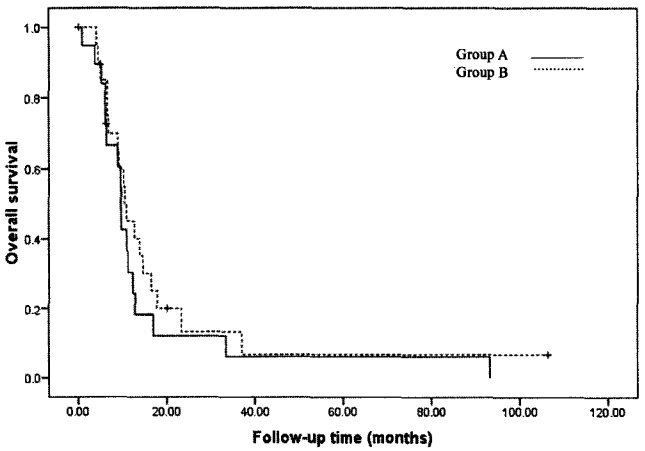

Fig. 2. Graph showing Kaplan-Meier estimates of overall survival after resection in patients with multifocal or multicentric glioblastoma (Group A) and patients with solitary glioblastoma (Group B).

of clearly defined guidelines regarding optimal management.[1]

Multicentric and multifocal gliomas have been reported in the literature, but no previous study has clearly reviewed the use of multiple craniotomies for resection of all multifocal or multicentric glioblastomas in the same session. Prather et al.[26] described one case each of multifocal and multicentric glioblastoma that were verified at autopsy examination. The patient with multicentric glioblastoma, who did not receive any treatment, lived for 7.5 months after the radiological diagnosis was established. The other patient, who had multifocal disease that was treated palliatively with radio- and chemotherapy, lived for 10 months after radiological diagnosis.

Chadduck et al.[7] described 2 patients with multicentric glioblastomas in whom a biopsy was followed by irradiation and chemotherapy. One patient lived for 5 months, and the other died during the course of radiotherapy. Salvati et al.[28] described a series of 7 patients with multicentric gliomas in which the maximum survival interval was 7 months. Two patients underwent biopsy that revealed glioblastoma with anaplastic astrocytoma in one patient and glioblastoma with adenocarcinoma in the other patient; one patient died within 2 months and the other died after 15 days.

Kyritsis et al.[12] reported on the radiological features in a series of 51 patients with multifocal gliomas in which the median survival duration was 6 months. Salvati et al.[27] reported 40 cases of multifocal or multicentric gliomas. In all cases the tumor(s) was removed and radiotherapy was performed. The median survival time was 6 months for patients with multifocal gliomas and 10 months for those who had multicentric gliomas. Benveniste et al.[2] described the case of a patient with multifocal glioblastomas diagnosed by stereotactic biopsy of only one of the lesions; the patient underwent radio- and chemotherapy, but no data on survival were reported. These studies have not produced a consensus on (or guidelines for) management of multifocal or multicentric glioblastomas.

Several investigators have evaluated the extent of resection as a predictor of survival in patients with glio-

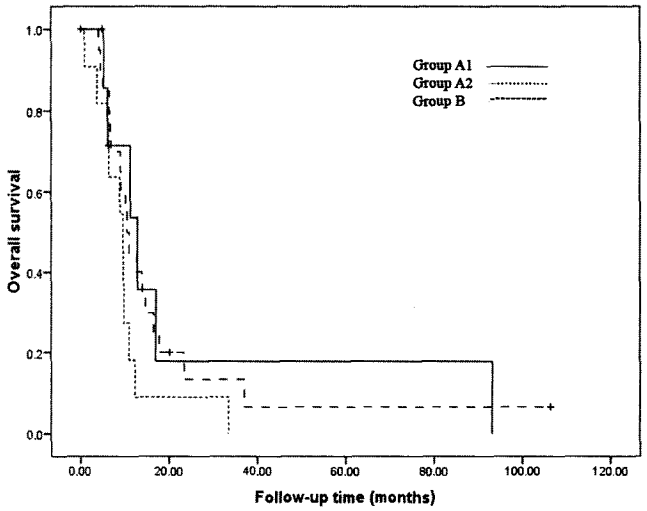

FIG. 3. Graph showing Kaplan-Meier estimates of overall survival after resection in patients who presented with new or recurrent lesions at diagnosis. Patients in Group A_1 had multicentric glioblastoma, those in Group A_2 had multifocal glioblastoma, and those in Group B had a solitary glioblastoma.

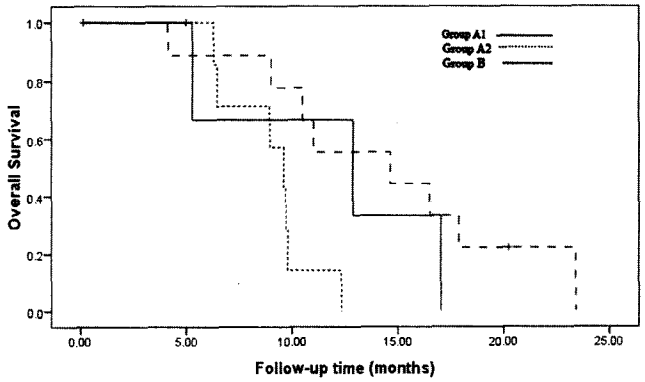

FIG. 4. Graph showing Kaplan-Meier estimates of overall survival after resection in patients who presented with new lesions at diagnosis.

blastoma. Lacroix et al.[14] found that resection of 98% or more of the tumor was associated with the longest survival duration (range 11.4–14.6 months). This factor was independent of age, KPS score, or subsequent treatment modalities. The findings of Buckner[5] and Laws and associates[18] also supported these results. Most recently, McGirt and colleagues[19] reported that gross-total resection was associated with a significantly improved survival in patients with primary (13-month) and recurrent (11-month) malignant astrocytomas. These survival benefits were also independent of age, extent of disability, or subsequent treatment modalities. We found that a high median extent of resection could be reached in lesions in patients with multifocal or multicentric glioblastoma who underwent resection via multiple craniotomies. Our finding of a median 10.5-month survival in cases of solitary glioblastoma is within the range reported in the literature. Our study included patients with both primary and recurrent glioblastomas.

Our results agree with the previous reports regarding the demographics of patients with multifocal or multicentric glioblastomas, including a male preponderance, the presence of different tumor histological types, and the occurrence of multifocal gliomas after treatment of a solitary glioblastoma. However, our study included a select sample of patients that may not be representative of the entire patient population with multifocal or multicentric glioblastomas.

Patients with multicentric glioblastoma often have lesions located too far apart to allow resection via a single craniotomy. Our data showed that multiple craniotomies were not associated with increased complications per surgery. These results are consistent with the previously published report by Bindal et al.[3] regarding the use of multiple craniotomies in the excision of multiple metastatic lesions. Indeed, advances in surgical adjuncts such as ultrasonography, navigation techniques (including intraoperative MR imaging), cortical mapping, and the evolution of awake craniotomy tend to promote safer aggressive resection.

Although Kyritsis et al.[12] mentioned that the distinction between multicentric and multifocal gliomas had no practical clinical value, this finding is not supported by our study. Our results showed that the median survival in patients with multicentric glioblastomas treated by aggressive multiple-craniotomy resection of all lesions in the same session was 12.9 months, whereas it was 9.6 months in patients with multifocal disease. With respect to the survival in patients with newly diagnosed lesions, the analysis showed no significant differences between patients with multicentric glioblastomas and those with solitary glioblastomas. However, there was a statistically significant difference in survival between patients with multifocal disease and those with solitary lesions.

The management of patients with multifocal or multicentric glioblastoma is multimodal. The current treatment paradigm at M. D. Anderson Cancer Center is safe cytoreductive resection of all lesions, when feasible, and followed by postoperative radiotherapy and concomitant chemotherapy.

Although cytoreductive surgery is a crucial element in the treatment of patients with glioblastoma, we believe that these other modalities should be included in its management.

Pooled analysis of 6 randomized trials that compared tumor resection with and without postoperative adjuvant radiotherapy in patients with glioblastoma indicated a significant improvement in survival duration in patients receiving radiotherapy.[16,39] Although whole-brain radiation therapy (WBRT) was frequently reported in the management of multifocal and multicentric glioblastoma,[7,28,37] limited-field irradiation was recommended in some studies.[1,31] Patients with multifocal glioblastoma who were treated postoperatively with either WBRT or 3D conformal radiotherapy showed no significant differences in the median time to tumor progression or the median survival time.[31]

The addition of temozolomide concomitantly with the standard dose of postoperative radiotherapy improved the median survival interval and the 2-year survival rate relative to the administration of postoperative radiotherapy alone.[36] Stupp et al.[35] reported that postoperative ir-

radiation administered concurrently with temozolomide improved survival during 5 years of follow-up. Moreover, patients whose tumors had a methylated promoter for the gene-encoding O-6-methylguanine-DNA methyltransferase, MGMT, were more likely to benefit from the addition of temozolomide.[9]

Limitations of the Study

This study has multiple limitations. The small sample size may have resulted in insufficient statistical power to permit detection of significant differences in outcomes. This study was limited to a select group of patients with multifocal or multicentric glioblastomas who underwent resection of all lesions via multiple craniotomies, and we were unable to compare our study group with matched groups of patients who had undergone other types of surgical intervention (such as biopsy or resection of a single glioblastoma in patients with multiple glioblastomas) because our database did not contain sufficient numbers of such patients to permit such matches.

Conclusions

Our study showed that a patient undergoing resection of multifocal or multicentric glioblastoma via multiple craniotomies during a single operation is not at a higher risk for morbidity than a patient undergoing resection of a solitary glioblastoma via a single craniotomy. The survival duration of patients with multifocal or multicentric glioblastoma in whom all lesions were removed via multiple craniotomies was similar to that of patients in a matched cohort who underwent surgery for a single glioblastoma. We believe our findings indicate that conventional wisdom related to a minimal role for surgical treatment of these lesions should at least be questioned.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Hassaneen, Levine. Acquisition of data: Hassaneen, Levine, Suki, Salaskar, Lima, McCutcheon, Lang, DeMonte, Rao, Weinberg, Aldape, Sawaya. Analysis and interpretation of data: Wildrick, Hassaneen, Levine, Suki, Salaskar, McCutcheon, Prabhu, Lang, Aldape, Sawaya. Drafting the article: Wildrick, Hassaneen. Critically revising the article: Wildrick, Hassaneen, Levine, Suki, McCutcheon, Prabhu, DeMonte, Rao, Weinberg, Sawaya. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Suki. Study supervision: Sawaya.

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