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A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival

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Object. The extent of tumor resection that should be undertaken in patients with glioblastoma multiforme (GBM) remains controversial. The purpose of this study was to identify significant independent predictors of survival in these patients and to determine whether the extent of resection was associated with increased survival time.

Methods. The authors retrospectively analyzed 416 consecutive patients with histologically proven GBM who underwent tumor resection at the authors' institution between June 1993 and June 1999. Volumetric data and other tumor characteristics identified on magnetic resonance (MR) imaging were collected prospectively.

Conclusions. Five independent predictors of survival were identified: age, Karnofsky Performance Scale (KPS) score, extent of resection, and the degree of necrosis and enhancement on preoperative MR imaging studies. A significant survival advantage was associated with resection of 98% or more of the tumor volume (median survival 13 months, 95% confidence interval [CI] 11.4–14.6 months), compared with 8.8 months (95% CI 7.4–10.2 months; $p < 0.0001$) for resections of less than 98%. Using an outcome scale ranging from 0 to 5 based on age, KPS score, and tumor necrosis on MR imaging, we observed significantly longer survival in patients with lower scores (1–3) who underwent aggressive resections, and a trend toward slightly longer survival was found in patients with higher scores (4–5). Gross-total tumor resection is associated with longer survival in patients with GBM, especially when other predictive variables are favorable.

KEY WORDS • glioblastoma multiforme • glioma • prognosis • surgery • survival

THE treatment of patients with high-grade gliomas remains a challenge for modern therapy. The prognosis for these patients is poor; the median patient survival after diagnosis is approximately 1 year.[36,38] The need for a histological diagnosis of tumor tissue in each case and the importance of decompression in symptomatic patients are well established; however, there is still controversy regarding the extent of surgical resection to be performed. Although many neurosurgeons recommend that gliomas be resected as extensively as possible,[26,32] rigorous reviews of the literature[16,24,28] have revealed that there is little scientific evidence that aggressive surgical management significantly prolongs survival.

Most studies in which the role of surgery in the management of high-grade gliomas has been examined have lacked an objective measure of resected tumor volume.[8,22,27] The extent of tumor resection has traditionally been classified into the arbitrary categories of gross-total resection, subtotal resection, partial resection, and biopsy sampling. In several studies the extent of resection has been quantified on the basis of the surgeons' impressions;[5,11,25,30,31,34,36] however, the lack of precision of such estimates has been amply demonstrated.[24] Even in more recent studies, in which neuroimaging findings have been used to determine the extent of tumor resection,[1,3,4,18,20,23,26,39] the interpretation of results is complicated by the use of different imaging modalities, different methods to quantify tumor volumes, and irregular timing of the postoperative imaging.

Several variables affect the prognosis of patients with GBM, including age,[6] preoperative performance status according to the KPS,[13] tumor location,[12] and preoperative MR imaging characteristics of the tumor,[14] as well as whether the patient undergoes reoperation for recurrent tumor,[2,15] and whether the patient receives radiation therapy or chemotherapy.[38] Because these variables are interrelated, a multivariate analysis is required to determine the independent effect of surgical resection on survival and to identify the subset of patients for whom aggressive resection, if feasible, is most beneficial.

The purpose of this study was as follows: 1) to identify independent preoperative variables that were significant predictors of survival time in patients with GBM; 2) to establish whether the extent of surgical resection, deter-

Abbreviations used in this paper: CI = confidence interval; GBM = glioblastoma multiforme; KPS = Karnofsky Performance Scale; MR = magnetic resonance; SD = standard deviation.

TABLE 1
*Grading of intraparenchymal tumors according to functional location**

Grade	Functional Location
I: noneloquent brain	frontal or temporal pole of cerebrum
	rt parietooccipital lobe
	cerebellar hemisphere
II: near eloquent brain	near motor or sensory cortex†
	near calcarine fissure
	near speech center
	corpus callosum
	near dentate nucleus
	near brainstem
III: eloquent brain	motor or sensory cortex
	visual center
	speech center
	internal capsule
	basal ganglia
	hypothalamus or thalamus
	brainstem
	dentate nucleus

* Adapted from Sawaya, et al.
† Includes tumors in the supplementary motor area.

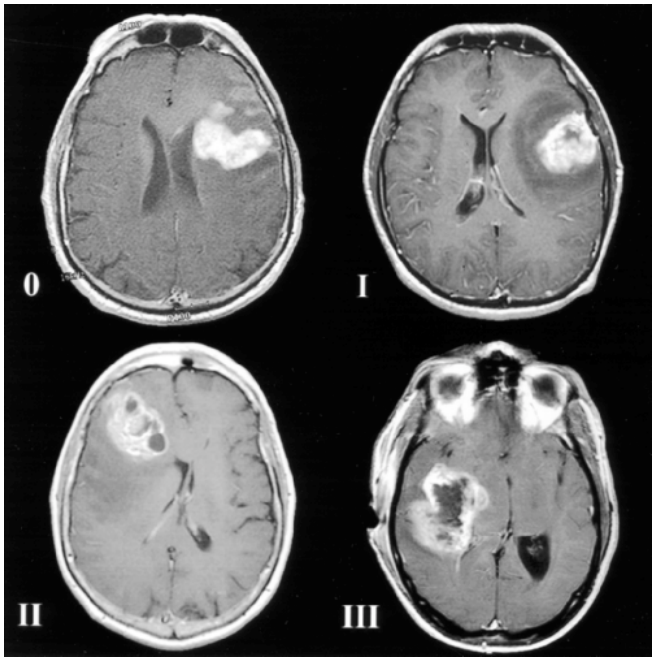

FIG. 1. Grades of tumor necrosis adapted from Hammoud, et al. are demonstrated on MR images. The amount of tumor necrosis, which appears as an area of decreased signal intensity on T_1-weighted images, was divided into four grades as follows: Grade 0, no necrosis apparent on the MR image; Grade I, amount of necrosis less than 25% of the tumor volume; Grade II, amount of necrosis 25 to 50% of the tumor volume; and Grade III, amount of necrosis greater than 50% of the tumor volume.

mined on the basis of objectively quantified preoperative and postoperative tumor volumes, has prognostic value with regard to patient survival time after surgery; and 3) to examine survival times in defined subpopulations of patients as they relate to the extent of tumor resection.

Clinical Material and Methods

Patients and Treatment Characteristics

In a database search, we identified 420 consecutive patients with GBM who underwent craniotomy and tumor resection at The University of Texas M. D. Anderson Cancer Center between June 1993 and June 1999. Our neuropathologists reviewed the histopathological material in each case. Because histological evidence of tumor necrosis was an essential diagnostic feature of GBM, all cases were equivalent to GBM by the Ringertz classification,[29] Grade IV astrocytoma by the World Health Organization classification,[21] and Grade 4 astrocytoma by the St. Anne–Mayo classification.[9] Four patients with incomplete imaging data were excluded from the analysis; the remaining 416 patients constituted the study population.

We reviewed the medical records to obtain information on the patients and treatment characteristics. The patient's age, sex, and KPS score at the time of presentation were noted. Previous treatment received at another center, including cytoreductive surgery or a biopsy procedure with or without adjuvant chemotherapy or radiation therapy, which indicated that the patient had residual or recurrent tumor at the time of presentation at our institution, was also recorded. Such patients are referred to hereafter as the treated group. All patients underwent radiation therapy in addition to surgical resection. Factors such as age and KPS score determined whether patients also qualified for chemotherapy; the type of chemotherapy administered depended on the protocols.

Data from the University of Texas M. D. Anderson tumor registry were used to determine each patient's vital status at the time of analysis. The tumor registry enables us to ascertain the vital status of all patients seen at our institution through sources such as the National Death Index and letters or phone calls to patients and their families.

Imaging Protocol

The preoperative MR images were reviewed prospectively in all patients and several tumor imaging characteristics were identified. With respect to tumor location, deep lesions were defined as those that involved the insula, thalamus, basal ganglia, or posterior fossa; superficial lesions involved only the cortex outside the insula. Tumor location with regard to proximity to eloquent brain was characterized by the functional grade as described by Sawaya, et al.[33] (Table 1). Tumor necrosis observed on MR images was quantified using the methods of Hammoud, et al.[14] (Fig. 1). The degrees of mass effect, surrounding edema, and enhancement of the tumor mass were also measured (Table 2).

The MR studies were obtained shortly after surgery in all patients. Tumor volume was quantified prospectively in all patients on the basis of preoperative and postoperative MR images. Tumor volume was defined as the area of increased signal intensity on contrast-enhanced T_1-weighted MR images. For nonenhancing tumors, volume was defined as the area of increased signal intensity on T_2-weighted images corresponding to the defined mass lesion (Fig. 2). Volumetric assessments were performed using the MedVision 1.41 computer software program (Evergreen Technologies, Inc., Castine, ME). This software cal-

TABLE 2
Grading of tumor characteristics on preoperative MR images

Characteristic	Grade
mass effect	
none apparent	0
minimal midline shift (<0.5 cm)	1
moderate midline shift (0.5–1 cm)	2
significant midline shift (>1 cm), subfalcian or uncal herniation	3
edema*	
none apparent	0
less than tumor volume	1
approximately equal to tumor volume	2
greater than tumor volume	3
enhancement†	
none	0
low–intermediate signal intensity	1
high–intermediate signal intensity	2
signal intensity equal to that of fat	3

* Edema on T_2-weighted images is seen as an area of increased signal intensity surrounding the gadolinium-enhanced region of tumor (modified from Hammoud, et al.).

† Enhancement of the tumor nodule as seen on gadolinium-enhanced T_1-weighted images (modified from Hammoud, et al.).

culates the area of the tumor as outlined on selected axial or coronal images and then estimates the tumor volume based on the known thickness of the tissue. This method has been shown to be reliable.[37]

Statistical Methods

Cumulative survival duration from the time of surgery at our institution (hereafter referred to as the "index surgery") was computed using the Kaplan–Meier method.[17] Survival curves for the various subgroups were compared using the log-rank test. The Cox proportional hazards model[7] was used to identify the univariate and multivariate predictors of survival. Crude and adjusted rate ratios and their 95% CIs were calculated.

After identifying the significant ($p < 0.05$) independent predictors of survival in the multivariate analysis, we selected certain variables to define subpopulations of patients with different survival times. To be chosen, these variables had to fit the following criteria: 1) characterize a large proportion of the patient population; 2) be readily measurable; and 3) be strong predictors of survival as identified by the rate ratios on multivariate analysis. In addition, the chosen variables had to embrace all of the important aspects considered in the evaluation of these patients, namely patient demographics, functional status, and imaging characteristics. The variables were then used to classify patients into groups with distinct survival patterns, and the adjusted rate ratios for these groups were used to generate a scoring system. Variables associated with a higher rate ratio on multivariate analysis were given a greater relative score. Scores were then classified into different outcome groups. The survival times following different degrees of surgical resection in patients in each of the outcome groups were determined. Statistical analyses were performed using the Statistical Package for the Social Sciences 9.0 (SPSS, Inc., Chicago, IL).

Results

Patient, Imaging, and Treatment Characteristics

Table 3 summarizes the clinical characteristics of all 416 patients. There were 263 men (63%) and 153 women (37%) with a median age of 53 years (SD 14 years). The preoperative KPS score was 80 or greater in 313 patients (75%). There were 183 treated patients (44%) and 233 untreated patients (56%). Before presentation at our institu-

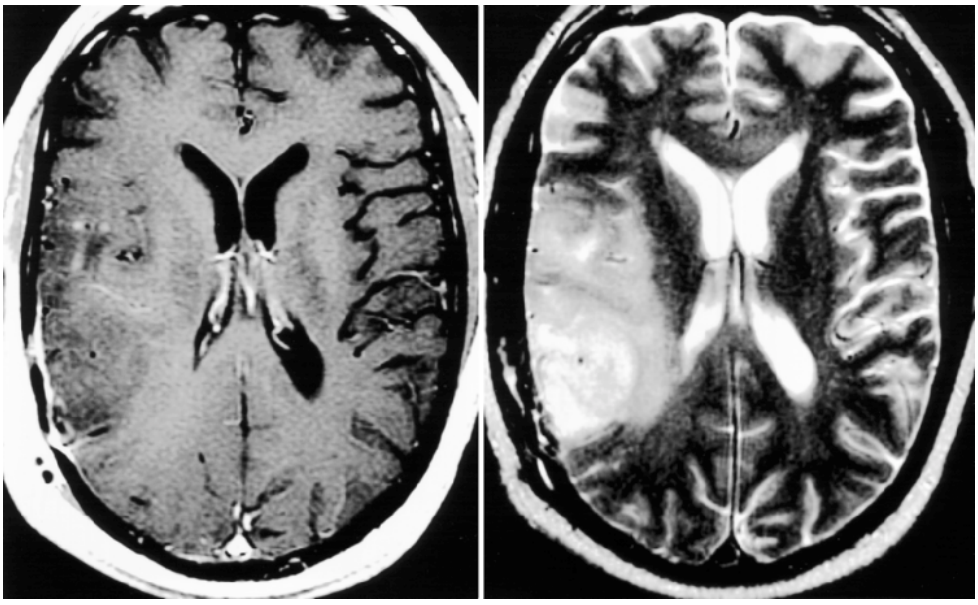

FIG. 2. Axial T_1- *(left)* and T_2-weighted MR images *(right)* obtained in a patient with GBM. There was no enhancement of the tumor on the gadolinium-enhanced T_1-weighted images. In such cases, tumor volume was defined as the region of T_2 signal abnormality corresponding to the mass seen on both T_1- and T_2-weighted images (excluding the ill-defined hyperintense signal abnormality surrounding the mass on T_2-weighted images).

tion, the treated patients had undergone cytoreductive surgery or biopsy sampling, with or without adjuvant chemotherapy or radiation therapy. Preoperative MR imaging demonstrated that most tumors were superficial (91%), located near (48%) or within (44%) eloquent brain, and that they exhibited intense contrast enhancement (86%).

The mean extent of tumor resection in all patients was 89% (SD 18%), as shown by comparing tumor volumes between preoperative and postoperative MR images. The median preoperative tumor volume was 34 cm^3 (range 0.8–255 cm^3) and the median postoperative tumor volume was 0.68 cm^3 (range 0–73 cm^3).

Length of Survival

The median length of survival for all patients from the time of diagnosis was 15.9 months (95% CI 14.6–17.3 months). The survival rates after diagnosis were 88% at 6 months, 64% at 1 year, 29% at 2 years, and 17% at 3 years. The median survival duration for all patients from the time of index surgery was 10.6 months (95% CI 9.6–11.7 months).

Univariate and Multivariate Analyses of Predictors of Survival

As shown in Table 4, the significant ($p < 0.05$) predictors of shorter survival duration from the time of index surgery in the univariate analysis included age (45–64 years and $\geq$ 65 years), preoperative KPS score of less than 80, and tumor functional Grade III. The extent of surgical resection was also associated with survival, as discussed later. Preoperative MR imaging findings that proved to be univariate predictors of shorter survival times were tumor necrosis, enhancement of the tumor mass (high-intermediate or high signal intensity [Grade 2 or 3] compared with no or low-intermediate signal intensity [Grade 0 or 1]), and edema. Of these significant variables, tumor functional grade and edema were not found to be independent predictors of survival in the multivariate analysis (Table 4). The patient's sex, tumor location (deep or superficial), preoperative tumor volume, mass effect, and treatment status (newly diagnosed compared with residual or recurrent tumor) did not appear to have a significant effect on survival.

Extent of Tumor Resection and Survival

Among all patients, resection of 89% or more of the tumor volume was necessary to significantly improve survival after index surgery (Table 5). Resection of 98% or more of the tumor volume (Fig. 3) was associated with a significant survival advantage both at the univariate and multivariate levels; in these patients the median survival time was 13 months (95% CI 11.4–14.6 months) after index surgery. This contrasts with only 8.8 months (95% CI 7.4–10.2 months, $p < 0.0001$) in patients with a less than 98% tumor resection (Fig. 4 and Table 5). To reduce any preselection bias resulting from the large proportion of patients who underwent treatment before referral to our institution, the statistical analysis was also performed separately in the 233 patients with newly diagnosed tumors who had received no prior treatment (Tables 5 and 6). In this group, the median survival time was 13 months (95% CI 11.4–14.6 months) after index surgery when the extent of resection was 98% or more, compared with 10.1 months (95% CI 8.5–11.7 months, $p = 0.02$) in previously untreated patients with a less than 98% tumor resection.

Furthermore, resection of 98% or more of the tumor volume was shown to be a significant independent predictor of survival in the multivariate analysis (adjusted rate ratio 1.6, 95% CI 1.3–2, $p < 0.0001$) for the whole group (Table 4), and for the previously untreated group (adjusted rate ratio 1.4, 95% CI 1.1–1.9, $p < 0.02$; Table 6).

There were 197 patients (47%) who underwent resection of 98% or more of the tumor volume, whereas 219 patients (53%) underwent resection of less than 98%. In

TABLE 3
*Clinical characteristics of 416 patients with GBM**

Characteristic	All Patients	Previously Untreated Patients
mean age in yrs (SD)	53 (14)	56 (14)
sex (no. [%])		
male	263 (63)	143 (61)
female	153 (37)	90 (39)
KPS score (no. [%])		
<70	103 (25)	54 (23)
80	117 (28)	64 (28)
90	136 (33)	80 (34)
100	60 (14)	35 (15)
previous treatment (no. [%])		
yes	183 (44)	NA
no	233 (56)	NA
tumor functional grade (no. [%])		
I	35 (8)	12 (5)
II	197 (48)	107 (46)
III	184 (44)	114 (49)
tumor location (no. [%])		
deep	39 (9)	26 (11)
superficial	377 (91)	207 (89)
necrosis (no. [%])		
0	51 (12)	29 (13)
I	130 (31)	63 (27)
II	104 (25)	57 (24)
III	131 (32)	84 (36)
mass effect grade (no. [%])		
0	46 (11)	23 (10)
1	177 (43)	98 (42)
2	116 (28)	66 (28)
3	77 (18)	46 (20)
edema grade (no. [%])		
0	19 (5)	15 (7)
1	150 (36)	113 (48)
2	119 (28)	61 (26)
3	128 (31)	44 (19)
enhancement grade (no. [%])		
0	12 (3)	11 (5)
1	6 (1)	5 (2)
2	42 (10)	27 (12)
3	356 (86)	190 (81)
median tumor vol in cm^3 (range)		
preop	34 (0.8–255)	35 (1–163)
postop	0.68 (0–73)	0.7 (0–73)
mean percentage reduction in tumor vol (SD)	89 (18)	88 (20)
extent of resection (no. [%])		
≥98%	197 (47)	107 (46)
<98%	219 (53)	126 (54)

* See Table 1 for description of tumor functional grades, Fig. 1 for examples of necrosis grades, and Table 2 for explanation of mass effect, edema, and enhancement grades. Abbreviations: NA = not applicable; vol = volume.

TABLE 4

Significant univariate and multivariate predictors of survival in 416 patients with GBM

Variable	Univariate Analysis			Median Survival (mos)	Multivariate Analysis		
	Rate Ratio	95% CI	p Value		Rate Ratio	95% CI	p Value
age (yrs)							
<45	1.0	NA	NA	15.9	1.0	NA	NA
45–64	1.8	1.3–2.3	0.0001	10.6	1.6	1.2–2.1	0.002
≥65	3.0	2.1–4.2	<0.0001	8.1	2.5	1.8–3.6	<0.0001
KPS score							
≥80	1.0	NA	NA	11.2	1.0	NA	NA
<80	1.5	1.2–1.9	0.0009	8.8	1.4	1.1–1.8	0.01
tumor functional grade							
I & II	1.0	NA	NA	11.3	NA	NA	NA
III	1.3	1.1–1.6	0.02	9.3	NA	NA	NA
necrosis grade							
0	1.0	NA	NA	21.0	1.0	NA	NA
I–III	2.3	1.6–3.4	<0.0001	10.1	1.9	1.3–2.7	0.002
edema grade							
0–1	1.0	NA	NA	12.1	NA	NA	NA
2–3	1.3	1.1–1.58	0.04	10.1	NA	NA	NA
enhancement grade							
0–1	1.0	NA	NA	27.1	1.0	NA	NA
2–3	2.8	1.6–5.2	0.0007	10.5	2.1	1.1–3.9	0.02
extent of tumor resection							
≥98%	1.0	NA	NA	13.0	1.0	NA	NA
<98%	1.7	1.4–2.1	<0.0001	8.8	1.6	1.3–2.0	<0.0001

TABLE 5

*Survival compared with extent of tumor resection**

Extent of Tumor Resection (%)	Median Survival in Mos (95% CI)	Rate Ratio (95% CI)	p Value
all 416 patients w/ GBM†			
≥85	10.9 (9.7–12.2)	1.2 (0.9–1.5)	0.22
≥87	10.8 (9.4–12.2)	1.2 (0.9–1.5)	0.15
≥89	10.9 (9.6–12.1)	1.3 (1.1–1.6)	0.04
≥90	10.9 (9.8–12.0)	1.4 (1.1–1.7)	0.02
≥93	11.2 (9.6–12.8)	1.3 (1.1–1.6)	0.01
≥94	11.3 (9.9–12.7)	1.4 (1.2–1.7)	0.01
≥95	11.6 (10.2–13.0)	1.4 (1.1–1.7)	0.005
≥96	12.6 (11.0–14.3)	1.5 (1.2–1.9)	0.0001
≥97	13.0 (11.4–14.6)	1.6 (1.3–2.0)	<0.0001
≥98	13.0 (11.4–14.6)	1.7 (1.4–2.1)	<0.0001
≥99	13.1 (11.6–14.6)	1.7 (1.4–2.1)	<0.0001
100	13.1 (11.6–14.7)	1.7 (1.4–2.2)	<0.0001
233 untreated patients w/ GBM‡			
≥85	10.8 (9.5–12.1)	0.9 (0.6–1.3)	0.61
≥90	10.9 (9.4–12.4)	1.1 (0.8–1.5)	0.62
≥93	11.6 (10.0–13.2)	1.1 (0.8–1.5)	0.48
≥94	11.9 (10.1–13.6)	1.2 (0.8–1.6)	0.36
≥95	12.1 (10.3–13.9)	1.2 (0.9–1.7)	0.15
≥96	12.6 (11.0–14.2)	1.3 (1.0–1.8)	0.06
≥97	12.6 (11.1–14.2)	1.4 (1.1–1.8)	0.04
≥98	13.0 (11.4–14.6)	1.4 (1.17–1.9)	0.02
≥99	13.1 (11.2–15.1)	1.5 (1.1–2.0)	0.006
100	13.1 (10.9–15.3)	1.5 (1.1–2.0)	0.006

* Comparing ≥ 85% with < 85%, ≥ 90% with < 90%, and so forth.

† Less than 89% tumor resection was not associated with increased survival time in this subgroup.

‡ Less than 97% tumor resection was not associated with increased survival time in this subgroup.

the latter group, however, the median extent of resection was still relatively high, at 88.1% (range 9.9–97.9%).

Outcome Scale

We identified five independent predictors of survival by using multivariate analysis; however, to meet the three criteria described in *Statistical Methods*, the only variables chosen for the outcome scale were age, preoperative KPS score, and the presence or absence of tumor necrosis on preoperative MR images (Table 7). On the basis of the adjusted rate ratios of these three variables, scores ranged from 0 to 5. As shown in Table 8, the scores were then collapsed into four groups according to survival (Fig. 5): Group A (score 0), Group B (score 1–2), Group C (score 3), and Group D (score 4–5).

The effect of the extent of tumor resection on the survival of patients in each of the four outcome groups was investigated (Fig. 6). A survival advantage for aggressive resection (≥ 98% of the tumor volume) was observed in patients in Group B (median survival 19 months compared with 10.9 months for resection of < 98% of the tumor volume, p = 0.001) and in Group C (median survival 13.1 months compared with 8.3 months, p = 0.005). There was a trend toward slightly longer survival duration in patients in Group D (median survival 8.6 months compared with 7.8 months, p = 0.13). Although there was also a trend toward longer survival times in patients in Group A who underwent aggressive tumor resection (median survival 35.3 months compared with 32.8 months), the number of patients was too small (15 patients) to achieve statistical significance (Table 8).

Discussion

The optimal extent of resection in any patient depends

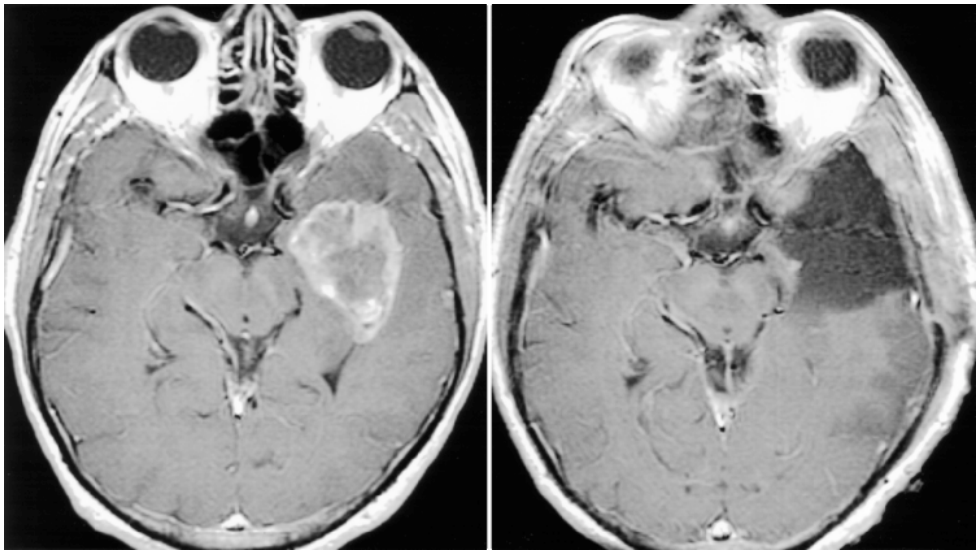

FIG. 3. Contrast-enhanced axial T_1-weighted MR images obtained in a patient with GBM. Preoperative *(left)* and postoperative images *(right)* demonstrate a gross-total tumor resection.

on the tumor size and location, the patient's general and neurological status, and the experience of the surgeon. In our series, the extent of resection in patients with GBM began to be associated with a survival advantage at 89% of the tumor volume. Aggressive resection of 98% or more of the tumor volume was a significant independent predictor of patient survival in both the entire patient population (adjusted rate ratio 1.6, 95% CI 1.3–2, $p < 0.0001$) and in the previously untreated subgroup (adjusted rate ratio 1.4, 95% CI 1.1–1.9, $p = 0.02$).

We also examined the survival times in subpopulations of patients defined by key variables. Among the variables associated with survival, we chose those with strong independent predictive value that characterized a large proportion of the patient population and that we believed would be the most practical and objective for general use, namely age, preoperative KPS score, and tumor necrosis on MR studies. Only 18 patients (4%) had Grade 0 to 1 enhancement in this series, limiting the usefulness of this variable in defining the outcome scale.

Aggressive cytoreductive surgery conferred the greatest survival advantage in patients with favorable combinations of these variables. Group D patients (scores 4–5) showed only a trend toward longer survival time with a higher extent of resection. This finding should be considered in light of the potential diagnostic and symptomatic advantages of extensive resections.[32] To preserve neurological function, tumors in eloquent brain areas may only undergo biopsy procedures or partial resection, whereas lesions in noneloquent brain regions may be more aggressively resected. In an analysis of 400 patients who underwent craniotomy for the treatment of parenchymal tumors, Sawaya, et al.,[33] found that tumor functional grade was the most important variable for determining the risk of a new neurological deficit after surgery. Thus, in evaluating an association between survival and surgical treatment, it is important to take tumor location into account. In our series, involvement of eloquent brain (tumor functional Grade III) was associated with shorter duration of survival at the univariate level, but lost its effect when adjusted for other independent predictors. A survival difference was not seen between patients with deeply located tumors and those with superficial tumors. This may be due to the relatively small number of patients with deep lesions.

In addition to the clinical characteristics of age and preoperative KPS score, for which the relationship to survival is well established, we observed that many preoperative MR imaging characteristics were associated with survival in our series. In particular, the absence of necrosis on imaging studies was an important prognostically favorable variable in this series, confirming the findings of Hammoud, et al.[14] Low-intensity necrotic areas within a glioma are a common imaging feature and are believed to indicate rapid growth and malignant behavior.[35] Although all patients in this series had histological evidence of tumor necrosis, 51 patients (12%) showed no necrosis on MR images.

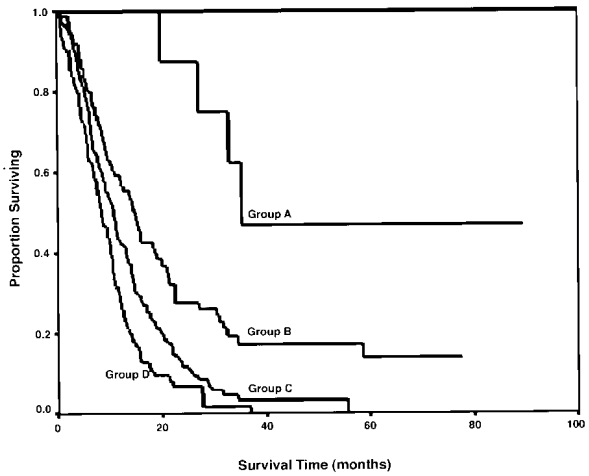

FIG. 4. Graph showing Kaplan–Meier estimates of overall survival after index surgery in all patients. Overall survival time was significantly longer among patients who underwent resection of 98% or more of the tumor volume (197 of 416, $p < 0.0001$) than among patients with a less than 98% tumor resection (219 of 416).

TABLE 6

Significant univariate and multivariate predictors of survival in 233 untreated patients with GBM

Variable	Univariate Analysis			Median Survival (mos)	Multivariate Analysis		
	Rate Ratio	95% CI	p Value		Rate Ratio	95% CI	p Value
age (yrs)							
<65	1.0	NA	NA	13.4	1.0	NA	NA
≥65	2.2	1.6–3.1	<0.0001	8.3	2.1	1.5–3.0	<0.0001
KPS score							
≥90	1.0	NA	NA	14.5	1.0	NA	NA
<90	1.8	1.3–2.4	0.0002	10.1	1.8	1.3–2.4	0.0002
necrosis grade							
0	1.0	NA	NA	19.9	1.0	NA	NA
I–III	2.7	1.6–4.4	0.0002	10.5	2.8	1.6–4.6	0.0001
mass effect grade							
0–2	1.0	NA	NA	12.8	NA	NA	NA
3	1.8	1.3–2.7	0.001	8.2	NA	NA	NA
enhancement grade							
0–2	1.0	NA	NA	17.1	NA	NA	NA
3	2.2	1.4–3.3	0.0002	10.5	NA	NA	NA
extent of tumor resection							
≥98%	1.0	NA	NA	13.0	1.0	NA	NA
<98%	1.4	1.1–1.9	0.02	10.1	1.4	1.1–1.9	0.02

Consistent with an earlier report,[14] an increasing degree of enhancement of the tumor nodule was also an independent predictor of shorter survival duration. This can be explained by the fact that the blood–brain barrier must be disrupted for contrast agents to accumulate within the tumor mass. The histopathological correlate of tumor enhancement is pathological neovascularization and endothelial proliferation.[10] Thus, the poor prognosis associated with greater contrast enhancement in our series could be related to the degree of tumor angiogenesis.

The region of hyperintensity on T_2-weighted MR images, traditionally considered to be edema, has been shown to have a variable tumor component.[10,19] Grades 0 and 1 for peritumoral edema on the preoperative MR images were shown to be associated with a significantly longer survival time on univariate analysis ($p = 0.04$). This effect disappeared, however, when adjusted for other significant predictors in the multivariate analysis. Neither mass effect nor preoperative tumor volume showed any association with survival in either the univariate or multivariate analysis.

Ours is the largest and most comprehensive series to date in which the survival of patients with GBM has been explored based on neuroradiological quantification of the extent of tumor removal. A further advantage of our study was that the diagnosis was uniform throughout the cohort and based on histological evidence of tumor necrosis. In addition, resections took place over the relatively limited period of 6 years. The computerized technique used to measure tumor volumes was also objective and reliable.[37] Finally, the effect on survival of each variable considered in this study was reviewed in a multivariate analysis.

Like almost all modern studies on the subject, our series is retrospective,[16,24,28] and thus potentially subject to sources of bias and variation. An important exception here, however, is that the imaging data were collected prospectively, by using preoperative and postoperative MR images in all cases. The difficulty of conducting a randomized trial to evaluate the relative merits of extent of tumor resection has been previously documented.[16]

TABLE 7

*M. D. Anderson clinical outcome scale for patients with GBM**

Characteristic	Score
tumor necrosis on MR images†	
yes	2
no	0
age (yrs)	
<45	0
45–64	1
≥65	2
KPS score	
<80	1
≥80	0

* The assignment of scores relied on the multivariate rate ratios presented in Table 4 and is described in text.

† Presence of necrosis includes Grades I to III, and absence of necrosis is equivalent to Grade 0, as shown in Fig. 1.

TABLE 8

Clinical outcome groups and length of survival in 416 patients with GBM

Total Score	Outcome Group	No. of Patients	Median Survival in Mos (95% CI)*	Median Survival in Mos†		p Value‡
				≥98% Resection	<98% Resection	
0	A	15	35.3 (not defined)	35.3 (8)	32.8 (7)	0.85
1–2	B	89	14.9 (11.7–18.0)	19.0 (49)	10.9 (40)	0.001
3	C	184	10.7 (9.2–12.2)	13.1 (79)	8.3 (105)	0.005
4–5	D	128	8.2 (6.6–9.8)	8.6 (61)	7.8 (67)	0.13

* Log-rank test significant at $p < 0.0001$.

† Values in parentheses indicate the number of patients for each group.

‡ Log-rank test for difference in median survival.

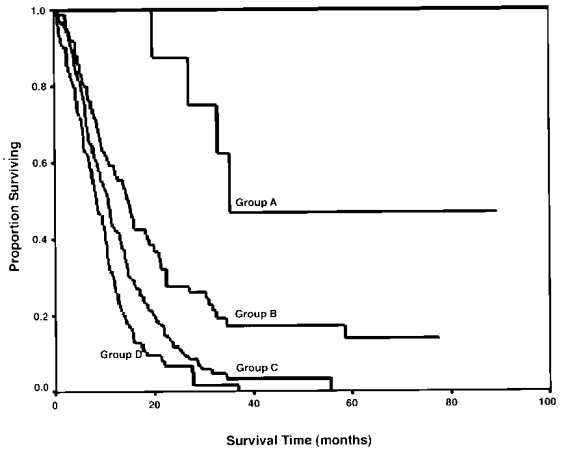

FIG. 5. Graph showing Kaplan–Meier estimates of survival after index surgery for the entire patient population with respect to the different outcome groups. Log-rank test probability value is less than 0.0001.

Conclusions

We have found that resection of 98% or more of the tumor volume, as shown by computer-assisted volumetric studies, is an independent variable associated with longer survival times in patients with GBM. We conclude that a gross-total resection should be performed whenever possible for these patients, although not at the expense of neurological function. Tumor removal that falls short of the 89% statistical cutoff point determined in this study may still provide diagnostic and symptomatic benefits.[32] In addition to the established clinical prognostic factors of age and preoperative KPS score, the degrees of necrosis and enhancement on preoperative MR studies were significantly associated with survival in patients with GBM. Finally, we have presented a simplified outcome scale that identifies subgroups of patients with varying survival rates. Further validation of this system in prospective studies (which is ongoing in our institution at present) and in

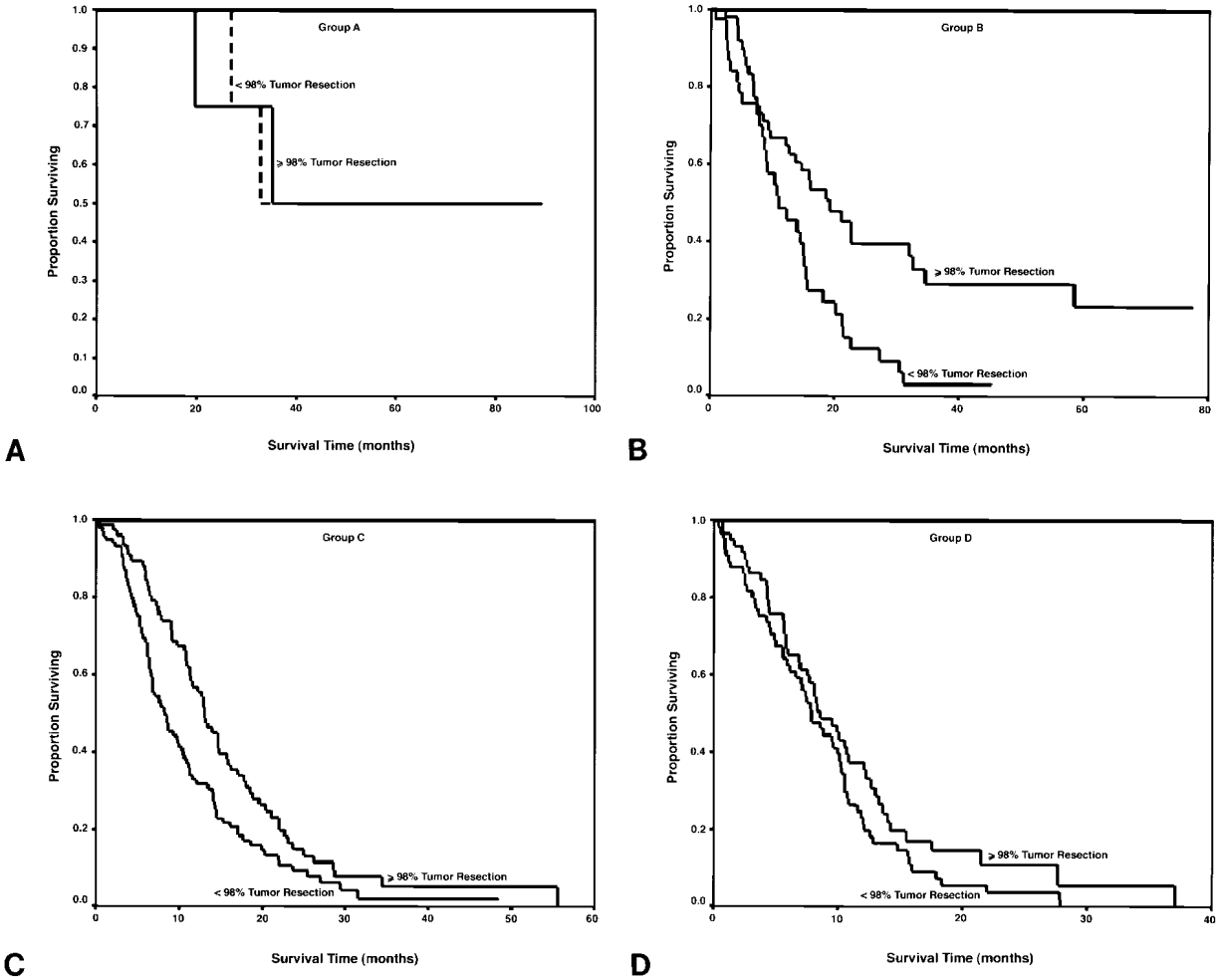

FIG. 6. Graphs showing Kaplan–Meier estimates of survival after index surgery for the entire patient population with respect to different outcome groups and by extent of tumor resection. A trend toward longer survival was found in Group A patients (A) who underwent resection of 98% or more of the tumor volume; however, the number of patients was too small to reveal significance. The median survival time was longer in Group B patients (B) who underwent resection of 98% or more of the tumor volume ($p = 0.001$) than in those whose resections were below that level; the same was found in Group C patients (C) ($p = 0.005$). There was a trend toward slightly longer survival times after more aggressive resections in Group D patients (D) ($p = 0.13$).

other patient populations is warranted to determine its usefulness as a prognostic tool.

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