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Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project

SUSAN M. CHANG, M.D., IAN F. PARNEY, M.D., PH.D., MICHAEL MCDERMOTT, M.D., FRED G. BARKER II, M.D., MEIC H. SCHMIDT, M.D., WEI HUANG, M.S., EDWARD R. LAWS, JR., M.D., KEVIN O. LILLEHEI, M.D., MARK BERNSTEIN, M.D., HENRY BREM, M.D., ANDREW E. SLOAN, M.D., MITCHEL BERGER, M.D., AND THE GLIOMA OUTCOMES INVESTIGATORS

Brain Tumor Research Center, Department of Neurological Surgery, University of California, San Francisco, California; Brain Tumor Center, Massachusetts General Hospital and Harvard University; Center for Outcomes Research, University of Massachusetts Medical School, Boston, Massachusetts; Department of Neurosurgery, University of Utah, Salt Lake City, Utah; Department of Neurological Surgery, University of Virginia Health Sciences Center, Charlottesville, Virginia; Division of Neurosurgery, University of Colorado, Denver, Colorado; Division of Neurosurgery, University of Toronto, Ontario, Canada; Departments of Neurosurgery and Oncology, The Johns Hopkins University, Baltimore, Maryland; and Department of Neurological Surgery, Wayne State University, Detroit, Michigan

Object. In many new clinical trials of patients with malignant gliomas surgical intervention is incorporated as an integral part of tumor-directed interstitial therapies such as gene therapy, biodegradable wafer placement, and immunotherapy. Assessment of toxicity is a major component of evaluating these novel therapeutic interventions, but this must be done in light of known complication rates of craniotomy for tumor resection. Factors predicting neurological outcome would also be helpful for patient selection for surgically based clinical trials.

Methods. The Glioma Outcome Project is a prospectively compiled database containing information on 788 patients with malignant gliomas that captured clinical practice patterns and patient outcomes. Patients in this series who underwent their first or second craniotomy were analyzed separately for presenting symptoms, tumor and patient characteristics, and perioperative complications. Preoperative and intraoperative factors possibly related to neurological outcome were evaluated.

There were 408 patients who underwent first craniotomies (C1 group) and 91 patients who underwent second ones (C2 group). Both groups had similar patient and tumor characteristics except for their median age (55 years in the C1 group compared with 50 years in the C2 group; $p = 0.006$). Headache was more common at presentation in the C1 group, whereas papilledema and an altered level of consciousness were more common at presentation in patients undergoing second surgeries. Perioperative complications occurred in 24% of patients in the C1 group and 33% of patients in the C2 group ($p = 0.1$). Most patients were the same or better neurologically after surgery, but more patients in the C2 group (18%) displayed a worsened neurological status than those in the C1 group (8%; $p = 0.007$). The Karnofsky Performance Scale score and, in patients in the C2 group, tumor size were important neurological outcome predictors. Regional complications occurred at similar rates in both groups. Systemic infections occurred more frequently in the C2 group (4.4 compared with 0%; $p < 0.0001$) as did depression (20 compared with 11%; $p = 0.02$). The perioperative mortality rate was 1.5% for the C1 group and 2.2% for the C2 group (p = not significant). The median length of the hospital stay was 4 days in each group.

Conclusions. Perioperative complications occur slightly more often following a second craniotomy for malignant glioma than after the first craniotomy. This should be considered when evaluating toxicities from intraoperative local therapies requiring craniotomy. Nevertheless, most patients are neurologically stable or improved after either their first or second craniotomy. This data set may serve as a benchmark for neurosurgeons and others in a discussion of operative risks in patients with malignant gliomas.

KEY WORDS • malignant glioma • craniotomy • postoperative complication • outcome

MAXIMUM, safe resection is the primary goal of surgical therapy for malignant glioma.[9,24,29] This allows for a definitive diagnosis[16] and can improve neurological outcome by relieving mass effect and pressure on normal brain structures. In many retrospective studies researchers have addressed the potential impact of the extent of resection on overall survival in these patients. Most have shown prolonged survival in response to more extensive surgery,[11,22,29,36] although this remains controversial.[10,21] Perioperative complications after craniotomy and tumor resection have been reported in retrospective studies for both primary and metastatic brain tumors. Factors affecting morbidity and mortality have been identified. These include patient characteristics (age, KPS score,[18] and medical history), tumor characteristics (histological type, location, and size),

Abbreviations used in this paper: GO = Glioma Outcome; KPS = Karnofsky Performance Scale; NS = not significant.

TABLE 1

Characteristics of patients who underwent craniotomy

Characteristic	C1 Group	C2 Group	p Value
male (%)	57	50	0.29
caucasian (%)	86	85	0.88
rt-handed (%)	92	94	0.60
median age (yrs)	55	50	0.006
median KPS score	90	80	0.10

and intraoperative factors (electrophysiological mapping, image guidance, and awake procedures).[4–6,8,9,12,24,26,29,30,32,34]

Once a malignant glioma has recurred after radiation therapy, options for further treatment are limited. In selected patients, a repeated operation can be performed.[1,3,15,33] The perioperative complications have been reported to vary both in type and severity in this group for a number of reasons. Some authors have suggested that a repeated operation for malignant glioma is not associated with increased risk,[27,35] some have shown statistically insignificant trends toward increased complications,[6,29] and some have suggested that there clearly is an increased risk.[32]

Although many surgeons advocate craniotomy for maximum tumor resection, data that were prospectively collected on patients with malignant gliomas undergoing craniotomy during the last 5 years have not been reported. Recent technical advances including intraoperative electrophysiological motor, sensory, and speech mapping, as well as interactive image-guidance systems, may have had an impact on surgical outcome.[4,5,17,24,30,31] The GO Project offered a unique opportunity to collect data prospectively from a large number of North American medical centers. We sought to describe the medical and neurological complications associated with first and second craniotomies for patients with malignant gliomas. This project provides new Class II data for neurosurgeons and neurooncologists involved in clinical trials to use as a benchmark for future clinical trials that involve surgical interventions.

Clinical Material and Methods

The GO Project is a prospective longitudinal database, initiated in 1997, that tracked clinical practice patterns and outcomes among North American patients with malignant gliomas. The data were collected from patient and physician questionnaires, which were completed at 3-month intervals, and were stored at a data coordinating unit established at the Center for Outcomes Research at the University of Massachusetts Medical School. The major objective of the GO Project was to provide prospectively captured benchmark data to enable comparisons among individual practice patterns and outcomes.

Fifty-two clinical sites across North America participated in the GO Project. The enrollment criteria included adult patients with primary World Health Organization[19] Grade III or IV gliomas who were undergoing a first or second operation for diagnosis or treatment. Informed consent was obtained from all patients included in the database. The data collection instruments included questionnaire forms that were completed at enrollment, during the perioperative period, and at follow-up intervals. Patients were followed prospectively at intervals of 3 months until death or 24 months.

TABLE 2

*Preoperative signs and symptoms**

Preop Sign or Symptom	% of Patients		p Value
	C1 Group	C2 Group	
altered LOC	16	26	0.04
papilledema	4.2	11	0.03
headache	59	46	0.02
memory loss	35	39	0.46
nausea/vomiting	14	10	0.31
motor deficit	32	39	0.18
seizures	31	33	0.64

* LOC = level of consciousness.

Between December 1997 and July 2000, 134 physicians enrolled 788 patients at 52 clinical sites. On November 30, 2001, when patient follow up was concluded, 596 (75.6%) of the study patients were known to have died.

The primary outcome measures included treatment, morbidity, and survival. Sociodemographic and related patient characteristics were also collected. Physicians recorded each patient's neurological outcome 21 days after surgery as it compared with their preoperative assessment. This was reported as better, same, or worse. Self-reported changes in functional capacity, quality of life, and satisfaction with care were also captured.

All patients enrolled in the GO Project who underwent craniotomy were included in the analysis. Patients who underwent a first or second craniotomy were analyzed separately with respect to presenting symptoms, tumor and patient characteristics, and perioperative complications. The perioperative period was defined as the first 21 postoperative days. In univariate analysis, the Student t-test, Wilcoxon rank-sum tests, and one-way analysis of variance were used for continuous variables, and the chi-square and Fisher exact test were used for categorical variables. Logistic regression was used for the multivariate analysis.

Results

Of the 788 patients enrolled in the GO Project, 408 underwent a first craniotomy (C1 group) and 91 patients underwent a second craniotomy (C2 group). The remaining 289 patients underwent stereotactic biopsy. The C1 and C2 groups had similar patient and tumor characteristics, except for the median age of the patient (55 years in the C1 group compared with 50 years in the C2 group; $p = 0.006$) (Table 1). Presenting signs and symptoms for the two groups were also similar, except for altered level of consciousness and papilledema, which occurred more frequently in the C2 group, and headache, which was more common in the C1 group (Table 2). Tumor characteristics for the two groups are outlined in Table 3. There were similar distributions of tumor size, laterality, and histological grade between the two groups. Intraoperative electrophysiological mapping was used equally in both groups and the extent of resection (biopsy or subtotal and gross-total resections) was also similarly distributed between groups. Perioperative complication rates for the two groups are shown in Table 4. There were no significant differences between the two groups with respect to perioperative rates of thromboembolic disease, hemorrhage, seizures, wound infection, or length of

TABLE 3

*Characteristics of tumors in the two craniotomy groups**

Tumor Characteristic	% of Patients		p Value
	C1 Group	C2 Group	
size (cm)			0.54
<2	3.3	3.4	
2–4	40	42	
>4	56	55	
laterality			0.28
rt	52	56	
lt	46	39	
bilat	2	6.6	
GBM present	75	67	0.63
cortical mapping performed	22	29	0.17
extent of resection			NS
biopsy	1	0	
subtotal resection	35	42	
gross-total resection	56	54	

* GBM = glioblastoma multiforme.

TABLE 4

Perioperative complications

Complication	% of Patients		p Value
	C1 Group	C2 Group	
depression	11	20	0.02
deep vein thrombosis	4.2	5.6	0.56
pulmonary embolism	0.5	2.2	0.16
intracranial bleeding	1.6	4.4	0.09
systemic infection	0	4.4	<0.0001
seizure	7.5	10.0	0.44
wound infection	0.5	1.1	0.52
adverse drug reaction	5.2	2.2	0.22
postop neurological status*			0.007
worse	8.1	18	
same	39	42	
better	53	40	
median length of hospital stay (days)	4	4	0.86

* Postoperative neurological status compared with preoperative status.

hospital stay when examined individually. The systemic infection rate was higher in the C2 group (4.4 compared with 0% in the C1 group; $p < 0.0001$). A worse neurological outcome occurred more frequently in this group as well (18% in the C2 group compared with 8.1% in the C1 group; $p = 0.007$). There were six perioperative deaths in the C1 group (1.5%) and two in the C2 group (2.2%; p = NS). Depression was noted to be higher in the C2 group ($p = 0.02$).

To facilitate comparison with other reports in the literature, complications were categorized as neurological, regional (hemorrhage, wound infection, and seizures), and systemic (thromboembolic disease, systemic infection, and adverse drug reaction). Among patients in the C1 group, postoperatively 53% were neurologically improved, 8.1% were neurologically worse, 10% sustained regional complications, and 9.2% sustained systemic complications. In this group the overall complication rate was 24.2% and the perioperative mortality rate was 1.5%. Among patients in the C2 group, 40% were neurologically improved, 18% were neurologically worse, 13% sustained regional complications, and 8.7% sustained systemic complications. In that group the overall complication rate was 32.6% and the perioperative mortality rate was 2.2%. Differences between the C1 and C2 groups were not statistically significant for regional complications ($p = 0.38$), systemic complications ($p = 0.88$), or for the overall complication rate ($p = 0.1$). These data are summarized in Tables 5 and 6.

A more comprehensive evaluation of the individual craniotomy groups was performed to assess preoperative and intraoperative factors that may have been related to neurological outcome. After the first craniotomy, patient age and tumor size and location were not significant univariate predictors of neurological outcome; however, the patient's KPS score was a significant predictor ($p < 0.0001$) (Table 7). Multivariate logistic regression showed that the KPS score was a significant predictor for "better" or "same" neurological outcome, but not for "worse" outcome (Table 8). Among patients who underwent a second craniotomy, patient age and tumor location were not significant neurological outcome predictors, but tumor size ($p = 0.02$) and the KPS score ($p = 0.003$) were (Table 9). A multivariate logistic regression model was not performed in this group because of the small sample size. Intraoperative electrophysiological mapping and the extent of resection did not significantly affect neurological outcomes according to either univariate analysis or multivariate logistic regression analysis for either the C1 or C2 groups.

Discussion

Perioperative complication rates for patients undergoing craniotomy for resection of an intraaxial brain tumor have been reported previously. Several largely retrospective studies spanning the decade prior to initiating the GO Project and including patients with both primary and metastatic tumors have been published.[5,6,9,11,12,21,29,31,35] We present a prospective analysis of perioperative complication rates for a large number of patients with malignant gliomas who underwent a first or second craniotomy as part of their therapy. Between 1997 and 2000, 134 physicians enrolled 788 patients at 52 clinical sites in North America. Four hundred ninety-nine of these patients underwent craniotomy and are included in this analysis. These Class II data on perioperative complications and factors associated with neurological outcome in patients undergoing surgery for malignant gliomas provides a modern benchmark in this patient group.

Postoperative deterioration in neurological function occurred in 8.1% of patients in the C1 group and 18% of those in the C2 group. There was a higher proportion of patients in the C2 group who were neurologically worse, despite the fact that this group had a younger median age than the C1 group. It should be noted that the C2 group appeared to have a higher proportion of patients with increased intracranial pressure prior to surgery than the C1 group, as evidenced by the percentage of patients with an altered level of consciousness and papilledema. This may be a contributing factor to these patients' poorer neurological outcomes. Additionally, factors that may be associated with neurological outcome included KPS score for both patient groups and tumor size in patients who underwent a second craniotomy. This is consistent with data from other reports in the literature.[4–6,8,9,12,24,26,29,30,32,34] It also emphasizes that patient selection for surgical clinical trials is an important consideration in study design and analysis.

The number of patients who were worse neurological-

TABLE 5

*Published reports of neurological outcomes, regional complications, and systemic complications after craniotomy for intraaxial tumor resection**

Authors & Year	Patient Accrual	Tumor Classification†	No. of Patients	No. of Repeated Ops	% of Patients: Postop Neurological Status		% of Patients: Reg Comp	% of Patients: Syst Comp	% of Patients: Total Morbid Rate	% of Patients: Mortal Rate
					Better	Worse				
Ciric, et al., 1987	1987	Grade II–IV gliomas	42	—	33	7	14	7	—	0
Fadul, et al., 1988	1985–1987	Grade II–IV supratentorial gliomas	213	62	8	26	13.6	8.9	31	3.3
Devaux, et al., 1993	1984–1988	Grade III & IV gliomas	103	—	—	20	—	—	—	0
Kreth, et al., 1993	1986–1991	Grade IV gliomas, patient age >65 yrs	59	—	—	—	10.5	3.5	—	3.4
Sawaya, et al., 1998	1992–1994	Grade II–IV gliomas, mets	400	61	32	20.75	7	7.75	32	1.7
Vorster & Barnett, 1998	1993–1998	Grade II–IV gliomas, mets, other	224	17	—	19.2	—	12.5	10.6	2.7
Taylor & Bernstein, 1999	1991–1997	Grade II–IV gliomas, mets, other	200	42	—	13	2.5	6	16.5	1
Brell, et al., 2000	1993–1998	Grade II–IV gliomas, mets	200	25	31	20.5	16	4.5	27.5	2.5
Bohinski, et al., 2001	1998–1999	Grade II–IV gliomas	40	21	—	12.5	12.5	5	—	2.5
present study										
C1 group	1997–2000	Grade III & IV gliomas	408	0	53	8.1	10	9.2	24.2	1.5
C2 group	1997–2000	Grade III & IV gliomas	91	91	40	18	13	8.7	32.6	2.2

* Comp = complications; mets = metastatic lesions; morbid = morbidity; mortal = mortality; reg = regional; syst = systematic; — = data not given.
† Tumor grading based on the World Health Organization classification.

ly after surgery in this series is lower than those cited in several other published series. The overall percentage of patients who worsened neurologically in both groups was 9.8%. In seven comparable modern reports of complications after craniotomy for intraaxial brain tumors, neurological deterioration has been reported in 13 to 26% of patients.[5,6,11,12,29,31,35] Only Ciric, et al.,[9] have published a lower rate of neurological worsening (7%), in a study that included significant numbers of low-grade gliomas. Possibly, this reflects improvements in neurosurgical technique such as the incorporation of electrophysiological mapping and image guidance. This seems unlikely, however, because several of the most recent (and largest) of these studies included patients in whom these modalities were used intraoperatively.[6,29,31,35] It is possible that neurological complications have been underestimated in the GO Project by using 21 days as a cutoff for perioperative events, instead of the more commonly used 30-day time period.[6,29,31,35] Given that neurological deficits seldom present late after craniotomy, however, this also seems unlikely. Authors of some studies have suggested that tumor location in eloquent cortex is a predictive factor for worse neurological outcome,[29,31,35] although this finding has not been universal.[6] Whether the site of the operation was in an eloquent or noneloquent location was not recorded in the GO Project, and it is possible that this series contains a smaller proportion of patients with tumors in eloquent locations. This seems particularly plausible because the GO Project reflects community practice patterns, whereas other reported series reflect the experience of specialized referral centers, where surgeons may be more inclined to attempt resection of lesions in eloquent cortex. Additionally, a selection bias toward better surgical candidates by referring neurosurgeons may have contributed in part to lower neurological complication rates.

There was a trend toward a moderately increased risk for regional complications with second craniotomy (10% in the

TABLE 6

Published reports of neurological outcomes, regional complications, and systemic complications after second craniotomy for malignant glioma

Authors & Year	Patient Accrual	Tumor Classification	No. of Patients	% of Patients: Postop Neurological Status		% of Patients: Reg Comp	% of Patients: Syst Comp	% of Patients: Total Morbid Rate	% of Patients: Mortal Rate
				Better	Worse				
Young, et al., 1981	1966–1974	supratentorial Grade III & IV gliomas	24	25	54	25	—	—	16.7
Salcman, et al., 1982	1978–1981	Grade III & IV gliomas	60	—	—	8.3	—	—	0
Ammirati, et al., 1987	1972–1983	Grade III & IV gliomas	55	45	25	14.5	5.5	16	1.4
Harsh, et al., 1987	1975–1984	Grade III & IV gliomas	70	7.1	7.1	—	—	—	4.3
Vick, et al., 1989	1989	Grade III & IV gliomas	15	—	0	0	0	0	0
Landy, et al., 1994	1994	Grade III & IV gliomas	33	33	2.1	—	—	—	0
Barker, et al., 1998	1988–1993	Grade IV gliomas	46	28	23	—	—	—	0
present study, C2 group	1997–2000	Grade III & IV gliomas	91	40	18	13	8.7	32.6	2.2

TABLE 7

Results of univariate analysis of preoperative factors that may be associated with neurological outcome in patients undergoing first craniotomy

Factor	Postop Neurological Status			p Value
	Worse	Same	Better	
mean age of patient (yrs)	55.6	53.1	53.9	0.72
mean KPS score	82.4	88.3	78.0	<0.0001
tumor size (cm)*				0.13
<2 (13 patients)	15.9	53.9	30.8	
2–4 (155 patients)	10.3	41.9	47.7	
>4 (216 patients)	6.0	36.6	57.4	
tumor laterality*				0.88
lt (193 patients)	7.3	38.3	54.4	
rt (177 patients)	9.6	38.4	51.9	
midline (2 patients)	0.0	50.0	50.0	
bilat (10 patients)	10.0	50.0	40.0	

* Values represent percentages of patients.

TABLE 8

Results of multivariate analysis of preoperative factors that may be associated with neurological outcome in patients undergoing first craniotomy

Preop Factor	Odds Ratio	95% Confidence Interval	p Value
factors for worse outcome			
patient age	1.018	0.987–1.051	0.26
KPS score	1.029	0.989–1.069	0.15
tumor size <2 cm	2.236	0.243–20.58	0.48
tumor size 2–4 cm	1.523	0.604–3.842	0.37
tumor location: rt side	0.809	0.329–1.988	0.64
factors for same outcome			
patient age	1.004	0.987–1.022	0.63
KPS score	1.061	1.036–1.087	<0.0001
tumor size <2 cm	1.603	0.585–11.585	0.21
tumor size 2–4 cm	1.016	0.600–1.720	0.95
tumor location: rt side	1.066	0.635–1.789	0.81
factors for better outcome			
patient age	0.990	0.972–1.008	0.27
KPS score	0.938	0.916–0.960	<0.0001
tumor size <2 cm	0.272	0.052–1.438	0.12
tumor size 2–4 cm	0.858	0.509–1.444	0.56
tumor location: rt side	1.005	0.601–1.681	0.98

C1 group and 13% in the C2 group), but this was not statistically significant (p = 0.38). These rates for regional complications are similar to those of previous studies (2.5–16% of patients undergoing craniotomy for intraaxial brain tumors; Table 5).[5,6,9,12,21,29,31] Interestingly, there was no significant difference in wound infections between the C1 and C2 groups (0.5 compared with 1.1%, respectively; p = 0.52). The systemic infection rate was increased in the C2 group (0% in the C1 group and 4.4% in the C2 group; p < 0.0001), but the overall systemic complication was not (9.2% in the C1 group and 8.7% in the C2 group; p = 0.88). It is possible that this reflects prolonged use of corticosteroid medication or previous chemotherapy in patients in the C2 group compared with those in the C1 group. These systemic complication rates are similar to those cited in previously published series (3.5–12.5%; Table 5).[5,6,9,12,21,29,31,35] The perioperative mortality rate in patients in the C1 group was 1.5% and that in patients in the C2 group was 2.2% in C2 (p = NS). This is similar to rates published for previous series (1–3.4%; Table 5).[5,6,9,12,21,29,31,35]

Depression was also recorded in the GO Project. Although the existence of depression in patients with brain tumor has been described previously,[2] it has not been systematically recorded in an intraaxial tumor surgical series.[5,6,9,12,21,29,31,35] The overall incidence of physician-reported depression in this series was 13%, but this rate differed significantly between the C1 and C2 groups (11 compared with 20%, respectively; p = 0.02). It is possible that this increase reflects both local alterations in neurophysiological characteristics secondary to brain tumor invasion and a normal psychological reaction to tumor progression. In any event, these data provide important insight into the quality of life of a patient harboring a malignant glioma. The relatively high depression rate in this series should alert physicians to the possibility that patients with brain tumors may be suffering from this treatable disorder.

Increasingly, tumor-directed therapies, such as chemotherapy wafers, gene therapy, brachytherapy, and conjugated toxin therapy, are being developed that require a craniotomy as part of the treatment plan.[7,13,14,20,25] Neurosurgeons and neurooncologists need to be aware of the incidence of complications from craniotomy alone so they can put the safety of these new therapies in context. This is particularly true for repeated craniotomies, in which the risk of complication may be higher than that for the initial surgery. The data from the GO Project presented here are particularly helpful in defining the risks of repeated craniotomy compared with those of first craniotomy for malignant gliomas. These data indicate a modest, but acceptable trend toward increased perioperative complications among patients undergoing second craniotomy (24.2% in the C1 group and 32.6% in the C2 group; p = 0.1). The majority (82%) of patients were the same or improved neurologically after surgery. Relatively few reports of patients undergoing repeated craniotomy for malignant glioma have been published previously. Seven series from the last two decades, in which patients were accrued between 1966 and 1993, are summarized in Table 6.[1,3,15,23,28,33,37] These largely retrospective stud-

TABLE 9

Results of univariate analysis of preoperative factors that may be associated with neurological outcome in patients undergoing second craniotomy

Factor	Neurological Status			p Value
	Worse	Same	Better	
mean age of patients (yrs)	51.0	48.7	49.9	0.89
mean KPS score	75.3	86.3	72.0	0.003
tumor size (cm)*				0.02
<2 (3 patients)	33.3	33.3	33.3	
2–4 (35 patients)	22.9	57.1	20.0	
>4 (47 patients)	12.8	34.0	53.2	
tumor laterality*				0.72
lt (48 patients)	14.6	43.8	41.7	
rt (34 patients)	20.6	38.2	41.2	
midline (2 patients)	50.0	50.0	0.0	
bilat (3 patients)	33.3	33.3	33.3	

* Values represent percentages of patients.

ies, ranging in size between 15 and 70 patients each, are not always consistent with each other with respect to recording complications and are heterogeneous in their results (for example, there is a range of neurological worsening of 0–54%);[33,37] this makes a direct comparison with the present series difficult. In general, the prospective data obtained from the 91 patients enrolled in the GO Project who underwent second craniotomies compares well with data published in these reports, and represents a more comprehensive and less biased evaluation of perioperative outcome in this patient population.

Although the GO Project provides significant information about the patterns of care and neurosurgical outcomes for a large group of patients with malignant gliomas, there are limitations. Patient selection in this study was probably skewed toward the "best" patients in factors such as KPS score and, hence, in outcomes. Although attempts were made at contributing institutions to enroll consecutive patients, this was not performed over a specific time period and was often impossible due to logistical and other reasons. This may have allowed for selection bias. Also, the centers at which these patients enrolled were self-selected for an interest in surgical management of malignant gliomas and may not reflect universal practice patterns. Nevertheless, the project was not limited to academic institutions and we believe that it reflects a community experience with craniotomy for patients with gliomas. In addition, in this study examined complications occurring within the first 21 days postoperatively. As a result it is possible that complication rates have been underestimated in this study. In most other series the researchers have defined perioperative complications as those occurring within the first 30 days after surgery.[6,29,31,35] Despite these limitations, our results probably represent some of the best population-based data for the modern era on which to base a discussion of the perioperative complications facing patients with malignant gliomas.

Conclusions

We present perioperative complications of first and second craniotomy among 499 patients undergoing open surgery enrolled in the GO Project. Rates of wound infection, seizures, thromboembolic disease, hemorrhage, and length of hospital stay were similar among patients in the C1 and C2 groups, but systemic infection and depression occurred more frequently in those in the C2 group. Furthermore, neurological outcome was worse for patients undergoing second craniotomy. The KPS score was an important predictor of neurological outcome among both groups. For patients who underwent a second craniotomy, tumor size was also predictive. Nevertheless, the increased risk associated with second craniotomy for malignant glioma is modest and most patients were neurologically unchanged or improved postoperatively. Investigators studying experimental therapies involving craniotomy for the intratumoral or interstitial administration of novel agents to patients with newly diagnosed or recurrent malignant glioma should consider these results when evaluating the toxicity of these treatments.

Disclosure

Under a licensing agreement between Guilford Pharmaceuticals and The Johns Hopkins University, Dr. Brem is entitled to a share of royalties received by the University on sales of products described in this work. Dr. Brem and the University own Guilford Pharmaceuticals stock, which is subject to certain restrictions under University policy. Dr. Brem is also a paid consultant to Guilford Pharmaceuticals. The terms of this arrangement are being managed by The Johns Hopkins University in accordance with its conflict-of-interest policies.

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Address reprint requests to: Susan M. Chang, M.D., Department of Neurological Surgery, University of California, San Francisco, 400 Parnassus Avenue, A808, San Francisco, California 94143-0372. email:changs@neurosurg.ucsf.edu.