

Patterns of Care for Adults With Newly Diagnosed Malignant Glioma

Susan M. Chang, MD

Ian F. Parney, MD, PhD

Wei Huang, MS

Frederick A. Anderson, Jr, PhD

Anthony L. Asher, MD

Mark Bernstein, MD

Kevin O. Lillehei, MD

Henry Brem, MD

Mitchel S. Berger, MD

Edward R. Laws, MD

for the Glioma Outcomes Project
Investigators

MALIGNANT GLIOMAS (World Health Organization grade III or IV) are the most common primary brain tumor, and their incidence is increasing over time. They are the second-most common cause of cancer-related death in the young-adult age group and are associated with tremendous morbidity.¹ Despite intensive research, the prognosis for patients with malignant glioma remains poor. Median survival for patients with grade III glioma is 3 to 5 years and is less than 1 year for patients with glioblastoma multiforme (grade IV glioma). Current treatment for patients with malignant glioma includes maximum safe resection, radiation therapy, and chemotherapy²⁻⁶; however, few clear evidence-based treatment guidelines can be drawn from the literature. In terms of supportive care, only practice guidelines for antiepileptic prophylaxis have been published.⁷

See also p 615 and Patient Page.

Context Patients with malignant glioma (grade III or IV) face a poor prognosis, and few evidence-based treatment guidelines are available. There is a dearth of prospective data on patterns of care for these patients.

Objective To provide benchmark data to enable comparison of individual practice patterns and outcomes.

Design, Setting, and Patients The Glioma Outcomes (GO) Project enrolled 788 patients at 52 clinical sites, both academic and community practices, between December 1997 and July 2000. The enrollment criteria included adult patients with primary grade III or IV glioma undergoing a first or second operation for diagnosis or treatment. The data collection instruments included questionnaire forms given at enrollment, during the perioperative period, and at follow-up intervals of 3 months until death or a maximum of 24 months. Of the patients recorded in the GO database, 565 patients with newly diagnosed tumors were used for this analysis.

Main Outcome Measures Patterns of care (surgical management, perioperative care, postoperative management).

Results Most patients underwent magnetic resonance imaging (n=518; 92%) and an attempt at tumor resection (n=425; 75%). Cortical mapping (n=107; 19%) and intraoperative image guidance (n=161; 29%) were uncommon. Most received perioperative corticosteroids (n=535; 99%) and antiepileptic medications (n=497; 88%), but few received antidepressants (n=38; 8%) or prophylactic heparin (n=42; 7%). Most received adjuvant radiation therapy (n=479; 87%), but fewer received chemotherapy (n=300; 54%). Practice patterns varied significantly between academic and community settings.

Conclusions Reliance on magnetic resonance imaging, surgery, and radiation is generally accepted; however, relatively infrequent chemotherapy use may conflict with published literature, and frequent use of prophylactic antiepileptic medications contradicts established practice guidelines. Other practice patterns involving surgical adjuncts, prophylactic heparin, and antidepressants require further investigation to clarify appropriateness. Establishing further clinical guidelines may help reduce variability in practice patterns.

JAMA. 2005;293:557-564

www.jama.com

Although neurosurgeons and neurooncologists are a part of the multidisciplinary team of physicians caring for these patients, family physicians, neurologists, and general internists are involved in the evaluation of the patients' initial clinical presentation and ongoing follow-up care until death. Community practice patterns likely vary widely in the treatment of malignant glioma, in such diverse areas as preoperative and postoperative management and the application of recent

Author Affiliations: Department of Neurological Surgery, University of California, San Francisco (Drs Chang, Parney, and Berger); Center for Outcomes Research, Department of Surgery, University of Massachusetts Medical School, Worcester (Ms Huang and Dr Anderson); Carolina Neurosurgery and Spine Associates, Charlotte, NC (Dr Asher); Division of Neurosurgery, University of Toronto, Toronto, Ontario (Dr Bernstein); Department of Neurological Surgery, University of Colorado, Denver (Dr Lillehei); Department of Neurological Surgery and Oncology, Johns Hopkins University, Baltimore, Md (Dr Brem); and Department of Neurological Surgery, University of Virginia, Charlottesville (Dr Laws).

Corresponding Author: Susan M. Chang, MD, Neuro-Oncology Service, Department of Neurological Surgery, University of California, San Francisco, 400 Parnassus Ave, A808, San Francisco, CA 94143-0350 (chang@neurosurg.ucsf.edu).

technologic advances such as intraoperative electrophysiologic mapping and image guidance.

The Glioma Outcomes (GO) Project is a prospective longitudinal database begun in 1997 that tracked clinical practice patterns and outcomes among North American patients with malignant glioma, with the major objective of providing benchmark data to enable comparison of individual practice patterns and outcomes. We have previously reported on the prognostic factors and survival outcome for patients who had newly diagnosed malignant glioma and were enrolled in this study.⁸ This database also presented a unique opportunity to describe clinical presentation in a modern population of malignant glioma patients, allowed analysis of current community practice patterns, and delineated the areas that should be considered for future rigorous evaluation and research in patients with malignant glioma.

METHODS

Between December 1997 and July 2000, 134 physicians enrolled 788 patients at 52 clinical sites. Patients were recruited by a physician or nurse in the neurosurgery or neuro-oncology clinic at participating institutions. The enrollment criteria included adult patients with primary grade III or IV glioma (glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, mixed anaplastic oligo/astrocytoma, and other anaplastic gliomas) undergoing a first or second operation for diagnosis or treatment. Excluded were potential new enrollees scheduled for their third or subsequent glioma operation, patients who refused to give written consent to participate, patients who could not read or understand English, and patients 18 years of age or younger. Participating clinical sites were requested to enroll consecutive patients, but no funds were budgeted to audit all hospital discharge lists for compliance. Details of a direct audit of the 4 centers with the highest enrollment numbers, with representative participation data, are given in a previous report from the GO

Project.⁹ All enrolled patients gave informed consent, and the study was reviewed and approved by the institutional review board at each participating institution.

Detailed information on data collection is available from previous reports from the GO Project.^{9,10} Briefly, completed data forms were sent to a central coordinating center (Center for Outcomes Research at the University of Massachusetts Medical School), where the data were double keyed into a central database. Electronic audit was performed to detect out-of-range values, inconsistencies, and omissions, and queries were faxed to study coordinators for resolution. Direct audit of initial perioperative physician report forms against patient medical records was performed at 4 of the centers with the highest number of enrollments. The data collection instruments included questionnaire forms given at enrollment, during the perioperative period, and at follow-up intervals of 3 months until death or a maximum of 24 months. The data were stored at a study-coordination center established at the Center for Outcomes Research at the University of Massachusetts Medical School.

Clinical presentation, surgical management, perioperative care, adjunctive therapies after definitive diagnosis, and survival outcome were recorded. Use of modern imaging techniques, specialized operative techniques, intraoperative therapies such as carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea) biodegradable wafers or brachytherapy, perioperative cerebral edema management, and thromboembolic and seizure prophylaxis was specifically captured. Primary outcome measures included treatment, morbidity, and survival. Periods of depression were recorded by physicians and patients. Karnofsky Performance Status¹¹ (KPS; a standard measure of the ability of cancer patients to perform daily tasks) was used by physicians as a surrogate measure of general health status, and patients were asked several questions about their general health since diagnosis. Sociodemographic and

related patient characteristics were also collected. Ethnicity was assessed to track relative incidence and possible variations in treatment; patients classified themselves by using racial categories defined by the National Cancer Institute. The full questionnaires for the GO Project are available online at <http://www.glioma.org>.

All patients with newly diagnosed malignant glioma enrolled in the GO Project were included in this analysis (n=565). Patients with glioblastoma multiforme or grade III glioma were analyzed both aggregately and separately with respect to clinical characteristics and patterns of care. A previous report of this cohort reported in detail on prognostic factors and survival outcome.⁸

For the purpose of this analysis, statistical tests were performed with a data set containing patient demographic information updated from previous reports from the GO Project.^{8,9,12,13} The statistical analysis was performed with SAS version 8.2 (SAS Institute Inc, Cary, NC). Significance was set at $P < .05$. For univariate analysis, categorical variables were analyzed using the χ^2 test or Fisher exact test, and continuous variables were analyzed using the Wilcoxon rank-sum test. The log-rank test and the Cox proportional hazards model were used for survival analyses, as described in a previous article from the GO Project.⁸ The model was adjusted using the variables of patient's age, KPS score, extent of resection, and the use of radiation therapy or chemotherapy. Adjustment variables were selected according to results from the univariate analysis and expert clinical opinion. All variables in the final models met the same assumptions used in our proportional hazards model. Multivariable Cox proportional hazards regression was used to test differences between academic vs nonacademic centers, alternative medicine use, and clinical trial participation with respect to patient survival.

RESULTS

Data were relatively complete for most variables, although there were some

missing responses for all questions. Initial patient questionnaires were not received for approximately 153 of 788 patients, although follow-up data were received for many of these patients. There were a total of 565 patients with newly diagnosed malignant glioma (59% male). Twenty-six percent of patients had tumors with grade III histology. Data are presented in the tables aggregately, as well as separately, according to histology to assess whether clinical characteristics or patterns of care differed between the grades.

Demographics, tumor characteristics, and clinical presentation are summarized in TABLE 1. As expected, patients with grade III histology were younger, had better performance status, and were more likely to present with seizures. They were also more likely to have nonenhancing masses on neuroimaging. Headache was the most common presenting symptom. Seizures had occurred in 32% at presentation overall. Symptom duration was less than 1 month in most cases. There was no significant difference in symptom duration between patients with grade III tumors and patients with grade IV tumors. In 0.4% of patients, the tumor was found incidentally.

Diagnostic tests performed are summarized in TABLE 2. MRI was the most commonly performed diagnostic test (91.7%); computed tomography (CT) was the second-most common (73.5%). There was no difference in the selection of diagnostic tests between tumor grades.

Perioperative medical management is summarized in TABLE 3. Perioperative corticosteroids (98.6%) and anti-epileptic medications (88.4%) were administered frequently, but few patients received antidepressants (6.7%) or antipsychotics (1.8%). No significant differences were noted between patients with grade III tumors and patients with grade IV tumors. Few patients received heparin (n=42/561; 7%).

Surgical management is summarized in TABLE 4. Patients underwent either closed biopsy or craniotomy. By surgeons' reports (not postoperative imag-

Table 1. Patient Demographics, Tumor Characteristics, and Clinical Presentation

	No. (%)*			P Value†
	Total (n = 565)	Grade III (n = 147)	Grade IV (n = 418)	
Patient characteristics				
Sex				
Male	328 (58.7)	78 (53.8)	247 (60.4)	.17
Female	231 (41.3)	67 (46.2)	162 (39.6)	
Ethnicity				
White	438 (86.6)	117 (87.3)	318 (86.4)	.79
Black	18 (3.6)	8 (56.0)	10 (2.7)	.10
Asian/Pacific Islander	2 (0.4)	0 (0)	2 (0.5)	>.99
Hispanic	9 (1.8)	3 (2.2)	6 (1.6)	.71
Other	6 (1.2)	1 (0.8)	4 (1.1)	>.99
Handedness				
Right	417 (88.4)	121 (91.7)	292 (86.9)	.33
Left	37 (7.8)	8 (6.1)	29 (8.6)	
Ambidextrous	18 (3.8)	3 (2.3)	15 (4.5)	
Age, y				
<40	96 (17.6)	54 (37.5)	39 (9.8)	<.001
40-60	226 (41.4)	61 (42.4)	165 (41.5)	
>60	224 (41.0)	29 (20.1)	194 (48.7)	
Tumor characteristics				
No. of sites				
Single	498 (88.3)	131 (89.1)	364 (88.4)	.80
Multiple	66 (11.7)	16 (10.9)	48 (11.7)	
Size, cm				
<2	31 (5.7)	7 (4.8)	24 (6.1)	.19
2-4	224 (41.0)	69 (47.6)	151 (38.1)	
>4	291 (53.3)	69 (47.6)	221 (55.8)	
Location				
Right	253 (46.9)	58 (41.4)	191 (48.4)	.19
Left	257 (47.6)	70 (50.0)	186 (47.1)	
Midline	8 (1.5)	4 (2.9)	4 (1.0)	
Bilateral	22 (4.1)	8 (5.7)	14 (3.5)	
Enhanced masses on imaging				
Yes	528 (93.8)	119 (81.5)	407 (98.8)	<.001
No	35 (6.2)	27 (18.5)	5 (1.2)	
Symptoms				
Changes in consciousness	91 (16.2)	16 (10.9)	75 (18.3)	.04
Headache	314 (56.0)	77 (52.7)	235 (57.3)	.34
Memory loss	200 (35.5)	39 (26.5)	161 (39.2)	.006
Nausea/vomiting	74 (13.1)	12 (8.2)	61 (14.8)	.04
Language deficit	183 (32.5)	33 (22.5)	149 (36.2)	.002
Personality change	130 (23.1)	16 (10.9)	113 (27.4)	<.001
Motor deficit	186 (33.0)	37 (25.2)	148 (35.9)	.02
Seizure	180 (31.9)	83 (56.5)	97 (23.5)	<.001
Cognitive changes	194 (34.4)	33 (22.5)	160 (38.8)	<.001
Sensory deficit	71 (12.6)	22 (5.0)	49 (11.9)	.34
Papilledema	26 (4.6)	7 (4.8)	19 (4.6)	.94
Visual problems	122 (21.6)	34 (23.1)	87 (21.1)	.61
Other	98 (17.4)	21 (14.3)	76 (18.5)	.25
Functional status, KPS, No. (mean score)‡	536 (81)	143 (86)	380 (79)	<.001

*Percentages based on the number of patients who answered each question. Not all 565 patients answered all questionnaire questions. Because of missing data, the total aggregate does not always equal grade III + grade IV data.
 †P values for comparison of grade III vs grade IV.
 ‡The Karnofsky Performance Status (KPS) is a standard measure of cancer patients' ability to perform daily tasks ranging from 100 (normal, no evidence of disease) to 0 (dead).

ing), patients undergoing craniotomy were more likely to have a gross total resection (43.1%) than a subtotal resection (27.0%) or a biopsy (5.3%). Patients with grade IV tumors were more likely to undergo gross total resection than patients with grade III tumors (46.5% vs 33.6%; $P = .007$). Intraoperative electrophysiological mapping was used in 19% of craniotomies. Intraoperative image guidance was used in 29% of resections and was used more fre-

quently for grade III than for grade IV tumors (37.7% vs 25.4%; $P = .005$). Implantable chemotherapy wafers were used infrequently (11%) but more often for grade IV than for grade III tumors (15.1% vs 1.4%; $P < .001$). Brachytherapy seed implantation was rare (0.7%). Mean length of stay in hospital was 4.1 days for patients who underwent biopsy and 6.5 days for patients who underwent resection. The duration of stay was slightly longer for patients with grade IV tumors compared with patients with grade III tumors, irrespective of their extent of resection, and patients with grade IV tumors were less likely to be discharged home.

Postsurgical management is summarized in TABLE 5. Most patients received adjuvant external beam radiation therapy (86.5%), but this varied for grade III and IV tumors (78.2% vs 89.7%; $P < .001$). Chemotherapy was given to 54.2% of patients and was more common among patients undergoing craniotomy than closed biopsy (58.4% vs 40.9%; $P < .001$). Treatment with chemotherapy was associated with increased survival.⁸ Brachytherapy, radiosurgery, and stereotactic radiation therapy were rare (<4%). Fifteen percent of patients participated in clinical trials. There was no significant difference in survival for participants according to participation in a formal clinical trial. Twenty-nine percent reported using alternative medicine; this was more common in patients younger than 60 years (35% vs 18% in those ≥ 60 years; $P < .001$). Types of alternative medicine as categorized by the GO questionnaires were high-dose vitamins, herbs, a macrobiotic diet, shark cartilage, antineoplastons, hydrazine, acupuncture, a faith healer, meditation, or "other." The most commonly used alternative medicines were meditation (9.5%), herbs (6.7%), and vitamins (6.6%). No difference in patients' survival was observed with alternative medicine use.

More patients were treated at academic institutions than community centers (59% vs 42%). Median KPS was 90 in both groups. Median age was younger for patients treated at academic institu-

Table 2. Diagnostic Tests

Modality	No. (%) [*]			P Value [†]
	Total (n = 565)	Grade III (n = 147)	Grade IV (n = 418)	
MRI	518 (91.7)	138 (93.9)	375 (90.8)	.25
CT	415 (73.5)	98 (66.7)	313 (75.8)	.03
EEG	31 (5.5)	10 (6.8)	21 (5.1)	.43
Angiogram	17 (3.0)	5 (3.4)	12 (2.9)	.78
Isotope brain scan	2 (0.4)	1 (0.7)	1 (0.2)	.46
PET	8 (1.4)	4 (2.7)	4 (1.0)	.22
fMRI	12 (2.1)	6 (4.1)	6 (1.5)	.09
Skull radiograph	5 (0.9)	0	5 (1.2)	.33
Other	26 (4.6)	6 (4.1)	20 (4.8)	.71

Abbreviations: CT, computed tomography; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography.

^{*}Percentages based on the number of patients who answered each question. Not all 565 patients answered all questionnaire questions. Because of missing data, the total aggregate does not always equal grade III + grade IV data. [†]P values for comparison of grade III vs grade IV.

Table 3. Perioperative Medical Management

Medication	No. (%) [*]			P Value [†]
	Total (n = 565)	Grade III (n = 147)	Grade IV (n = 418)	
Corticosteroids				.07
Preoperative	25 (4.4)	3 (2.0)	22 (5.4)	
Postoperative	63 (11.2)	23 (15.7)	39 (9.5)	
Both	467 (83.0)	118 (80.3)	345 (83.9)	
Neither	8 (1.4)	3 (2.0)	5 (1.2)	
Antiepileptics				.23
Preoperative	24 (4.3)	3 (2.0)	21 (5.1)	
Postoperative	62 (11.0)	14 (9.5)	46 (11.2)	
Both	411 (73.1)	116 (78.9)	292 (71.2)	
Neither	65 (11.6)	14 (9.5)	51 (12.4)	
Antidepressants				.82
Preoperative	4 (0.7)	1 (0.7)	3 (0.7)	
Postoperative	16 (2.8)	4 (2.7)	12 (2.9)	
Both	18 (3.2)	3 (2.0)	15 (3.7)	
Neither	525 (93.3)	139 (94.6)	381 (92.7)	
Antipsychotics				.15
Preoperative	1 (0.2)	0 (0)	1 (0.2)	
Postoperative	5 (0.9)	1 (0.68)	4 (1.0)	
Both	4 (0.7)	3 (2.0)	1 (0.2)	
Neither	553 (98.2)	143 (97.3)	405 (98.5)	
Other				.13
Preoperative	22 (3.9)	4 (2.7)	18 (4.4)	
Postoperative	36 (6.4)	15 (10.2)	21 (5.1)	
Both	37 (6.6)	11 (7.5)	26 (6.3)	
None	468 (83.1)	117 (79.6)	346 (84.2)	

^{*}Percentages based on the number of patients who answered each question. Not all 565 patients answered all questionnaire questions. Because of missing data, the total aggregate does not always equal grade III + grade IV data. [†]P values for comparison of grade III vs grade IV.

tions (54.8 vs 59.1 years; $P < .001$). Grade IV tumors accounted for similar percentages of patients treated at academic institutions and community centers (71.5% vs 76.2%; $P = .20$). Patients treated at academic institutions were slightly more likely to have MRI scans performed (94% vs 89%; $P = .02$), less likely to have CT scans performed (70% vs 78%; $P = .03$), and were more likely to receive medications other than corticosteroids, antiepileptics, antidepressants, or antipsychotics (25.5% vs 7.3%; $P < .001$); these included anxiolytics and antiulcer medications. Craniotomy was performed with similar frequency in both groups (79.3% vs 75.3%; $P = .25$). Image guidance and electrophysiological mapping were used more frequently for resection in academic institutions than in community practices (47.1% vs 25.2% [$P < .001$]; and 28.6% vs 8.4% [$P < .001$], respectively). Surgeon-reported subtotal resection was more common in academic centers (39.5% vs 28.2%; $P = .01$), and implantable chemotherapy wafer use was less common (4.4% vs 18.9%; $P < .001$). Median length of stay after resection in academic centers was shorter (4 days vs 6 days; $P < .001$). Patients from academic centers were more likely to receive chemotherapy (59% vs 41%; $P = .001$) or radiation therapy (90% vs 82%; $P = .006$) and to participate in clinical trials (18.6% vs 12.4%; $P = .04$). Patients treated at community centers were more likely to go directly to supportive or hospice care (6.4% vs 1%; $P < .001$). Median survival was longer for patients treated at academic institutions than at community centers (54.6 weeks vs 40.1 weeks; $P = .002$); however, this was not an independent predictor of survival in a multivariate analysis examining tumor grade, patient age, KPS, resection vs biopsy, use of radiation or chemotherapy, and treatment at an academic institution vs community center, likely a reflection of the importance of the younger age of patients treated at academic institutions.

COMMENT

The GO Project afforded a unique opportunity to describe modern patterns of care for adult patients with malignant

glioma. Demographics and tumor characteristics were similar to those of previous reports.^{1,14} Whites were the predominant ethnic group, and men had tumors slightly more often than women. Patients with grade IV tumors were older on average than patients with grade III tumors. Grade IV tumors were more likely to demonstrate contrast enhancement on CT or MRI; as in previous studies,¹⁵ this demonstration was not universal. Just more than half of patients

presented with headache. Memory loss, progressive motor deficits, or seizures each occurred in approximately one third of patients at diagnosis. Seizures were more common in patients with grade III tumors than in patients with grade IV tumors ($P < .001$). These clinical features and demographics are similar to those of previous reports,¹⁶⁻¹⁸ suggesting that the GO Project captured a relatively representative population of patients with malignant glioma.

Table 4. Surgical Management

Surgical Features	No. (%)*			P Value†
	Total (n = 565)	Grade III (n = 147)	Grade IV (n = 418)	
Extent of resection				
Biopsy	30 (5.3)	10 (6.9)	19 (4.6)	.29
Subtotal	152 (27.0)	37 (25.3)	113 (27.4)	.64
Gross total	243 (43.1)	49 (33.6)	192 (46.5)	.007
Technical adjuncts				
Cortical mapping	107 (19.1)	32 (21.8)	73 (17.9)	.30
Image guidance: biopsy	153 (27.1)	51 (34.9)	100 (24.2)	.01
Image guidance: resection	161 (28.6)	55 (37.7)	105 (25.4)	.005
Treatment adjuncts				
Chemotherapy wafers	64 (11.4)	2 (1.4)	62 (15.1)	<.001
Radioactive seeds	4 (0.7)	0 (0)	4 (1.0)	.49
Length of stay				
Biopsy	121 (23.0)	40 (28.0)	80 (21.1)	.03
Days, mean (SD)	4.1 (5.6)	2.7 (2.9)	4.7 (6.5)	
Resection	406 (77.0)	103 (72.0)	299 (78.9)	<.001
Days, mean (SD)	6.5 (9.6)	6.3 (16.5)	6.6 (5.6)	
Disposition				
Home	459 (83.6)	132 (91.7)	324 (81.0)	.04
Rehabilitation	65 (11.8)	12 (8.3)	51 (12.8)	
Nursing facility	18 (3.3)	0 (0)	18 (4.5)	

*Percentages based on the number of patients who answered each question. Not all 565 patients answered all questionnaire questions. Because of missing data, the total aggregate data do not always equal grade III + grade IV data. †P values for comparison of grade III vs grade IV.

Table 5. Postsurgical Management

Postsurgical Management	No. (%)*			P Value†
	Total (n = 565)	Grade III (n = 147)	Grade IV (n = 418)	
Systemic chemotherapy	300 (54.2)	76 (53.5)	222 (54.6)	.83
External beam radiation	479 (86.5)	111 (78.2)	365 (89.7)	<.001
Brachytherapy	3 (0.5)	0 (0)	3 (0.7)	.57
Stereotactic radiosurgery	21 (3.8)	2 (1.4)	19 (4.7)	.08
Stereotactic radiation therapy	9 (1.6)	1 (0.7)	8 (2.0)	.31
Observation	93 (16.8)	30 (21.1)	62 (15.2)	.11
Hospice	20 (3.6)	2 (1.4)	18 (4.4)	.10
Alternative medicine	99 (28.5)	25 (25.0)	74 (30.3)	.32
Other	56 (10.1)	15 (10.6)	40 (9.8)	.80

*Percentages based on the number of patients who answered each question. Not all 565 patients answered all questionnaire questions. Because of missing data, the total aggregate does not always equal grade III + grade IV data. †P values for comparison of grade III vs grade IV.

One limitation of this study, as of any large registry database, is the limited assurance of compliance in the completion of questionnaire forms. In addition to the patient enrollment form, completed by the physician, the GO Project used 7 separate patient questionnaires, which arrived in the mail separately. Key patient demographic and clinical characteristics—eg, age, sex, tumor grade—were similar in patients with and without missing data points for the main study end points. This finding provides some level of reassurance that missing data points for key end points did not bias our conclusions.

Practice Patterns in Keeping With Published Literature

Most patients in this study underwent contrast-enhanced MRI at diagnosis (92%), craniotomy and attempted resection (75%), and postoperative radiation therapy (87%). Contrast-enhanced MRI is almost universally accepted as the imaging test of choice for malignant glioma,⁶ and several randomized controlled trials have shown the efficacy of radiation therapy in this population.⁴ The value of surgical resection (vs closed biopsy) is slightly more controversial, but maximum safe resection is still generally advocated.^{8,19} The practice patterns for imaging, surgery, and radiation therapy documented in the GO Project are in keeping with data available in the literature.

Practice Patterns That Contradict Established Guidelines

Antiepileptic prophylaxis for patients with newly diagnosed brain tumors is one of the few areas of brain tumor treatment in which practice guidelines have been published.⁷ The American Academy of Neurology's practice parameters are based on a review of 12 studies (including 4 randomized controlled trials with subsequent meta-analysis) comparing seizure frequency in newly diagnosed brain tumor patients who did or did not receive seizure prophylaxis. Although it is accepted that patients who

present with seizures should receive antiepileptic drugs (AEDs), there is strong evidence that prophylactic AEDs have little value for seizure-free patients with newly diagnosed brain tumors. Furthermore, AEDs are associated with significant adverse effects, requiring change in medication in up to 23% of patients. The American Academy of Neurology's practice parameters state that prophylactic AEDs should not be administered routinely to patients with newly diagnosed brain tumors (standard) and should be discontinued in the first postoperative week in patients who have not experienced a seizure (guideline).⁷ In this light, it is somewhat surprising that 89% of patients in this study received AEDs, whereas only 32% presented with seizures. Clearly, administering prophylactic AEDs remains a common practice pattern. Eleven of the 12 studies the guidelines were based on were published before initiation of the GO Project. We hope this report will further highlight the limited value of prophylactic AEDs in newly diagnosed brain tumor patients and bring this to the attention of treating physicians.

Practice Patterns That May Conflict With Reported Literature

The modest efficacy of nitrosourea-based chemotherapy in the treatment of malignant glioma has been demonstrated with randomized controlled trials and subsequent meta-analyses.²⁰⁻²² In addition, since the completion of this study, temozolomide administered concurrently with radiation has been shown to be associated with improved survival.²³ In this study, only 54% of patients received chemotherapy, which was found to correlate significantly with increased survival.⁸ Patients receiving chemotherapy tended to be younger (median age, 53.9 vs 60.6 years; $P < .001$) but had similar KPS scores (both groups had a median score of 90) and accounted for a percentage of grade III tumors (25.5% vs 26.3%) similar to that of patients who did not receive chemotherapy, which could be a result of a bias against treating older patients with chemotherapy that is not

supported by the literature^{20,21} or patients or family choosing to decline treatment with chemotherapy; however, it may be that some patients and clinicians thought that modest efficacy did not justify the adverse-effect profile for carmustine and lomustine (the most widely used chemotherapy agents for malignant glioma available during the GO Project). The preliminary positive results of a European phase 3 study of radiation and temozolomide may further change practice patterns.²⁴

Practice Patterns Suggesting Further Research

Practice patterns for several perioperative medications highlight areas for further study. For example, only 7% of patients received prophylactic low-dose heparin despite deep venous thrombosis occurring in 3% to 60% of patients within 6 weeks of surgery for malignant glioma.²⁵ The literature about the safety and efficacy of low-dose heparin prophylaxis for brain tumor patients is conflicting.²⁶⁻²⁸ Carefully designed and implemented trials such as the Dalteparin in Malignant Gliomas Study recently initiated by the Ontario Clinical Oncology Group of Cancer Care Ontario (James R. Perry, MD, oral communication, June 2003) will be required to resolve this issue. Thirteen percent of newly diagnosed patients enrolled in the GO Project had symptoms of depression reported by their physician,^{9,12} but only 28.6% of these and 7% of all newly diagnosed patients were given antidepressant medication. One possible reason may be concern about interactions with antiepileptics, though 35 patients did receive antiepileptics and antidepressants. Further prospective studies need to be done to explore this finding and its implications. Finally, administration of corticosteroids to reduce neurologic symptoms (99% of patients in this study received corticosteroids) is supported by numerous reports^{6,29,30} but can have well-known, significant adverse effects such as immunosuppression, hypertension, diabetes, and my-

opathy that may be ameliorated by lower doses.³¹ It may be reasonable to consider developing consensus guidelines to optimize corticosteroid dosing.

Intraoperative image guidance and electrophysiologic mapping were used in a minority of patients (29% and 19%, respectively). These are well-established adjuncts to surgical resection of tumors in eloquent cortex; however, despite reports of the value of these modalities in the resection of malignant gliomas,³²⁻³⁵ no controlled prospective trials have established that they improve outcome. In the GO Project, they were not associated with any change in postoperative neurologic outcome¹² or survival; however, it is possible that they allowed resection of tumors that would otherwise have been inoperable, which could have significant prognostic implications because patients in this study who underwent craniotomy and resection had improved survival compared with patients who underwent closed biopsy.⁸ Unfortunately, the factors that influence the decision for extent of resection, such as tumor location and size or comorbidity, were not recorded in the GO Project, and the utility of these techniques is an important area for further study. The availability of surgical adjuncts at the participating centers was not captured, so it is unclear what percentage of surgical procedures recorded by the GO Project could make use of these technologies. Only 11% of patients had chemotherapy wafers implanted, the majority in grade IV patients. Since the completion of accrual to the GO project, Westphal et al²² have reported the results of a phase 3 randomized study in patients with newly diagnosed malignant glioma, which resulted in US Food and Drug Administration approval of this intervention at initial surgery. It would be interesting to assess the use of this modality since the publication of this study in 2003.

The overall poor survival for patients in this study who were diagnosed with malignant gliomas (40.9 weeks)⁸ confirms the importance of developing novel therapeutic strategies. Only 15.1% of patients participated in

clinical trials; details on clinical trial participation are presented in a previous article from the GO Project.¹³ Multivariable Cox proportional hazards regression was used to test for differences between patients who participated in a clinical trial or not with respect to patient survival. This analysis was adjusted using the model variables from an earlier article from the GO Project.⁸ There was no significant difference in survival for participants according to participation in a formal clinical trial. Twice as many patients (29%) used some form of alternative medicine than participated in clinical trials. No difference in patients' survival was observed with alternative medicine use when statistical methods similar to those used for analyzing the effects of participation in clinical trials were used. Physicians and investigators should notice the relatively high rates of alternative medicine use because there could be drug interactions that affect metabolism of concomitant medications such as chemotherapeutics or AEDs.

Impact of Practice Patterns on Survival Outcome

Significant variations in patterns of care were noted between academic and community practices. Patients treated at academic institutions were more likely to report the use of medications unrelated to the central nervous system, such as anxiolytics and antiulcer agents. Academic institutions were also more likely to use image guidance and electrophysiologic mapping to aid tumor resection, and patients tended to have a shorter length of hospital stay, to receive radiation and chemotherapy, and to participate in clinical trials. Surgeons at academic institutions were less likely to report gross total resection or to use chemotherapy wafers. Treatment at an academic center was associated with improved survival in univariate analysis but was not significant in multivariate analysis, which probably largely reflects the younger age of patients and the increased volume of patients treated at academic centers^{36,37} and the increased use of radiation and

chemotherapy at these institutions. The average volume of patients treated at the individual academic or community centers, or per individual surgeon, was not captured in the GO Project and could not be evaluated.

CONCLUSION

We present patterns of care for a large group of patients with newly diagnosed malignant glioma treated in the modern era. Some common practice patterns are in keeping with published literature (eg, use of radiation therapy), some contradict published guidelines (eg, frequent prophylactic AED administration) or may conflict with published literature (eg, relatively infrequent use of chemotherapy), and still others point out areas for further investigation in this population, including heparin prophylaxis for venous thromboembolism, antidepressant medication, corticosteroid dosing, and use of surgical adjuncts. Variations in patterns of care were associated with differences in survival; establishing further practice guidelines may help reduce this variability. One of the major benefits of the GO Project is that it provides a broad historical cohort that can be used as a comparison for future prospective studies.

Author Contributions: Dr Chang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chang, Brem, Berger, Laws.
Acquisition of data: Huang, Anderson, Asher, Bernstein, Lillehei, Brem, Laws.

Analysis and interpretation of data: Chang, Parney, Huang, Anderson, Bernstein, Brem, Laws.

Drafting of the manuscript: Chang, Parney, Huang.
Critical revision of the manuscript for important intellectual content: Chang, Parney, Anderson, Asher, Bernstein, Lillehei, Brem, Berger, Laws.

Statistical analysis: Huang.

Obtained funding: Anderson, Brem, Berger.

Administrative, technical, or material support: Parney, Huang, Anderson, Asher, Brem.

Study supervision: Chang, Huang, Bernstein, Lillehei, Berger, Laws.

Financial Disclosures: Under separate licensing agreements between the Johns Hopkins University and Guilford Pharmaceuticals Inc and the Johns Hopkins University and Angiotech Pharmaceuticals Inc, Dr Brem is entitled to a share of royalty received by the university on sales of products described in this article. Dr Brem owns 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. No other authors reported financial disclosures.

Funding/Support: Dr Parney is an Accelerate Brain Cancer Cure (ABC²) Foundation fellow. The GO Project was supported by unrestricted educational grants from Aventis Pharma and Guilford Pharmaceuticals to the

Center for Outcomes Research, University of Massachusetts Medical School. This study was also supported in part by NIH/NCI grant PO1 CA13525 to the University of California, San Francisco.

Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; col-

lection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Acknowledgment: We thank Sharon Reynolds, BA, Department of Neurological Surgery, University of California, San Francisco, for extensive editorial support.

REFERENCES

1. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neurooncology*. 2002;4:278-299.
2. Devaux BC, O'Fallon JR, Kelly PJ. Resection, biopsy, and survival in malignant glial neoplasms: a retrospective study of clinical parameters, therapy, and outcome. *J Neurosurg*. 1993;78:767-775.
3. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95:190-198.
4. Laperriere N, Zuraw L, Cairncross G. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. *Radiother Oncol*. 2002;64:259-273.
5. Parney IF, Chang S. Current chemotherapy for glioblastoma. *Cancer J*. 2003;9:149-156.
6. Frappaz D, Chinot O, Bataillard A, et al. Summary version of the standards, options and recommendations for the management of adult patients with intracranial glioma (2002). *Br J Cancer*. 2003;89(suppl 1):S73-S83.
7. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;54:1886-1893.
8. Laws ER, Parney IF, Huang W, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. *J Neurosurg*. 2003;99:467-473.
9. Litofsky NS, Farace E, Anderson F Jr, Meyers CA, Huang W, Laws ER Jr. Depression in patients with high-grade glioma: results of the Glioma Outcomes Project. *Neurosurgery*. 2004;54:358-366.
10. Anderson FA Jr, and the Glioma Outcomes Project Advisory Board. The Glioma Outcomes Project: a resource for measuring and improving glioma outcomes. *Neurosurg Focus*. 1998;4:Article 8.
11. Karnofsky D, Abelman W, Craver L, Burchenal J. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer*. 1948;1:634-656.
12. Chang S, Parney IF, McDermott M, et al. Perioperative complications and neurological outcome of first versus second craniotomy among patients enrolled in the Glioma Outcomes (GO) Project. *J Neurosurg*. 2003;98:1175-1181.
13. Chang SM, Barker FG II, Schmidt MH, et al. Clinical trial participation among patients enrolled in the Glioma Outcomes Project. *Cancer*. 2002;94:2681-2687.
14. Chen P, Aldape K, Wiencke JK, et al. Ethnicity delineates different genetic pathways in malignant glioma. *Cancer Res*. 2001;61:3949-3954.
15. McDermott MW, Krouwer HG, Asai A, Ito S, Hoshino T, Prados MD. A comparison of CT contrast enhancement and BOLD labeling indices in moderately and highly anaplastic astrocytomas of the cerebral hemispheres. *Can J Neurol Sci*. 1992;19:34-39.
16. Cascino GD. Epilepsy and brain tumors: implications for treatment. *Epilepsia*. 1990;31(suppl 3):S37-S44.
17. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. *Neurology*. 1993;43:1678-1683.
18. McKeran RO, Thomas DGT. The clinical study of glioblastomas. In: Graham DL, ed. *Brain Tumors: Scientific Basis, Clinical Investigation and Current Therapy*. Baltimore, Md: Johns Hopkins University Press; 1990:194-230.
19. Sawaya R. Extent of resection in malignant gliomas: a critical summary. *J Neurooncol*. 1999;42:303-305.
20. Fine HA, Dear KBG, Loeffler JS, Black PM, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer*. 1993;71:2585-2597.
21. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet*. 2002;359:1011-1018.
22. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neurooncology*. 2003;5:79-88.
23. Stupp R, Dietrich PY, Ostermann Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol*. 2002;20:1375-1382.
24. Stupp R, Mason WP, Van Den Bent MJ, et al. Concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM): conclusive results of a randomized phase III trial by the EORTC Brain and RT Groups and NCIC Clinical Trials Group. Paper presented at: American Society of Clinical Oncology 40th Annual Meeting; June 5-8, 2004; New Orleans, La.
25. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. *Cancer*. 2000;89:640-646.
26. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med*. 1998;339:80-85.
27. Nurmohamed MT, van Riel AM, Henkens CM, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thromb Haemost*. 1996;75:233-238.
28. Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery*. 1998;43:1074-1081.
29. Galicich JH, French LA, Melby JC. Use of dexamethasone in the treatment of cerebral edema associated with brain tumors. *Lancet*. 1961;81:46-53.
30. Wen PY, Marks PW. Medical management of patients with brain tumors. *Curr Opin Oncol*. 2002;14:299-307.
31. Vecht CJ, Hovestadt A, Verbiest HB, van Vliet JJ, van Putten WL. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. *Neurology*. 1994;44:675-680.
32. Kaibara T, Saunders JK, Sutherland GR. Advances in mobile intraoperative magnetic resonance imaging. *Neurosurgery*. 2000;47:131-137.
33. Matz PG, Cobbs C, Berger MS. Intraoperative cortical mapping as a guide to the surgical resection of gliomas. *J Neurooncol*. 1999;42:233-245.
34. Taylor MD, Bernstein M. Awake craniotomy with brain mapping as the routine surgical approach to treating patients with supratentorial intraaxial tumors: a prospective trial of 200 cases. *J Neurosurg*. 1999;90:35-41.
35. Bernstein M, Al-Anazi AR, Kucharczyk W, Manninen P, Bronskill M, Henkelman M. Brain tumor surgery with the Toronto open magnetic resonance imaging system: preliminary results for 36 patients and analysis of advantages, disadvantages, and future prospects. *Neurosurgery*. 2000;46:900-907.
36. Cowan JA Jr, Dimick JB, Leveque JC, Thompson BG, Upchurch GR Jr, Hoff JT. The impact of provider volume on mortality after intracranial tumor resection. *Neurosurgery*. 2003;52:48-53.
37. Long DM, Gordon T, Bowman H, et al. Outcome and cost of craniotomy performed to treat tumors in regional academic referral centers. *Neurosurgery*. 2003;52:1056-1063.