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Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project

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Object. The Glioma Outcomes Project represents a contemporary analysis of the management of malignant (Grade III and Grade IV/GBM) gliomas in North America. This observational database was used to evaluate the influence of resection, as opposed to biopsy, on patient outcome as measured by the length of survival. Attempts were made to reduce the impact of selection bias by repeating the data analysis after omitting patients with major negative prognostic factors.

Methods. Outcome data from 788 patients accrued from multiple sites over a 4-year period (1997–2001) were analyzed with the primary outcome measure being length of survival. Of these, 565 patients with recent diagnoses formed the basis of the present analysis. Patients were systematically followed up until death or up to 24 months after enrollment in the study, and survival data were correlated with the histopathological grade and location of the tumor, the extent of surgery, the patient's performance status, and demographic factors.

The median length of survival was 40.9 weeks for patients with recently diagnosed GBMs. The true median length of survival for patients with Grade III gliomas was not reached, although there was a 58% survival rate at 104 weeks. In multivariate analysis, resection rather than biopsy ($p < 0.0001$), age 60 years or younger ($p < 0.0001$), and a Karnofsky Performance Scale (KPS) score of 70 or greater ($p = 0.0004$) were associated with a prolonged survival time for patients with Grade III or IV gliomas. The prognostic value of resection compared with biopsy was maintained ($p < 0.0001$), even after eliminating patients considered to be "poor risk" (those with age > 60 years, KPS score < 70, or presence of multifocal tumors), who may have been overrepresented in the biopsy group. Survival "tails" at 24 months were 58% for Grade III gliomas and 11% for GBMs.

Conclusions. These data provide Class II evidence to support tumor grade, patient's age, and patient's functional status as prognostic factors for survival in individuals with recently diagnosed malignant gliomas. Resection (compared with biopsy) is also a strong prognostic factor; however, no quantitative attempt was made to assess the true extent of the resection.

KEY WORDS • glioma • survival • surgery • resection • biopsy

THE optimal management for patients harboring malignant gliomas continues to be controversial, despite decades of intense clinical and basic science investigation. Malignant gliomas represent the most common primary brain tumor, and the impact of brain tumors in general on the public health has become of heightened interest in recent years. New prevalence data indicate that the number of patients living with some form of brain tumor may be as high as 30 per 100,000 in the US.[12]

Abbreviations used in this paper: GBM = glioblastoma multiforme; GO = Glioma Outcomes; KPS = Karnofsky Performance Scale.

Current management strategies used for malignant glioma include surgery (either biopsy or tumor resection) followed by adjunctive radiation therapy and/or chemotherapy. Authors have concentrated on outcome data that have survival as the major end point. With the exception of a few randomized controlled trials, most studies have been retrospective in nature. Several prognostic factors have been identified, including patient age and functional status as well as tumor grade.[5,15,21,25]

In addition, the majority of studies published to date have shown a survival advantage for patients who undergo radical tumor resection.[1,13,15,18,21,24,27,32] The concern regarding these studies is that, in the absence of prospective random-

TABLE 1

Characterization of patient groups: a comparison between patients undergoing biopsy and those undergoing resection

Characteristic	Incidence (%)		p Value
	Biopsy (126 patients)	Resection (439 patients)	
men	65	57	0.1501
women	35	43	
mean age (yrs)	57	54	0.1033
age >60 yrs	45	36	0.2464
one tumor site	78	91	<0.0001
multifocal disease	22	9	
KPS score ≥70	76	87	0.0049
tumor size >4 cm	45	56	0.0032
GBM	67	76	0.0590
Grade III glioma	33	24	
chemotherapy	40	58	0.0003
radiotherapy	81	88	0.0578

ized data, significant selection bias may have occurred.[16] The actual difference between survival in patients treated with biopsy, as opposed to radical resection plus adjunctive therapy, may not be as profound as one might assume from the retrospective data. Indeed, authors of some studies have questioned the value of resection[11,20] or, at least, have questioned its value in all but the best possible candidates.[25]

The GO Project was organized in 1997 to generate a prospective database to track patients with malignant glioma. In this paper, we use data from the GO Project to evaluate potential clinical prognostic factors for patients with recently diagnosed malignant gliomas, and pay particular attention to the prognostic values of resection and biopsy. The major advantages of this data set are its prospective nature and completion in the modern era, as well as the wide spectrum of neurosurgical practices participating in the study, which reflect current patterns of care in North America.

Clinical Material and Methods

The GO Project consists of a prospective longitudinal database initiated in 1997 to track clinical practice patterns and outcomes among North American patients with malignant gliomas. The data are based on patient and physician responses to questionnaire forms, which were completed at 3-month intervals. The data are stored at a data coordinating center established at the Center for Outcomes Research at the University of Massachusetts Medical School. The major objective of the GO Project is to provide prospectively captured benchmark data to enable a comparison of 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 Grade III or IV gliomas[17] (according to the World Health Organization)[19] who were undergoing a first or second operation for diagnosis or treatment. Patients gave informed consent before admission into the study. The data collection instruments included questionnaire forms distributed 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 after enrollment. Between December 1997 and October 2000, 134 physicians enrolled 788 patients at 52 clinical sites. On November 30, 2001, when follow-up review of the patients was concluded, 596 enrolled patients (75.6%) were known to have died.

For the purposes of this analysis, only patients with recently diagnosed malignant glioma were included (565 patients). Five patients with incomplete survival data were excluded from this analysis. Demographic information, KPS score, and patterns of perioperative care were noted at the time of enrollment. No radiographic attempt was made to determine the extent of resection. The primary outcome measures included treatment, morbidity, and survival. Sociodemographic and related patient characteristics were also collected. Patients with GBMs or Grade III gliomas were analyzed separately with respect to prognostic factors for survival. These included the patient's age and KPS score, the extent of the resection, and the use of radio- or chemotherapy.

TABLE 2

Characterization of patient groups: a comparison between patients with Grade III gliomas and those with GBMs

Characteristic	Incidence (%)		p Value
	Grade III Glioma (147 patients)	GBM (413 patients)	
men	53	61	0.1286
women	47	39	
mean age (yrs)	45	58	<0.0001
age >60 yrs	17	47	<0.0001
one tumor site	89	88	0.8022
multifocal disease	11	12	
KPS score ≥70	90	82	0.0202
biopsy	28	20	0.0590
resection	72	80	
tumor size >4 cm	48	56	0.1385
chemotherapy	54	55	0.8329
radiotherapy	78	90	0.0005

TABLE 3

*Median lengths of survival for patients with Grade III or IV tumors who underwent biopsy or resection**

Characteristic	No. of Patients	Median Survival in Wks (range)	p Value
all patients	770	48.2 (0.3–104.3)	NA
patients who underwent biopsy	126	27.1 (1.6–104.3)	<0.0001
patients who underwent craniotomy	439	51.6 (1.9–104.3)	
patients w/ non-GBM/Grade III tumors	147	73.4 (2.7–104.3)	<0.0001
patients w/ GBM/Grade IV lesions	413	40.9 (1.6–104.3)	
patients w/ Grade III tumors who underwent biopsy	41	52.1 (2.7–104.3)	<0.0001
patients w/ Grade III tumors who underwent craniotomy	106	87 (11.1–104.3)	
patients w/ Grade IV tumors who underwent biopsy	84	21.0 (1.6–104.3)	<0.0001
patients w/ Grade IV tumors who underwent craniotomy	329	45.3 (1.9–104.3)	

* NA = not applicable.

TABLE 4

Patient distribution based on age and tumor grade

Characteristic	No. of Patients (%)		
	Age 20–40 Yrs	Age 41–60 Yrs	Age >60 Yrs
all patients	126 of 624 (20.2)	277 of 624 (44.4)	221 of 624 (35.4)
biopsy	17 of 92 (18.5)	37 of 201 (18.4)	45 of 181 (45.5)
craniotomy	75 of 92 (81.5)	164 of 201 (43.7)	136 of 181 (36.3)
non-GBM/Grade III tumor	53 of 89 (59.6)	57 of 201 (28.4)	22 of 180 (12.2)
GBM/Grade IV tumor	36 of 89 (40.5)	144 of 201 (71.6)	158 of 180 (87.8)

TABLE 5

Median length of survival by patient age group

Patient Age & Tumor Grade	Median Survival in Wks (range)
20–40 yrs	
non-GBM/Grade III (53 patients)	87.9 (2.7–104.3)
GBM/Grade IV (36 patients)	70.9 (10.1–104.3)
41–60 yrs	
non-GBM/Grade III (57 patients)	85.0 (10.4–104.3)
GBM/Grade IV (144 patients)	53.1 (1.6–104.3)
>60 yrs	
non-GBM/Grade III (22 patients)	31.3 (9.3–104.3)
GBM/Grade IV (158 patients)	36.1 (2.2–104.3)

Statistical Analysis

In a univariate analysis, the Student t-test and the Wilcoxon rank-sum test were used for continuous variables and the chi-square test and Fisher exact test were used for categorical variables. The log-rank test and the Cox proportional hazards model were used for the survival analysis.

Results

From December 1997 through October 2000, 788 patients from 52 institutions across North America were enrolled in the GO Project. Among these, 565 harbored recently diagnosed malignant gliomas. Complete survival data were available in 560 of these patients and they constituted the base population for data analysis. Major pathological distinctions were between Grade IV malignant gliomas (GBMs) and Grade III gliomas. The latter category included anaplastic astrocytoma, anaplastic oligodendroglioma, mixed anaplastic oligoastrocytoma, and anaplastic glioma not otherwise specified. Demographic data and the percentages of patients receiving adjuvant therapies are shown in Tables 1 and 2.

Table 1 shows a demographic breakdown in which patients undergoing biopsy and those undergoing resection as the initial procedure have been compared. Patients who underwent resection were more likely to have unifocal tumors (91 compared with 78%, $p < 0.0001$), KPS scores of 70 or higher (87 compared with 76%, $p = 0.0049$), and tumors larger than 4 cm (56 compared with 45%, $p = 0.0032$), and, subsequently, to receive chemotherapy (58 compared with 40%, $p = 0.0003$). Table 2 shows demographic data in which patients harboring Grade III gliomas have been compared with patients with GBMs. Patients with Grade III lesions were younger (mean age 45 compared with 58 years, $p < 0.0001$), more likely to have KPS scores of 70 or higher (90 compared with 82%, $p = 0.0202$), and less likely to receive postoperative radiotherapy (78 compared with 90%, $p = 0.0005$).

Survival analysis was performed using a number of different strategies and is depicted in Tables 3 through 5 and Figs. 1 through 4. Initially, the analysis was performed for the entire group of patients including those with GBMs and those with Grade III gliomas. The median length of overall survival for the entire cohort was 48.2 weeks (range 0.3–104.3 weeks). When patients were separated according to the histological subgroups of the tumors they harbored, the median survival time was 4.9 weeks for patients with GBMs and 73.4 weeks for patients with Grade III gliomas (based on the data available); however, the follow-up time for the Grade III cohort was relatively short and may not reflect a true median length of survival. This information is summarized in Table 3. As expected, the age of the patient was a powerful influence on the median survival time in both the GBM group and the Grade III glioma group. Median survival times for patients with Grade III gliomas and those with GBMs were 87.9 and 70.9 weeks, respectively, among patients between 20 and 40 years of age, 85 and 53.1 weeks, respectively, among patients between 41 and 60 years of age, and 31.3 and 36.1 weeks, respectively, for patients older than 60 years of age. Interestingly, differences in the median length of survival between patients with Grade III gliomas and those with GBMs were less marked as age increased. Differences in the median length of survival among patients older than 60 years were not significant. This information is summarized in Tables 4 and 5. Within each tumor grade, patients who underwent resection fared better. Among patients with Grade III gliomas, the median survival times were 52.1 weeks after biopsy and 87 weeks after resection ($p < 0.0001$). Similarly, the median survival times for patients with GBMs was 21 weeks after biopsy and 45.3 after resection ($p < 0.0001$). These data are summarized in Table 3.

Kaplan–Meier survival curves for patients with GBMs or Grade III gliomas who underwent either biopsy or resection are shown in Fig. 1. In a Cox proportional hazards model, survival data are significantly different for the categories of

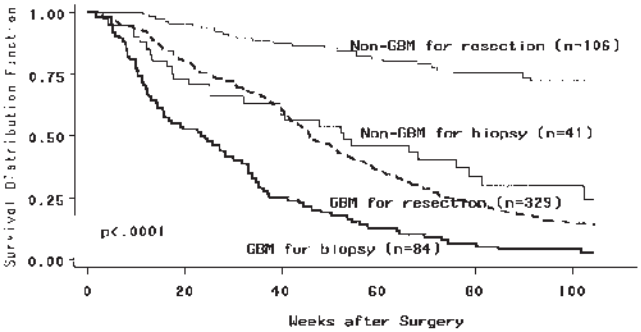

FIG. 1. Graph demonstrating differences in survival times among patients who underwent biopsy or resection for Grade III (non-GBM) gliomas or GBMs. In this and the other figures, probability values refer to differences within the same grade of tumor.

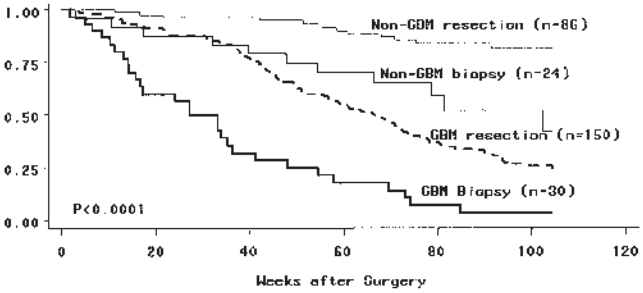

FIG. 2. Graph showing a comparison of survival times among patients 60 years of age or younger, who underwent biopsy or resection for Grade III gliomas or GBMs.

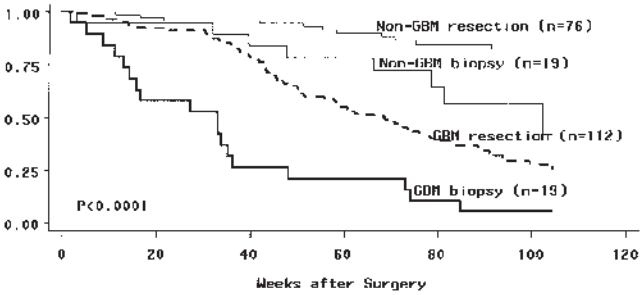

FIG. 4. Graph showing a comparison of survival times among patients 60 years of age or younger who had KPS scores of 70 or higher and underwent biopsy or resection for unifocal Grade III gliomas or GBMs.

biopsy and resection for patients within each tumor grade after adjusting for patient age, KPS score, presence of unifocal or multifocal disease, use of chemotherapy, and use of radiation therapy. The variables age younger than 60 years ($p < 0.0001$), KPS score greater than 70 ($p = 0.0003$), and use of chemotherapy ($p = 0.0158$) were important covariates, but a comparison of unifocal and multifocal diseases ($p = 0.2725$) and the use of radiation therapy ($p = 0.2668$) were not.

More patients who underwent biopsy in this study were considered to have negative risk factors (age $>$ 60 years, presence of multifocal tumors, and KPS score $<$ 70) than patients who underwent resection (Table 1). To demonstrate further that poorer outcomes in patients who underwent biopsy did not simply reflect their overall higher risk factors (in addition to the Cox proportional hazard model discussed earlier), we generated Kaplan–Meier survival curves for patients with GBMs and those with Grade III gliomas who underwent biopsy or resection, excluding patients older than 60 years (Fig. 2); patients older than 60 years and those with multifocal tumors (Fig. 3); and patients older than 60 years, those with multifocal tumors, and those with KPS scores lower than 70 (Fig. 4). Although the exclusion of these "poor-risk" patients decreased the numbers in each group, valid data were obtained. With each successive attempt to create a uniform comparison between "good-risk" patients in the two basic groups, there was a consistent survival advantage seen for patients who were undergoing resection rather than biopsy in both the GBM and Grade III glioma patient groups ($p < 0.0001$ in all cases).

The survival rates at 24 months were 58% for patients with Grade III gliomas and 11% for those with GBMs. Involvement in a clinical trial was reported by 14% of the patients overall.

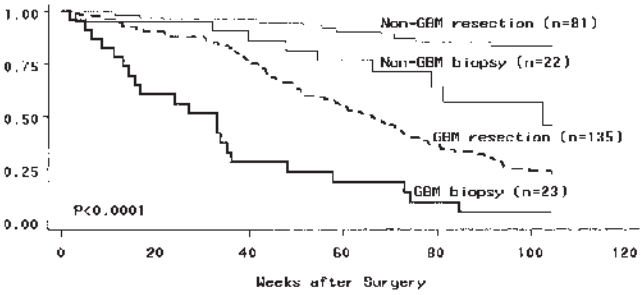

FIG. 3. Graph showing a comparison of survival times among patients 60 years of age or younger, who underwent biopsy or resection for unifocal Grade III gliomas or GBMs.

Discussion

Management of malignant gliomas usually consists of maximal safe resection followed by adjunctive therapies with radiation therapy and chemotherapy. Despite the fact that many clinical trials have been conducted to examine new treatments, interventions that have improved patient survival times have been limited. The GO Project was initiated to provide a prospective modern-era database on the treatment and outcomes of patients with malignant glioma who were cared for at academic or community institutions. We report survival data for patients who were enrolled with recently diagnosed malignant gliomas in the GO Project. Prognostic factors were examined, with particular emphasis on the role of resection as opposed to biopsy.

Advantages of the Study

The major advantage of this study is that it provides a contemporary benchmark analysis of patterns of care and outcomes for patients with malignant glioma. There was a broad-based accrual of a large number of patients with malignant gliomas, from both academic and private practices, and from many geographic areas of North America. Because of the time period covered, modern histopathological criteria were used for the diagnosis of the tumors. The participation of the Center for Outcomes Research at the University of Massachusetts Medical School, which produced consistent and comprehensive follow up on data derived from patients and caregivers, also conveyed a distinct advantage. This group provided skills, statistical analysis, and follow-up review that reflected its experience in outcome studies.

Disadvantages and Limitations of the Study

It is important to note that there were some inherent limitations to the study. The lack of a consistent confirmatory, central pathology review is a limitation. We know that significant discrepancies in opinion exist among pathologists with regard to the characterization and grading of malignant gliomas, and this is not taken into account in the study.[9] It must also be remembered that malignant gliomas have marked heterogeneity, even within a single tumor. Patho-

logical diagnoses of tissue samples obtained at biopsy (without attempted resection) may have underestimated tumor grade as a result of a sampling error.[17] On the other hand, data in this series do reflect standard practice patterns in North America, and the results may be more universally applicable as a result.

Although much of the analysis in this paper is focused on a comparison of resection and biopsy, there was no objective assessment of the actual extent of resection in the craniotomy cohort. Prior studies demonstrated that surgeons' estimates are often different from objective data provided by a careful review of immediate (24–72 hours) postoperative imaging studies.[7] Postoperative determination of the extent of resection or volumetric analyses of residual disease were not performed prospectively. We cannot, therefore, address the effect of the extent of resection on survival within the subgroup of patients who underwent craniotomy.

Although the follow-up survival data are excellent, the lack of complete follow-up data is a flaw for any outcome study. Furthermore, conclusions regarding younger patients or patients with Grade III tumors must be tempered by the fact that in the project the follow-up period lasted only up to 24 months. As a result, true median values of survival times may not have been reached for these patients. Despite these known limitations, it is encouraging that the demographic characteristics of the patient population, the nature of the therapies given, and the overall survival data are very similar to those reported in other published studies[1,10,13,18,20,21,32] (Table 6).

TABLE 6

Survival data in the present GO Project compared with those of other published reports

Authors & Year	Study Type	Pathology*	Extent of Resection	No. of Patients	Median Survival (wks)
Ammirati, et al., 1987	retrospective	III & IV	subtotal	12	90
			gross total	19	43
Winger, et al., 1989	retrospective	III & IV	biopsy	52	19
			subtotal	101	41
			subtotal + lobectomy	96	47
			gross total	36	76
Curran, et al., 1992†‡	retrospective	III	biopsy	31	72
			resection	72	196
Devaux, et al., 1993	retrospective	III	biopsy	37	94
		III	resection	13	98.3
		IV	biopsy	66	33
		IV	resection	49	50
Kreth, et al., 1993†	retrospective	IV	biopsy	58	32
			resection	57	39.5
Kiwit, et al., 1996	retrospective	III & IV	biopsy	40	26.3
			resection	40	41.7
Lacroix, et al., 2001	prospective	IV	<98%	219	40.4
			≥98%	197	52
present study (GO Project)	prospective	III	biopsy	41	52.1
		III	resection	106	87
		IV	biopsy	84	21
		IV	resection	329	45.3

* Grades of tumors based on the World Health Organization classification.

† Study did not show statistically significant improved survival following resection when compared with biopsy.

‡ This study failed to show a significant difference in survival between patients who underwent resection and those who underwent biopsy because resection was strongly associated with younger age. Only age proved to be a significant prognostic factor in the multivariate analysis performed in this study.

Survival Analysis

We report on the survival of patients with recently diagnosed malignant gliomas. On the basis of the data we suggest that the patient age and KPS score, as well as the histopathological grade of the tumor, are important prognostic factors for these patients. These factors have been reported previously.[5,15,21,25] Interestingly, although Grade III tumors are generally associated with a better prognosis than GBMs, this difference essentially disappeared in patients older than 60 years in this series (Table 5). This suggests either that the diagnosis of Grade III tumor may be the result of a sampling error or, more importantly, that Grade III tumors in an older host may behave just as aggressively as GBMs. Confirming age, KPS score, and histopathological grade of the tumor as strong prognostic variables in these new Class II data emphasizes the contention that these factors need to be clearly addressed during patient selection for clinical trials to enable an accurate interpretation. For large randomized trials, these factors should be stratified to ensure an appropriate balance between treatment arms.

It is evident that in any study of the effects of treatment on malignant gliomas, separate analyses must be performed for Grade III and Grade IV tumors/GBMs. Age stratification is essential because of the powerful impact a patient's age has on the length of survival for individuals with a tumor of any grade. Claims of improvement in the survival "tail" must be reconciled with the data presented in this report.

Biopsy Compared With Resection

In this series, patients who underwent biopsy had a worse survival outcome than patients who underwent resection via craniotomy. This is similar to the findings of several other published series[1,13,15,18,21,24,27,32] (Table 6). Not all authors of prior reports have been unanimous in their assessment of the value of resection compared with biopsy, however. For example, Kreth, et al.,[20] and Curran, et al.,[10] have suggested that survival is not statistically significantly improved in patients who have undergone resection. Interestingly, both of these studies did show a trend to improved survival with more aggressive resection. This was quite marked in Curran, et al., but "resection" was closely associated with "young age" in this study and only "age" was a significant prognostic factor in multivariate analysis. In any event, the prospective, rigorous, multiinstitutional nature and large enrollment of the present study make this new Class II evidence, which supports the prognostic significance of resection compared with biopsy, a benchmark for future studies.

In the present study, there were no criteria stated before surgery about the selection of surgical intervention. It is important to realize that this result does not confirm that aggressive resection will necessarily improve the prognosis for a given patient harboring a malignant glioma. This just means that, for whatever reason, in this study patients who underwent biopsy constitute a group with a different survival outcome from those patients who underwent craniotomy, and that this is another prognostic factor that may need to be stratified in the assessment of clinical trials.

There are specific reasons why patients are offered biop-

sy rather than resection. For example, a patient's medical status may preclude the use of a general anesthetic or a more aggressive surgical intervention. Although the individual's KPS score may capture this to some degree, it is not a particularly specific or sensitive surrogate for operative risk. A tumor's resectability is an obvious factor influencing surgical decision making. Patients harboring multifocal or bilateral tumors are more likely to undergo biopsy than resection (Table 1). The same is true for patients in whom tumors are located near eloquent areas of the brain. Therefore, unless a study addresses the selection of the surgical procedure systematically, regardless of whether resection is feasible, it is not possible to balance fully the important confounding factors regarding the extent of resection. To use an extreme example, it is not reasonable to discuss the value of the extent of resection in patients who are deemed ineligible for anything but a biopsy, nor is it appropriate to recommend biopsy for a resectable symptomatic tumor. These confounding factors can only be truly addressed in a randomized trial; however, the existing bias to offer radical resection for accessible lesions limits the feasibility of such a study.

One speculation is that tumor resectability may be a surrogate factor for tumor behavior. Molecular cytogenetic profiles may be different for multifocal, deep tumors located in eloquent areas of the brain, compared with those lesions located near the cortical surface in noneloquent areas. A better understanding of "gliomagenesis" and information about the origin of tumor development may shed light on this. The future availability of "tissue arrays" used to evaluate comprehensively molecular cytogenetic abnormalities in gliomas may help answer some of these questions, particularly if these methods can be combined with prospective tissue banking and clinical data collection.[23]

A corollary of the role of resection is the expansion of technological improvements permitting more radical resections of tumors previously considered inoperable. These include various forms of intraoperative monitoring, intraoperative imaging, diffusion tensor imaging techniques to localize subcortical motor pathways, methods of visualization of tumor, and confirmation of tumor resection at the time of surgery.[2–4,6,8,14,22,26,28–31] Prospective studies should be designed to ask and answer questions regarding the role of these adjunctive surgical technologies in the survival of patients undergoing resection for malignant glioma.

Conclusions

These carefully acquired and rigorously analyzed prospective data from a contemporary cohort demonstrate that patients with recently diagnosed malignant gliomas who undergo biopsy have a worse outcome than similar patients who undergo craniotomy for resection. This prognostic influence remains evident even when other known prognostic factors are considered in a multivariate analysis. We also confirmed the effect of known prognostic factors including the patient's age and KPS score, as well as the histopathological grade of the tumor. An accurate pathological diagnosis remains a major priority in the treatment of patients with malignant gliomas. The age of the patient is once again a paramount factor in determining outcome. For patients older than 60 years, there is very little difference in the length of survival between those patients with Grade III malignant gliomas and those with GBMs. Finally, survival data from this study provide a benchmark for future clinical trials focused on malignant glioma and for further sophistication in outcome studies directed toward patients with these tumors.

Disclosure

This study was supported by an unrestricted grant from Guilford Pharmaceuticals. 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 also is 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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