Does brain tumor histology influence cognitive function?

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This retrospective study investigated the relationship between tumor histology and postsurgical cognitive function in patients diagnosed with malignant brain tumors. The neuropsychological functioning of 24 adult patients diagnosed with glioblastoma multiforme (GBM) was compared with the neuropsychological functioning of 24 adult patients diagnosed with anaplastic astrocytoma (AA). The groups were matched with respect to patient age, gender, and education, as well as tumor location and tumor volume. The mean raw test scores of the AA patient group were superior to the mean scores of the GBM patient group on nearly all measures administered. However, significant performance differences were not detected for any of 5 neuropsychological domain scores (Intellectual, Language, Memory, Executive, and Motor Function). Analysis of covariance (ANCOVA) revealed that tumor histology was not a significant predictor of domain score after controlling for tumor volume. Multiple regression and correlation analyses supported the results of the ANCOVA by offering further evidence of weak relationships between tumor type, tumor volume, and neuropsychological test scores. We conclude that tumor histology is not clearly predictive of cognitive performance in adults with AA and GBM. *Neuro-Oncology 5, 255–260, 2003 (Posted to Neuro-Oncology [serial online], Doc 03-001, July 30, 2003. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152 8517 03 00001 2)*

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[2] Abbreviations used are as follows: AA, anaplastic astrocytoma; ANCOVA, analysis of covariance; GBM, glioblastoma multiforme; GTR, gross total resection.

Despite the many advances made in treatment modalities and surgical techniques, primary malignant brain cancer is a devastating illness, characterized by poor survival rates and significant morbidity as the disease progresses (Guthrie and Laws, 1994; Meyers and Kayl, 2002; Wrensch et al., 2002). For many patients, cognitive changes are part of the disease process, but the pattern of impairment can vary markedly in different patients. Although most researchers agree that the neuropsychological test performance of brain tumor patients is influenced by patient-related variables (i.e., age, education) and disease-related variables (i.e., tumor location, rate of growth, lesion size), the nature of the variable interactions has not been fully explicated.

The mechanisms through which brain tumors may compromise brain function are varied. For example, highly malignant tumors tend to grow more quickly than histologically lower grade types. As tumors grow, they tend to infiltrate and displace or "crowd" normal tissue, thereby disrupting brain function. Larger tumors or those that impinge on the ventricular system (directly or indirectly) may lead to increased intracranial pressure and a generalized decline in cognitive functioning. Tumors may also cause seizures, secrete hormones, alter endocrine patterns, or disrupt the afferent or efferent pathways between functional systems, causing cognitive dysfunction. In most instances, the likelihood of such occurrences increases as tumors grow larger.

In the limited studies available for review, tumor growth rate was a primary variable of interest and was often correlated with estimates of cognitive function in brain tumor patients (Fitzhugh et al., 1961, 1962; Keschner et al., 1936, 1938; Strauss and Keschner, 1935), as well as with prognosis. Research in this area offers general support for the belief that patients with the most rapidly appearing lesions tend to manifest relatively greater cognitive impairment (Anderson et al., 1990; Meyers et al., 1992). In one frequently cited study (Hom and Reitan, 1984), the profiles of patients with the highest grades

of malignant cerebral tumors (glioblastoma multiforme [GBM],[2] astrocytoma, grade III or IV, and metastatic carcinoma) demonstrated greater cognitive impairments than patients with more slowly growing tumors (astrocytoma, grade I or II, ependymoma, oligodendroglioma, or tuberculoma).

Although the results of the Hom and Reitan (1984) study are impressive and valuable, their study design had methodological shortcomings. For example, the study compared patients with rapidly and slowly growing tumors, but the inclusion criteria used for respective group membership were broad. Although the study included patients with several types of cerebral neoplasms, the differing pathologic characteristics of the tumors were not taken into consideration, and no attempt was made to match the age distributions of the 2 groups. Consequently, the median age of the rapidly growing tumor group was significantly greater than the group with slowly growing neoplasms. This difference alone could skew the results because patients in the rapidly growing tumor group could be expected to perform more poorly than individuals in the slowly growing tumor group on the basis of age alone (Byar et al., 1983; Levin et al., 1993). Finally, no estimates of tumor size (area) or volume were presented. In our clinical experience, patients with the most malignant tumors often present with larger lesions at diagnosis. Those larger lesions could be associated with more severe or more diffuse cognitive impairments.

In this study, a group of patients diagnosed with a GBM was compared with a group of patients with an anaplastic astrocytoma (AA) of comparable location and size. The groups were also equated on age, gender, and education since these variables are known to influence neuropsychological test results (Lezak, 1995). Prior studies of the neuropsychological correlates of the rate of growth of malignant brain tumors did not have a sufficient enrollment to permit this type of matched investigation.

Methods

Patients

In the last 20 years, more than 1500 patients have been referred for neuropsychological assessments at the University of Texas M.D. Anderson Cancer Center. For the majority of these patients, the neuropsychological assessment was completed as part of their standard, ongoing care for a brain tumor, and not for evaluation of a specific cognitive difficulty or complaint.

The individuals included in this study had a definite neurologic diagnosis of GBM or AA (based on tissue obtained during tumor resection). All subjects were right-handed individuals ranging in age from 25 to 52 who did not have a history of psychiatric disturbance, head trauma, or neurologic disease other than a single tumor. All study participants received a gross total resection (GTR) of their tumor, and all were evaluated with a comprehensive battery of neuropsychological tests prior to the initiation of radiation or chemotherapy.

Procedures

From a pool of cases with unilateral AA or GBM in the frontal, temporal, or parietal lobe, we attempted to "match" patients on selected anatomical and demographic variables. The variables of interest were tumor location (hemisphere and lobe), patient age at diagnosis, gender, and education. No formal matching procedures were employed. We simply attempted to form pairs of subjects who were comparable in terms of all variables except tumor histology. Matching across all of the selected factors proved quite difficult. However, we were able to compose 2 groups of subjects diagnosed with unilateral AA or GBM, in the frontal, temporal, or parietal lobe. Measurements of tumor volume were obtained by using the public domain program Image. A measure of total area of tumor involvement was obtained from preresection studies. To achieve the clearest differentiation between the neoplasm and associated edema, we used contrast-enhanced CT scans and gadolinium-enhanced T1-weighted MR images in this study. The measurements used considered only those areas clearly distinguishable as tumor. Surrounding areas of hypointensity, representing edema and infiltrating tumor, were not considered as definite boundaries, and it is likely that those areas retain some, if not all, normal functions.

The final sample included 48 patients. The histologic diagnoses were AA in 24 subjects (14 males and 10 females) and GBM in 24 subjects (15 males and 9 females). Demographic and clinical characteristics of subjects are summarized in Table 1. The GBM and AA groups were statistically equivalent with respect to mean patient age, education, and gender. Although the average volume of lesions in the GBM cases was smaller

Table 1. Demographic and clinical characteristics of patients (N = 48)

Characteristic	Patients No.	%	Median	Range
Age (years)			40	(25–52)
Education (years)			16	(10–20)
Sex				
Male	29	60		
Female	19	40		
Tumor Type				
AA	24	50		
GBM	24	50		
Side of Tumor				
Right	26	54		
Left	22	46		
Location of Tumor				
Frontal	18	37.5		
Temporal	18	37.5		
Parietal	12	25		
Tumor Volume (mm^3)				(303.6–101,240.0)
Surgery to Test Date Interval (days)	*		17	(7–89)

* Only 46 patients included. Two patients with AA were tested prior to resection.

Table 2. Subject characteristics by group

	AA Mean (SD)	GBM Mean (SD)	t_{46}	Significance
Age (years)	37.7 (6.7)	40.8 (6.2)	−1.6	NS
Education (years)	15.4 (2.8)	15.3 (2.0	0.17	NS
Tumor Volume (mm^3)	17,212.7 (19,833.8)	16,998.1 (9,448.8)	0.04	NS

Abbreviations: AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; NS, not significant.

than lesions in the AA group, this difference was statistically insignificant as well (Table 2). As evident in Table 3, the diagnostic groups were also evenly matched with respect to tumor location in 4 of the 6 possible locations (left frontal, left parietal, right temporal, and right parietal) and did not differ significantly in any of the remaining tumor locations ($\chi^2 = 0.9$, $P = 0.34$). The groups were composed without knowledge of the subject's test scores.

As previously noted, study participants had been evaluated with a comprehensive battery of neuropsychological tests representing measures of intellectual, memory, language, perceptual, motor, and executive functioning prior to the initiation of radiation or chemotherapy. We administered each test using standard procedures and instructions. During the evaluations, adjustments in test batteries were made according to the patient's level of cognitive and physical functioning. For this reason, data were not available for all subjects on all neuropsychological variables.

To facilitate statistical analyses and to allow graphic representations of results, the combined raw score distributions for the 2 diagnostic groups on each test were transformed into 2 Z-score distributions using relevant normative data. In some instances, age and education significantly affect cognitive test performance and must be taken into account with application of appropriate normative standards. One Z-score distribution consisted of the combination of the raw score performances of the GBM group. The other was composed of the combination of the raw score performances of the AA group.

To minimize the variable-to-subject ratio, we grouped individual tests into conceptualized domains including intelligence, memory, language, executive functioning, and motor skills (see Table 4), and domain scores (the average Z-score of selected tests) were calculated. Because of missing data values, not all subjects were included in each of the domain analyses. For most subjects, data from the Verbal and Nonverbal Selective Reminding Tests were used to obtain a Memory domain score. In the cases of 4 patients, data from the Hopkins Verbal Learning Test and the Benton Visual Retention Test were substituted.

Table 3. Frequency count of tumor diagnosis by location

Tumor Location	AA	GBM
Left frontal	4	4
Left temporal	5	3
Left parietal	3	3
Right frontal	4	6
Right temporal	5	5
Right parietal	3	3

Abbreviations: AA, anaplastic astrocytoma; GBM, glioblastoma multiforme.

Statistical Analyses

In the first stage of data analysis, the means and standard deviations of group performance on each neuropsychological measure and for each domain were calculated and

Table 4. Composition of cognitive domains

Domain	Measures	
Intellectual	WAIS-R subtests:	Information
		Digit Span
		Arithmetic
		Similarities
		Comprehension
		Block Design
		Digit Symbol
Memory	Buschke Selective Reminding (LTS measure)	
	Nonverbal Selective Reminding (LTS measure) or	
	Hopkins Verbal Learning Test (Total recall measure)	
	Benton Visual Retention Test (Correct reproductions)	
Executive	Booklet Category Test	
	Trail Making Test, Part A and B	
Language	Visual Naming	
	Controlled Oral Word Association	
	Token Test	
Motor	Right and Left Grip Strength	
	Right and Left Grooved Pegboard	

Abbreviation: LTS, long-term storage.

Table 5. Means and standard deviations of test performance by diagnostic group

Test	AA Mean (SD)	n	GBM Mean (SD)	n
WAIS-R:				
Information	10.2 (2.4)	23	10.9 (3.1)	21
Digit Span	10.0 (3.0)	24	9.7 (2.5)	24
Arithmetic	10.9 (2.7)	24	10.4 (2.9)	21
Similarities	10.1 (2.2)	24	9.4 (1.9)	23
Comprehension	10.4 (2.8)	21	9.5 (2.5)	18
Block Design	10.1 (2.7)	24	9.0 (2.7)	23
Digit Symbol	9.5 (2.8)	24	9.1 (2.4)	22
Buschke Verbal Selective Reminding (LTS)	90.4 (31.6)	19	75.2 (36.0)	19
Hopkins Verbal Learning (Recall)	19.3 (6.4)	3	19.0 (0.0)	3
Nonverbal Selective Reminding (LTS)	45.6 (15.0)	19	33.2 (12.5)	16*
Benton Visual Retention Test (Reproductions)	6.7 (2.6)	5	5.3 (2.5)	5
Trails, Part A†	30.6 (14.5)	24	47.0 (35.6)	22
Trails, Part B†	78.8 (40.9)	24	99.6 (50.5)	21
Visual Naming	55.0 (6.4)	23	54.1 (5.7)	24
COWA	35.7 (11.0)	24	32.7 (12.0)	23
Token Test	42.6 (3.2)	24	43.2 (0.9)	22
Category Test†	43.4 (28.3)	18	69.2 (26.1)	17*
Grip Strength, Right	36.8 (11.5)	21	37.4 (13.2)	23
Left	37.1 (11.7)	20	34.1 (12.3)	24
Pegboard, Right†	74.7 (16.0)	22	82.3 (47.4)	24
Left†	76.7 (15.2)	22	82.1 (23.5)	23

Abbreviations: AA, anaplastic astrocytoma; GBM, glioblastoma multiforme.

*Significant at $P < 0.05$.

†For these tests, lower numbers are superior scores.

compared (AA vs. GBM). In the second stage, an analysis of covariance (ANCOVA) was used to compare the domain scores of the 2 diagnostic groups after adjusting for the covariate (tumor volume). Next, a standard multiple regression analysis was performed. For that analysis, the independent variables (tumor volume, diagnostic group, patient age, and education) were entered into a model, and their effects on performance were evaluated. These models were applied to each of the five domain scores (Intellectual, Language, Memory, Executive, and Motor). In addition, a series of a posteriori analyses were completed to assess the effects and trends suggested by the ANCOVA and multiple regression analysis.

Results

Group Differences in Test Performance

Means and standard deviations of patients' performances on each neuropsychological measure (Table 5) and domain scores (Table 6) were calculated. For nearly all measures, the raw test scores of patients diagnosed with AA were superior to the raw scores of patients diagnosed with GBM. However, group performances were significantly different for only 2 measures: the long-term storage measure of the Nonverbal Selective Reminding Test ($t_{33} = 2.6$, $P = 0.01$) and the Booklet Category Test ($t_{33} = -2.7$, $P = 0.008$). In each of these cases, patients diagnosed with AA performed better than those diagnosed with GBM. The patient groups did not differ significantly for any of the 5 domain scores assessed.

Effect of Tumor Type, Volume, Patient Age, and Patient Education

An ANCOVA was carried out for each of the 5 domains to assess the significance of the effect of tumor type while controlling for variation in tumor volume. The results of this analysis were nonsignificant for the Intellectual ($P = 0.54$), Memory ($P = 0.08$), Executive ($P = 0.08$), Language ($P = 0.66$), and Motor ($P = 0.62$) domains.

A standard multiple regression analysis was performed, which examined the cumulative influence of

Table 6. Mean Z-scores of domains by diagnostic group

Domain	AA Z-score (SD)	n	GBM Z-score (SD)	n
Intellectual Domain	0.1 (0.6)	21	−0.005 (0.6)	18
Memory Domain	−0.7 (1.2)	20	−1.4 (1.2)	19
Executive Domain	−0.1 (1.4)	18	−1.0 (1.2)	17
Language Domain	0.1 (0.8)	23	0.6 (0.7)	22
Motor Domain	−0.5 (1.5)	20	−0.8 (2.4)	21

Abbreviations: AA, anaplastic astrocytoma; GBM, glioblastoma multiforme.

tumor volume, tumor type, age, and education on the domain scores. The results of the complete model as applied to the Executive, Language, and Motor domains were nonsignificant ($P > 0.05$). The results for the model as applied to the Intellectual and Memory domains were significant, with approximately 30% of performance variance accounted for by the model (Intellectual domain: F [4, 34] = 4.19, $P < 0.01$; Memory domain: F [4, 34] = 3.65, $P < 0.05$). Within the Memory domain, only the effect of age was significant (F [1, 34] = 9.8, $P < 0.01$). Within the Intellectual domain, the effect of education was the only significant predictor (F [1, 34] = 14.4, $P < 0.001$).

Pearson Correlations

For descriptive purposes, Pearson correlation coefficients were computed for test scores with age, education, and tumor volume. The correlations were evaluated at the 0.05 level and after Bonferroni adjustment. Age was found to be significantly correlated with variables related to memory and language function, specifically, the Digit Symbol subtest of the WAIS-R (r = -0.03, $P < 0.05$), the long-term storage measure of the Nonverbal Selective Reminding Test (r = -0.04, $P < 0.001$), COWA (r = -0.03, $P < 0.05$), and Token Test (r = -0.29, $P < 0.05$). Education was significantly correlated with measures of intellectual functioning, including the Information (r = 0.47, $P < 0.001$), Similarities (r = 0.32, $P < 0.05$), Comprehension (r = 0.43, $P < 0.005$) and Digit Symbol (r = 0.38, $P < 0.001$) subtests of the WAIS-R, as well as with grip strength of the right hand (r = 0.38, $P < 0.001$). Tumor volume was not significantly correlated with any of the 21 examined variables. Of note, none of the correlations were found to be significant following application of the Bonferroni adjustment.

Discussion

These results suggest that the postsurgical cognitive abilities of patients diagnosed with AA and GBM are not significantly different once tumor-related variables (location and size) and patient-related variables (age, gender, and education) have been taken into account. Although the mean scores of patients diagnosed with GBM revealed relatively greater impairment than the scores of patients diagnosed with AA, statistically significant group performance differences were found on only 2 of the measures. Statistical analyses failed to detect a significant effect of tumor histology or tumor volume on intellectual, memory, language, executive, or motor function. In fact, regression and correlation analyses suggest that patient age is of greater importance than tumor histology or tumor volume for determining neuropsychological test performance. Tumor volume was neither predictive of, nor reliably associated with cognitive performance in this patient sample. While these results affirm age as a marker for a worsened prognosis for the more advanced forms of anaplastic glioma, the statistically nonsignificant relationship of tumor volume to cognitive function was unexpected.

This study was not immune to methodological challenges. One concern was related to possible differences in the time between the completion of imaging procedures, surgery, and neuropsychological evaluation. Overall, the AA and GBM groups did not differ in the length of time transpiring between brain scans and surgery ($t_{46} = 0.15$, $P = 0.8$), the time between surgery and the completion of the neuropsychological evaluation ($t_{46} = -0.84$, $P = 0.4$), or the time between brain scans and the neuropsychological evaluation ($t_{46} = -0.64$, $P = 0.5$). However, the time periods between surgery and neuropsychological evaluation and between brain scanning and neuropsychological evaluation were slightly longer, on average, for patients diagnosed with GBM. Conversely, patients diagnosed with GBM underwent surgery slightly sooner following diagnostic imaging. For most patients, the neuropsychological evaluation was obtained approximately 1 month following the date the brain scans were obtained, with surgery occurring between these events. Two patients with AA (initially diagnosed via biopsy, confirmed on resection) were tested prior to surgical resection of the tumor. Although we interpreted neuropsychological results as a measure of impairment related to the size of the tumor, the effects of surgery have to be considered. As previously noted, no patient had received radiotherapy or chemotherapy before completing the neuropsychological assessment.

The patients involved in this study underwent gross total resection of their tumors. Although there are differences in the excised margins of the tumor depending on its location, these differences should be evenly distributed between the AA and GBM groups as a result of our equating procedure. The average 2-week period between surgery and neuropsychological evaluation should also minimize the possibility of recurrent tumor accounting for significant cognitive impairment.

Although research has shown that the adverse effects of brain injury on behavior tend to increase with age, this is not a simple linear relationship (Lezak, 1995). Whether age is a significant variable depends on other issues, including the breadth of the age intervals and the overall age range under study. The significance of age may also be affected by the nature and severity of the lesion. Given the relatively narrow age range of the sample in this study, it seems likely that age does significantly impact the severity of damage in patients diagnosed with brain tumors. At the same time, given the size and the narrow age range of the sample, we cannot discount the possible effects of diagnosis and tumor volume on the severity of deficits in a more general population followed over an extended period of time.

These findings stand in sharp contrast to what, in our opinion, is a commonly held belief among practitioners of neuro-oncology and many other professionals who work with patients diagnosed with brain tumors. Namely, patients with more malignant, rapidly growing disease tend to suffer greater cognitive impairment than do patients with a more slowly developing process. Once again, in this limited sample, postsurgical cognitive status is quite similar for patients with 2 different types of

malignant disease. Had our subject group included a comparison of low-grade tumors, perhaps some differences would have been evident. Unfortunately, as the disease progresses and the potentially detrimental effects of treatment mount, the majority of patients will experience some decline in cognitive status. However, with careful monitoring of the patient's cognitive status, responsiveness to the family's observations, and the timely implementation of appropriate therapy (including compensatory strategy training; physical, speech, or occupational therapy; stimulant therapy), quality of life may be optimized.

In summary, in this sample of young, well-educated individuals, age appeared to have a greater influence on neuropsychological test results than either tumor histology or tumor volume. In effect, there was no need to statistically control for tumor volume in this study, since the variable's effect on test performance was minimal to begin with. The implication of this finding is dramatic. If tumor volume is not associated with neuropsychological test scores, as these results indicate, there is little justification for the inclusion of volumetric measurements in future research examining the influence of disease-related factors on cognitive test performance. It will be important to confirm this finding in additional studies incorporating different histologic groups; through grouped analyses of the performances of subjects with small, medium, or large lesions; and across a wider age range. For now, however, volumetric measurements will continue to be valuable and necessary resources in the evaluation of treatment response and the continued monitoring of patients with stable disease.

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