*Journal of Neuro-Oncology* **67:** 245–253, 2004.


*Clinical Study*

# Prediction of neurocognitive outcome in adult brain tumor patients

Thomas A. Kaleita[1], David K. Wellisch[1], Timothy F. Cloughesy[2], Judith M. Ford[3], Donald Freeman[1], Thomas R. Belin[1,4] and Jeffrey Goldman
[1]*Department of Psychiatry,* [2]*Department of Neurology,* [3]*Department of Radiation Oncology, the UCLA Neuro-Oncology Program and the Henry E. Singleton Brain Cancer Research Program, David Geffen School of Medicine at UCLA;* [4]*Department of Biostatistics, the UCLA School of Public Health, Los Angeles, CA, USA*

*Key words:* attention functional index, brain tumor, cognitive functioning, glioblastoma multiforme, neurocognitive outcomes

## Summary

*Purpose:* To determine the relative contributions of patient, disease and therapy specific factors on neurocognitive outcome of brain tumor patients.

*Patients and methods:* Seventy-nine patients (mean age = 41.1 years; range: 17–75 years; 54% male, 46% female) with glioblastoma multiforme (37%), anaplastic astrocytoma (17%), low grade astrocytoma (13%), and oligodendroglioma (10%) predominantly in the frontal regions (45%) were evaluated in an outpatient neuro-oncology clinic. A neuropsychological test battery emphasized elements of attention/concentration. Multiple regression analyses determined relationships between functional outcomes and demographic and clinical predictors.

*Results:* Key predictors of neurocognitive functioning included age of the patient (36–59 years, $p < 0.01$; $\geq$60 years, $p < 0.05$) and frontal region tumor location ($p < 0.01$). As expected, older patients did not perform as well as younger patients in absolute terms on neuropsychological tests; decrements persisted when comparisons were based on age-standardized versions of neurocognitive outcomes. Major depressive disorder was marginally associated with outcomes, while surgical interventions and radiotherapy did not show strong associations with test performances.

*Conclusions:* Primary malignant brain disease was found to be less negative on neurocognitive outcomes for younger than for either middle-aged or older patients. Treatments were not as predictive of neurocognitive outcomes as age. No single test outcome measure was as sensitive to neurocognitive status as the empirically derived index of attention and concentration.

## Introduction

The prediction of neurocognitive outcome in adult brain tumor patients is influenced by a host of factors involving disease types, various treatments, and characteristics of the patients themselves. Regarding disease types, it has been shown that highly malignant tumors (grades III and IV) produce greater neurocognitive deficits than those of lesser grade (grades I and II) [1]. In contrast, other investigators have found no differences in neurocognitive outcome based on tumor grade, and have shown that these differences are based on therapy factors and tumor lateralization [2]. The few systematic studies of the neurocognitive effects of primary brain tumors in adults support the interpretation that both focal and diffuse neurocognitive impairments may result [3].

Of particular concern are the effects of various treatments for brain tumors on neurocognitive functioning. Radiation therapy has been associated with deficits due to variables such as total dose of radiation, volume irradiated, and the fractionation of individual doses [4–6]. Most studies of these effects have been performed with children receiving whole brain radiotherapy in the treatment of acute leukemia [7] or medulloblastoma [8]. Far less is known about partial-brain irradiation effects on both children and adults. Many of the neurocognitive outcome studies

of adult brain tumor patients have limitations due to small sample sizes [9–11], use of measures that were not sensitive to impairment [12,13] and/or considerable heterogeneity in terms of pathology [14] and tumor locations [15]. A study of 245 patients found that the effects of surgical interventions are more prominent than the effects of tumor grade on neurocognitive functioning [2]. A recently published longitudinal study involving patients receiving radiotherapy concluded that cognitive deficits were associated with tumor and surgical procedures [16]. Most studies, however, have not attempted to determine the relative effects from the various treatments on neurocognitive outcome [17]. Patient-specific factors which predict neurocognitive outcome have been largely identified using overall performance status, age, and psychological status (especially level of depression) [18,19].

The present study was initiated with the aim of differentiating the contributions of patient, disease, and therapy specific factors on neurocognitive outcome. Three major working hypotheses to evaluate and clarify these issues in terms of their contributions to neurocognitive status were established. They include: (1) treatment variables (i.e., radiation and/or craniotomy) will be major (independent variable) predictors of neurocognitive outcome; (2) major depressive disorder (MDD) will be a major (independent variable) predictor of neurocognitive outcome; and (3) given the sample characteristics predominately involving patients with frontal region tumors, the Trail Making B test, which emphasizes cognitive flexibility plus perceptual motor functioning under time pressure, will be the most sensitive measure (in the test battery) of neurocognitive outcome.

## Methods

### *Patients*

Patients for this study were in treatment for a primary malignant brain disease in the UCLA Neuro-Oncology Program (NOP). This study included 79 consecutively referred patients to the neuropsychologist and the psychiatrist on the NOP team in 1998. Referrals were made as part of the multidisciplinary model of the clinic and were not made because of a special need for neuropsychological assessment or psychiatric evaluation and care. Mean age of the patient group was 41.1 years at the time of examination with a range of 17–75 years. The patient/gender ratio compared closely to the NOP matrix (i.e., Study males 54.4% vs. NOP males 54%). In terms of education levels, 33.3% had high school or less education; 48.5% had some college or a baccalaureate degree, and 18.2% had post-graduate education and/or training. Most of the patients were not employed (56%) at the time of interview and testing, while the remainder were employed full-time (27.3%), or part-time (17%). The majority of the patients (61%) were married/cohabitating, while the remainder were never married, separated/divorced, or widowed. Range of Karnofsky performance scale (KPS) [20] ratings were 40–100%. Breakdowns showed 28.2%, with KPS = 100; 33.3%, with KPS = 90; 23.1%, with KPS = 80; and 15.4%, with KPS of 70 or less.

### *Diseases and treatments*

Table 1 shows the frequencies of tumor locations (A) and pathology types (B). The greatest number of

*Table 1A*. Tumor locations

| Location | Left (*N*) (%) | Right (*N*) (%) | Total (*N*) (%) |
|---|---|---|---|
| Frontal | 20 (25.3) | 16 (20.2) | 36 (45.5) |
| Temporal | 8 (10.1) | 7 ( 8.9) | 15 (19.0) |
| Parietal | 4 (5.1) | 6 (7.6) | 10 (12.7) |
| Occipital | 0 | 4 (5.1) | 4 (5.1) |
| Brain stem | | | 5 (6.2) |
| Cerebellum | | | 4 (5.1) |
| Pineal region | | | 2 (2.5) |
| Spinal cord | | | 1 (1.3) |
| Thalamus | | | 1 (1.3) |
| Corpus callosum | | | 1 (1.3) |

*Table 1B*. Tumor pathology

| Pathology | Total (%) |
|---|---|
| Glioblastoma multiforme | 37.2 |
| Anaplastic astrocytoma | 16.7 |
| Low grade astrocytoma | 12.7 |
| Low grade oligodendroglioma | 10.1 |
| Anaplastic mixed glioma | 5.1 |
| Meningioma | 3.8 |
| Low grade mixed oligoastrocytoma | 2.6 |
| Anaplastic oligodendroglioma | 1.3 |
| Pilocytic astrocytoma | 1.3 |
| Cyst aspiration | 1.3 |
| Ependymoma | 1.3 |
| Germinoma | 1.3 |
| Hemangiopericytoma | 1.3 |
| Lymphoma | 1.3 |
| Medulloblastoma | 1.3 |
| Pineoblastoma | 1.3 |

patients in the study matrix had frontal region tumors (45.5%). The most frequently occurring pathologies were glioblastoma multiforme (GBM) (37.2%), anaplastic astrocytoma (16.7%), low grade astrocytoma (12.7%), and oligodendroglioma (10.1%). Tumor locations and pathology were compared to the population matrix of the NOP. The study sample compares closely with the clinic population on tumor locations (Study 45.5% frontal lobe tumors vs. 42% for the NOP) and on pathology type (Study, 37.2% GBM vs. 38% NOP). The patients in this study matrix had received multiple and varied treatments, including neurosurgical debulking (65.8%), radiotherapy (75.3%), and previous or current chemotherapy (51%). In addition, the diagnosis of MDD was determined by the NOP team psychiatrist, using the Diagnostic and Statistical Manual of Mental Disorders IV Edition (DSM-IV) criteria [21].

*Measures and procedures*

Patients were evaluated using a brief neuropsychological screening battery, emphasizing assessment of attentional processes, and a structured psychiatric interview incorporating DSM-IV criteria. For the purposes of this report, only the neuropsychological data will be presented. A previous publication reported the DSM-IV criteria and diagnostic findings [22]. The frequency of MDD was calculated as 27.8% in this population.

Attention is the main building block for complex forms of neurocognitive ability [23]. Difficulties in higher order processing (e.g., memory, reasoning, etc.) due to malignant disease and various treatments have been associated with an underlying defect in the ability to sustain attention [24,25]. The neuropsychological screening battery was, therefore, composed of standardized instruments requiring various elements of attention/concentration for successful completion. For the purposes of this study, five separate outcome measures were defined from these three instruments, as they have other inherent components (e.g., immediate memory, mental processing speed, and visual-motor coordination) to assess cognitive processes known to be affected by malignant disease and CNS treatments [26]. The standardized tests and the range of cognitive abilities measured by each of them, other than attention, are elaborated in Table 2. They were chosen from the many available measures using the following criteria: (1) brevity and ease of administration in the clinic setting of the NOP, and repeated administrations without significant practice effects; (2) availability of objective scoring criteria; (3) availability of normative standards across the broad age range of the patients in this study, and age stratification of normative data; (4) demonstrated practicality in terms of cost and burden for the patient; (5) demonstrated reliability and validity in clinical research.

*Table 2*. Neuropsychological tests and cognitive abilities measured

| Name of test | Cognitive abilities |
|---|---|
| Trail Making A | Visual/perceptual sequencing, visual motor speed |
| Trail Making B | Cognitive/perceptual set switching, visual/perceptual sequencing, visual motor speed |
| SDM Oral response mode | Visual perception, symbolic processing speed, oro-motor speed |
| SDM Written response mode | Visual perception, symbolic processing speed, fine motor speed |
| Digit Span Sub-Test (From Wechsler Adult Intelligence Scale – III) | Immediate memory for numbers, forward and backward |

The neuropsychological screening battery was administered in the following fashion. For each of the 79 patients, a referral was made to the neuropsychologist during a routine medical appointment in the clinic. A short interview was performed to document each patient's concerns about cognitive functions and to obtain a brief disease and treatment history. Information about education and occupation for each patient was obtained. The neurocognitive tests were administered in the same sequence for each of the 79 patients: Trail Making Forms A and B [27], Digit Span [28], and the Symbol Digit Modalities (SDM) test [29].

Trail Making A measures a person's ability to sequence circled numbers from 1 to 24 by connecting the circles with a pencil. This task relies on attention, visual perception, and visual motor speed for successful completion, as the circled numbers are randomly positioned on an 8.5" $\times$ 11" form. Trail Making B depends on shifting of cognitive/perceptual sets (i.e., numbers and letters) as well as the demand characteristics of Trail Making A. The classic Digit Span relies on a person's ability to repeat sets of numbers of increasing length both forwards and backwards. As such, it is considered a measure of both working memory and attention/concentration. The oral and written portions of the SDM test assess expression by subjects when they are presented with tasks requiring

encoding/decoding visual processing of nine separate geometric form/number combinations in 90-sec time limits. This test depends on visual perception, visual perceptual speed, oral and manual expression, and processing of symbols, some of which are unfamiliar and, therefore, meaningless to the individual taking the test. An attempt was made to administer each test to every patient. In spite of this systematic intention, some patients in the study matrix were too ill or too disabled to perform one or more tests. Of the 79 patients in the study matrix, 15 did not complete at least one test. The reasons for inability to fully complete the test battery involved six conditions. These included: (1) visual field loss ($N = 8$); (2) weakness in dominant hand ($N = 1$); (3) psychiatric factors affecting test performance ($N = 2$); (4) insufficient fluency in English ($N = 1$); (5) nausea and vomiting ($N = 1$); and (6) severe manual and/or expressive language abnormalities ($N = 2$).

*Statistical analyses*

Beyond our descriptive summaries for this unique sample, analyses focused on relating functional outcomes to demographic and clinical predictors (see Table 3). Our initial reports summarize analyses of the raw scores from Trail Making A, Trail Making B, SDM Oral, SDM Written, and Digit Span tests. We also analyzed age-standardized versions of functional outcome assessments, namely Trail Making A percentile category (with scores of 1, 2, 3, 4, 5, 6 corresponding to percentile categories 0–10, 10–25, 25–50, 50–75, 75–90, 90–100); Trail Making B percentile category (scored the same way), SDM Oral Standard Score; SDM Written Standard Score; and Digit Span Standard Score. Predictor variables included yes–no indicators for craniotomy, radiation treatment, frontal region tumor location, GBM pathology, age 36–59 years (vs. 35 and under), age 60+ years (vs. 35 and under), and diagnosis of Major Depression.

*Table 3*. Independent variable definitions

| Independent variable | 0 | 1 |
|---|---|---|
| Craniotomy | No | Yes |
| Radiation | No | Yes |
| Frontal lobe tumor | All other regions | Frontal lobe tumor |
| Glioblastoma multiforme (GBM) | All other tumor pathologies | GBM pathology |
| At time of examination | | |
| Age 36–59 (vs. age ≤35) | No | Yes |
| Age 60+ years (vs. age ≤35) | No | Yes |
| Major depressive disorder (MDD) | All other DSM-IV diagnoses | MDD DSM-IV diagnoses |

The choice of age categories was motivated by the desire to allow for possible non-linear effects of age and by the desire to define groups of patients with broadly similar health profiles. The resulting categories featured 27 subjects aged 35 or under (34%), 44 subjects aged 36–59 (56%), and 8 subjects aged 60 or order (10%). To understand patterns of differences across age groups, we followed our regression analyses with one-way analysis of variance across age groups using Duncan's multiple-range test to address multiple-comparison concerns.

The individual functional outcomes were combined into an 'Attention Functional Index' (AFI) that was used as a composite outcome variable. We sought to summarize the information on a scale that could be interpreted as a standard score, thus capturing departures from population norms with negative values reflecting less-than-average performance. Specifically, we averaged (Trail Making A percentile category – 3.5), Trail Making B percentile category – 3.5), the SDM Oral Standard Score, the SDM Written Standard Score, and Digit Span Standard Score. The last variable reflected a population mean of 10 and standard deviation of 3; the subtraction of 3.5 from the Trail Making percentile category scores gave the resulting scales a range of $-2.5$ to $+2.5$ with a mean of 0 as a population norm.

Relationships among outcome and predictor variables were then explored in multiple linear regression analyses. The analyses were started with models that included all the above-mentioned predictors, which form the basis for the detailed results reported. To assess whether the importance of individual predictors might have been shrouded due to confounding with other predictors, a stepwise procedure was carried out with alpha $= 0.10$ used as a criterion for a predictor to enter. Except where noted, the results were qualitatively similar.

In addition to treating the AFI as an outcome in regression analyses, the correlation between the AFI and the KPS was investigated. Based on previous studies which empirically derived constructs of neurocognitive outcome [30], Cronbach's alpha and item-total correlations were calculated to determine the internal consistency of the AFI component

variables to summarize a broad construct of attention/concentration. Relationships between the AFI and KPS were determined in two ways. First, the actual KPS scores were correlated with each patient's AFI. Second, the categorical version of each patient's KPS score (KPS categories (CAT) = 100–90, 90–80, 80–70, scores less than 70 all coded to 70) was correlated with the patient's AFI.

## Results

Table 4 shows means, standard deviations, percentiles, and ranges of standard scores for each of the dependent test variables and the AFI. In Table 4, for all the dependent variables, mean scores are somewhat to moderately below average for standard scores (i.e., 0.00). Patients obtained the highest scores on the Digit Span test. In contrast, patients obtained a substantially lower mean score on Trail Making A, and an even lower score on Trail Making B. Lowest for the five individual tests were the mean scores on the oral and written portions of the SDM. The mean score for AFI, a composite of the five individual tests, was also substantially below the average for standard score units. The AFI reflected the smallest standard deviation of the six dependent measures, thus indicating a smaller dispersion of patient scores around the mean.

Table 5 shows a series of multiple regressions predicting the raw scores (i.e., without age-standardization) of the neurocognitive outcomes. Craniotomy showed only a borderline significant difference in predicting the SDM Oral score, while radiation therapy showed no indication of being a significant predictor of neurocognitive outcomes. Frontal region location of the tumor was associated with significantly faster times on the Trail Making A test, and while not significant, the direction of the effect on the Trail Making B test was the same. Borderline significant differences on the SDM Oral and Written tests associated with frontal region location of the tumor were also in the direction of better scores. In contrast, patients with GBM scored less well on these same measures, with significant differences on the Trail Making A and SDM Oral tests and borderline significant differences on the Trail Making B and SDM Written tests. A diagnosis of Major Depression was not associated with significant differences in test performance, although

*Table 4*. Descriptive statistics of the dependent variables

| Dependent variable (test) | *N* | Percentile | SD | Standard score | | |
|---|---|---|---|---|---|---|
| | | | | Minimum | Maximum | Mean |
| Trail Making A | 79 | 27 | 1.481 | −2.500 | 1.500 | −0.601 |
| Trail Making B | 78 | 16 | 1.475 | −2.500 | 1.500 | −0.987 |
| SDM Oral score | 79 | 7 | 1.339 | −3.880 | 2.160 | −1.487 |
| SDM Written score | 79 | 8 | 1.316 | −3.730 | 1.560 | −1.385 |
| Digit Span | 79 | 35 | 1.278 | −2.333 | 2.000 | −0.376 |
| Attention functional index | 78 | 17 | 1.186 | −2.667 | 1.300 | −0.952 |

*Table 5*. Multiple regressions predicting neurocognitive outcomes before age-standardization

| Independent variables | Dependent variables | | | | |
|---|---|---|---|---|---|
| | Trail Making A | Trail Making B | SDM Oral | SDM Written | Digit Span raw score |
| Intercept | 26.666$^{***}$ | 90.899$^{***}$ | 63.465$^{***}$ | 56.537$^{***}$ | 18.209$^{***}$ |
| Craniotomy | 1.533 | 5.557 | −6.576$^{++}$ | −3.970 | −1.096 |
| Radiation | 0.183 | −23.590 | −2.361 | −4.403 | −0.096 |
| Frontal | −14.913$^{**}$ | −15.836 | 5.807$^{+}$ | 5.656$^{++}$ | 1.736 |
| GBM | 17.213$^{**}$ | 21.954$^{+}$ | −7.004$^{*}$ | −5.288$^{++}$ | 0.301 |
| Age: 36–59 vs. ≤35 | 18.684$^{***}$ | 45.413$^{***}$ | −9.037$^{*}$ | −7.627$^{*}$ | −2.740$^{*}$ |
| Age: ≥60 vs. ≤35 | 45.049$^{***}$ | 133.473$^{***}$ | −25.590$^{***}$ | −18.911$^{***}$ | −7.034$^{**}$ |
| MDD | 4.306 | 2.837 | −4.042 | −3.666 | −1.138 |

$^{+} = p < 0.20$, $^{++} = p < 0.10$, $^{*} = p < 0.05$, $^{**} = p < 0.01$, $^{***} = p < 0.001$.
GBM: Glioblastoma multiforme, MDD: Major depressive disorder, SDM: Symbol digit modalities.

all the coefficients of Major Depression were in the direction of poorer test performance. Table 5 further shows that the strongest predictors of performance on each test were the indicators of age category. As expected, the oldest patients demonstrated the poorest test performance.

In Table 6, we elaborate on which pairs of age groups emerge as significantly different from one another in one-way analysis of variance using Duncan's multiple-range test to address multiple-comparisons concerns. Differences emerge in almost all cases (except for the SDM Written $Z$-score) between the age $\geq$60 group and the age $\leq$35 group. For Table 6, differences between the age group $\geq$60 and the age group 36–59 were not as frequent.

*Table 6*. Pairwise significant differences across age groups using Duncan multiple-range test in one-way analysis of variance

| Outcome | Pairs of age groups between which significant differences were found[a] |
|---|---|
| Trail Making A raw score | (1,2) (1,3) (2,3) |
| Trail Making A percentile group | (1,2) (1,3) |
| Trail Making B raw score | (1,2) (1,3) (2,3) |
| Trail Making B percentile group | (1,2) (1,3) |
| SDM Oral raw score | (1,3) (2,3) |
| SDM Oral $Z$-score | (1,3) |
| SDM Written raw score | (1,3) (2,3) |
| SDM Written $Z$-score | None |
| Digit Span raw score | (1,3) (2,3) |
| Digit Span standard score | (1,3) (2,3) |
| Attention functional index | (1,2) (1,3) |

[a]Age group 1: Age $\leq$35, Age group 2: Age 36–59, Age group 3: Age $\geq$60.
SDM: Symbol digit modalities.

In Table 7, we present multiple regression analyses predicting the AFI and its five component measures, namely the age-standardized versions of the neurocognitive outcomes. Frontal region tumor location emerges as an important predictor across the various outcomes, as again do the age predictors. However, after age-standardization of test results, the performances of the oldest age group are more similar to those of the 36–59 age group, meaning that the oldest subjects perform more poorly on tests, yet not much worse than expected for their age compared to the 36–59 year old group.

Regarding internal consistency, Cronbach's alpha for the five individual tests ranged from 0.87 to 0.92, with item-total coefficients between 0.62 and 0.87. In the 77 patients where both were available, the correlation between the AFI and KPS scores was $r = 0.61$ ($p < 0.0001$ for testing the null hypothesis of zero correlation); the correlation between the AFI and category scores was $r = 0.63$ ($p < 0.0001$).

## Discussion

The present study of neurocognitive functioning in adult brain tumor patients is an important reminder of why it is essential to test one's clinical assumptions in a data-based approach. For the three working hypotheses, the investigators' clinical assumptions were incorrect when viewed in the context of the actual study results. We expected that treatment effects (i.e., craniotomy and radiotherapy) would be robust and definitive predictors of neurocognitive functioning. Also, we expected that the existence of MDD

*Table 7*. Multiple regressions predicting AFI and its age-standardized components

| Independent variables | Dependent variables | | | | | |
|---|---|---|---|---|---|---|
| | Percentile category | | $Z$ | | Digit Span standard | AFI |
| | Trail Making A | Trail Making B | SDM Oral | SDM Written | | |
| Intercept | 3.932$^{***}$ | 3.170$^{***}$ | −0.367 | −0.318 | 0.287 | −0.062 |
| Craniotomy | −0.245 | −0.198 | −0.453$^{+}$ | −0.409 | −0.249 | −0.343 |
| Radiation | 0.103 | 0.370 | −0.124 | −0.320 | 0.033 | 0.032 |
| Frontal | 1.005$^{**}$ | 0.634$^{++}$ | 0.787$^{*}$ | 0.960$^{**}$ | 0.609$^{++}$ | 0.788$^{**}$ |
| GBM | −0.812$^{*}$ | −0.369 | −0.573$^{++}$ | −0.512$^{+}$ | 0.283 | −0.409$^{+}$ |
| Age: 36–59 vs. $\leq$35 | −1.174$^{***}$ | −1.153$^{**}$ | −0.803$^{**}$ | −0.658$^{*}$ | −0.745$^{*}$ | −0.876$^{**}$ |
| Age: $\geq$60 vs. $\leq$35 | −0.893$^{+}$ | −1.382$^{*}$ | −1.014$^{++}$ | −0.528 | −1.810$^{***}$ | −1.107$^{*}$ |
| MDD | −0.563$^{+}$ | −0.292 | −0.442$^{+}$ | −0.476$^{+}$ | −0.642$^{*}$ | −0.445$^{+}$ |

$^{+} = p < 0.20$, $^{++} = p < 0.10$, $^{*} = p < 0.05$, $^{**} = p < 0.01$, $^{***} = p < 0.001$.
GBM: Glioblastoma multiforme, MDD: Major depressive disorder, SDM: Symbol digit modalities; AFI: Attention functional index.

would be closely associated with neurocognitive functioning. Finally, we hypothesized that a single test measure would be most indicative of neurocognitive functional status, based on the characteristics of our study sample. In fact, none of these predictions were proven correct. Data analyses found either no relationship or only a modest relationship between the medical treatment variables, Major Depression, and neurocognitive functioning. Far more important to neurocognitive functioning were the indicators of tumor location and patient age at the time of examination.

One of the most important findings of the present study was the relationship of patient's age with neurocognitive functioning. It was generally evident that older patients performed less well than younger patients. This comes as little surprise. Of greater concern, and therefore clinical relevance was the performance of the group aged 35–59 years old. Their test performances were more similar to those of the oldest group ($\geq$60 years) than that of the youngest group ($\leq$35 years). Thus, it appeared that the impact of this catastrophic illness can have nearly as much of a negative neurocognitive effect on this middle group as for the eldest group. These findings, therefore, may be important in issues such as future treatment planning and return to work considerations for this middle group. The theme for this middle group, as reflected by their neurocognitive performances, is 'younger is older.'

In addition, frontal region tumor location was found to be a significant predictor of neurocognitive functioning with or without age-standardization of test performances. In fact, frontal tumor location was associated with better neurocognitive outcomes than the aggregate of all other locations in our patient sample. This finding would appear counter intuitive, as attentional processes are usually thought to be frontal functions. However, brain tumors often impact regions with brain stem reticular activating system pathways not directly infiltrated or displaced by disease. Also, for some individuals with non-dominant hemisphere frontal lesions, neurocognitive functions, including attention may be relatively spared due to the circumscribed nature of the tumor and/or to increasingly precise treatments made possible by modern imaging methods.

Major depressive disorder was the focus of the first manuscript in this study. As a diagnostic entity, it was found to be present in 28% of the study sample. However, in the present data analyses focusing on mediators and moderators of the AFI, it contributed far less predictive value than anatomical location of tumor and patient age. It remains important as a potential avenue for intervention even though it had a less decisive impact on neurocognitive status. In other words, it is possible to change depression 'status', but it is not possible to change tumor location or the age of the patient.

In a similar vein we considered time after treatments as a potentially important contributor to neurocognitive outcomes. Review of the data indicated, however, that numerous patients had such varied and multiple sequences of treatments over time so as to make this approach infeasible. We did attempt to enter time since diagnosis as an independent variable in the regression. When included, this variable did not account for sufficient variance to enter the equation. Therefore this variable does not appear in the final overall analyses of the study.

Table 4 reflects relatively poor neurocognitive status of our patients in a direct sense. Perhaps the most important data in this descriptive table are the means (which are expressed in terms of standard scores) and percentiles for each of the six outcome measures. It is important to note here for the reader that each one of the five standardized tests are based on a 'normal' curve of performances, and hence, the percentile represents where our patients fell on the normal curve of functioning for each test.

In regard to the idea that one test measure would emerge as the 'divining rod' of neurocognitive status, this was simply not evident in the eventual study results. The results of this study reaffirm the importance of a test battery which measures a set of neurocognitive abilities in an adult brain tumor patient population. In short, no one test was dynamic enough to carry the day. Of potential usefulness in future studies is the AFI, an empirically derived construct involving attention, which was calculated from the five individual outcome measures. The use of the AFI in a multidimensional approach to assessing Quality of Life in brain tumor patients would add an important cognitive perspective that does not exist in the traditional functional instruments, such as the KPS [31].

The development of the AFI started with the recognition of attention as the fundamental 'building block' of cognition [23]. In addition, attention has been found to be the cognitive variable most likely to be affected by malignant disease and treatments which affect the brain [24,25]. However, attention is not the only cognitive ability affected by these factors. Also important are functions such as memory and psycho-motor speed. The AFI was constructed as a measure of the dynamic

balance of these cognitive functions. Two basic operations were performed in its developmental process. First was calculation of Cronbach's alpha to determine the internal consistency among the individual cognitive outcome measures. Then item–item correlations were determined as a secondary measure of internal consistency. From these operations emerged a component scale which blended these cognitive functions, namely the AFI. An example of a widely known parallel concept is I.Q., which is a unifying concept, also having components but which assumes a conceptual status beyond the sum of its individual components. Such is our concept of the AFI.

The obvious caveats in this study are the cross-sectional nature of the data and the considerable heterogeneity in this brain tumor patient population in terms of disease location, pathology, and treatments. It is well known that there is a dynamic ebb and flow of cognitive status in brain tumor patients during and after treatments. The cross-sectional nature of this data analysis is limited by the lack of replication that in a longitudinal design might be able to estimate patient-specific effects more precisely. In addition, a future study would be enhanced by a focus on specific tumor types and sub-groupings based on more specific tumor locations.

## Acknowledgements

The authors are grateful to the Grengs family for their financial support of these research efforts in memory of their wife and mother, Patricia Grengs. The authors are thankful to Doris Finck, whose assistance and expertise are considered special contributions to the establishment of the study's database and to the preparation of this manuscript. The authors also express appreciation to Emily Chen for her editorial modifications in the final version of this manuscript.

## References

1. Horn J, Reitan RM: Neuropsychological correlates of rapidly or slowly growing intrinsic cerebral neoplasms. J Clin Neuropsychol 6: 309–324, 1984
2. Scheibel RS, Meyers CA, Levin VA: Cognitive dysfunction following surgery for intracerebral glioma: influence of histopathology, lesion location, and treatment. J Neuro-Oncol 30: 61–69, 1996
3. Walch SE, Ahles TA, Saykin AJ: Neuropsychological impact of cancer and cancer treatments. In: Holland JC (ed) Psycho-Oncology. Oxford University Press, New York, 1998, pp 500–505
4. Crossen JR, Garwood D, Glatstein E, Neuwelt EA: Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol 12: 627–642, 1994
5. Roman DD, Sperduto PW: Neuropsychological effects of cranial radiation: current knowledge and future directions. Int J Radiat Oncol Biol Phys 31: 983–998, 1995
6. Vigliani MC, Sichez N, Poisson M, Delattre JY: A prospective study of cognitive functions following conventional radiotherapy for supratentorial gliomas in young adults: 4-year results. Int J Radiat Oncol Biol Phys 35: 527–533, 1996
7. Stehbens J, Kaleita T, Noll R, MacLean W, O'Brien R, Waskerwitz M, Hammond D: CNS prophylaxis of childhood leukemia: What are the long-term neurological, neuropsychological, and behavioral effects? Neuropsychol Rev 2: 147–177, 1991
8. Ris MD, Noll RB: Long-term neurobehavioral outcome in pediatric brain tumor patients: review and methodological critique. J Clin Exp Neuropsychol 16: 21–42, 1994
9. Archibald YM, Lunn D, Ruttan LA, MacDonald DR, Del Maestro RF, Barr HW, Pexman JHW, Fisher BJ, Gaspar LE, Cairncross JE: Cognitive functioning in long-term survivors of high-grade glioma. J Neurosurg 80: 247–253, 1994
10. Hochberg FH, Slotnick B: Neuropsychologic impairment in astrocytoma survivors. Neurology 30: 172–177, 1980
11. Imperato JP, Paleologos NA, Vick NA: Effects of treatment on long-term survivors with malignant astrocytomas. Ann Neurol 28: 818–822, 1990
12. Maire JP, Coudin B, Guerin J, Caudry M: Neuropsychologic impairment in adults with brain tumors. Am J Clin Oncol 10: 156–162, 1987
13. Choucair AK, Scott C, Urtasun R, Nelson D, Mousas B, Curran W: Quality of life and neuropsychological evaluation for patients with malignant astrocytomas: RTOG 91-14. Int J Radiat Oncol Biol Phys 38: 9–20, 1997
14. Meyers CA: Neuropsychological deficits in brain tumor patients. Effect of location, chronicity, and treatment. Cancer Bull 38: 30–32, 1986
15. Taphoorn MJB, Schiphorst AK, Snoek FJ, Lindeboom J, Wolbers JG, Karim ABMF, Huijgens PC, Heimans JJ: Cognitive functions and quality of life in patients with low-grade gliomas: the impact of radiotherapy. Ann Neurol 36: 48–54, 1994
16. Lilja AM, Portin RI, Hamalainen PI, Salminen EK: Short-term effects of radiotherapy on attention, and memory performances in patients with brain tumors. Cancer 91: 2361– 2368, 2001
17. Weitzner MA, Meyers CA: Cognitive functioning and quality of life in malignant glioma patients: a review of the literature. Psycho-Oncology 6: 169–177, 1997
18. Grant R, Slatter J, Gregor A, Whittle IR: Recording neurological impairment in clinical trials of glioma. J Neuro-Oncol 19: 37–49, 1994
19. Murray KJ, Nelson DF, Scott C, Feschbach AJ, Porter A, Farnan N, Curran W: Quality-adjusted survival analysis of malignant glioma. Patients treated with twice-daily radiation (RT) and carmustine: a report of the Radiation Therapy

Oncology Group (RTOG). Int J Radiat Oncol Biol Phys 31: 453–459, 1995
20. Karnofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM (ed) Evaluation of Chemotherapeutic Agents. Columbia University Press, New York, 1949, pp 191–205
21. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th edn. American Psychiatric Association Press, Washington DC, 1994
22. Wellisch D, Kaleita T, Freeman D, Cloughesy T, Goldman J: Predicting major depression in brain tumor patients. Psycho-Oncology 11: 230–238, 2002
23. Mirsky AF, Anthony BJ, Duncan CC, Ahearn MB, Kellam SG: Analysis of the elements of attention: a neuropsychological approach. Neuropsychol Rev 2: 109–145, 1991
24. Brouwers P, Riccardi R, Poplack D, Fedio P: Attentional deficits in long-term survivors of childhood acute lymphoblastic leukemia. J Clin Exp Neuropsychol 6: 325–336, 1984
25. Rodgers J, Horrocks J, Britton PG, Kernahan J: Attentional ability among survivors of leukemia. Arch Dis Child 80: 318–323, 1999
26. Cousens P, Ungerer JA, Crawford JA, Stevens MM: Cognitive effects of childhood leukemia therapy: a case for four specific deficits. J Pediatr Psychol 16: 475–488, 1991
27. Davies A: The influence of age on Trail Making Test performance. J Clin Psychol 24: 96–98, 1968
28. Wechsler D: Wechsler Adult Intelligence Test, 3rd edn. The Psychological Corporation, San Antonio, 1997
29. Smith A: Symbol-Digit Modalities Test. Western Psychological Services, Los Angeles, 1982
30. Noll RB, Stith L, Gartstein MA, Ris MD, Grueneich R, Vannatta K, Kalinyak K: Neuropsychological functioning of youths with sickle cell disease: comparison with non-chronically ill peers. J Pediatr Psychol 26: 69–78, 2001
31. Giovagnoli AR, Tamburini M, Boiardi A: Quality of life in brain tumor patients. J Neuro-Oncol 30: 71–80, 1996

*Address for offprints*: Thomas A. Kaleita, Ph.D., Box 956967, 300 UCLA Medical Plaza, Los Angeles, California, 90095-6967, USA; Tel.: (310) 473-4755; E-mail: tkaleita@ucla.edu