REVIEW

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Relationship between cognitive function and prognosis in glioblastoma

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Practice Points

- Glioblastoma has an extremely poor prognosis with a median survival of well under 2 years.
- Cognitive deficits are frequently present at the time of glioblastoma diagnosis, but are often not recognized by healthcare providers.
- Clinical performance status is highly associated with survival, but performance status does not differentiate between the cognitive and physical symptoms.
- Neuropsychological evaluation is a far more sensitive method of detecting cognitive issues than use of the Mini Mental Status Examination or related tools.
- Cognition may be negatively impacted by glioblastoma itself or by other factors, including treatment-related toxicity.
- Poorer performance on cognitive tests is associated with shorter survival both from time of initial diagnosis and from time of tumor progression.

SUMMARY The association between increased signs and symptoms and poorer survival in glioblastoma is well recognized and confirmed in virtually every clinical trial and patient series. Measurement and consideration of performance status is, therefore, vital when counseling patients regarding their expected survival or evaluating the results of clinical trials. Unfortunately, measures of patient function in clinical trials have remained quite crude, in stark contrast to the rapid advances seen in the pathological characterization of brain tumors. Recently, clinical investigators have begun to examine the subcomponents of performance status in more detail, revealing that objective measures of cognition are significantly associated with patient survival in both newly diagnosed and recurrent glioblastoma. Furthermore, cognitive function does not appear to be a simple proxy for performance status but rather an independent predictor of survival, even within patient groups defined by currently available clinical prognostic systems. Therefore, objective measures of cognition must be evaluated for inclusion in future prognostic models and the simple addition of new tumor biomarkers to the current clinical prognostic models will likely prove insufficient. In order for the field of neuro-oncology to move forward in this regard, evaluation of cognition must become a routine part of future clinical trials, and the data must be recorded and analyzed with the same diligence as other trial end points.

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Despite significant recent progress in the treatment of glioblastoma, prognosis remains dismal, with median overall survival times of under 2 years in most clinical trials [1] and approximately 1 year in unselected community samples [2]. While glioblastoma prognosis is commonly discussed in terms of median survival, these figures mask a great deal of patient-to-patient variation, with some patients surviving only weeks after diagnosis and others living for in excess of a decade. It is extremely important for clinicians and researchers to be able to identify patients who may be reasonably expected to have prognoses notably better or worse than glioblastoma patients as a whole, in order to offer appropriate counseling and analyze the results of clinical trials.

Clinical performance status (PS) has long been recognized as one of the strongest predictors of survival amongst patients with glioblastoma. In this review, the authors will begin by examining the concept of PS and its various sub-components, including cognitive function. The authors will review the considerable evidence published to date that cognition, both globally considered and with respect to specific cognitive domains, is an independent prognostic factor in patients with glioblastoma. Finally, the authors will describe ongoing and future studies, which will build on current work and evaluate the role of cognition on survival while accounting for the full spectrum of recently recognized pathological predictors of prognosis in glioblastoma.

Clinical PS

Clinical investigators have long sought to identify patient-specific factors associated with glioblastoma prognosis. This information is useful to provide appropriate care to individual patients, as well as to design and appropriately analyze clinical studies with survival end points. The two clinical prognostic factors of greatest importance in glioblastoma are patient age and PS. PS is a single numerical score that summarizes a patients' overall clinical state, taking into account such factors as symptom burden, ability to work and need for assistance with self-care. Karnofsky PS (KPS) is the grading system in most widespread use [3], but alternative scoring systems such as Eastern Cooperative Oncology Group (ECOG) PS, also known as the WHO PS or Zubrod score, are also widely quoted in the medical literature [4]. [Table 1](#) displays these scoring systems. Measures of PS can be considered

independently, or combined with other clinical or pathological factors to categorize patients into distinct prognostic groups. The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification system, for example, is a validated prognostic scoring system that uses KPS, patient age and other patient-level factors to cluster patients into groups with expected similar prognoses [5].

There are a number of advantages to using PS as the primary marker of clinical state. First, several PS scoring systems have been extensively validated, and the correlation between poorer PS and shorter survival is not in question. Secondly, these scoring systems are easy to use, so scoring can be done by individuals with minimal medical training with a high degree of intra- and inter-rater reliability [6,7]. However, the use of PS as the sole marker of patient clinical state has a number of drawbacks that balance the previously noted strengths. First, PS scoring systems presume that degree of functional limitation is more important than the etiology of said limitation. This assumption may hold in systemic cancers, when PS is heavily influenced by factors such as fatigue, pain and cachexia, but not in brain tumors when patients may have no symptoms outside of those caused by dysfunction in focal regions of the brain. Two brain tumor patients, one of whom requires help with self-care due to paresis while remaining cognitively intact, and another who requires similar assistance due to cognitive dysfunction, may have identical PS scores although they are very different clinically. Furthermore, given the focus of PS scoring systems on 'activity', it is far more straightforward to accurately assign a score to a patient with weakness than to a patient with cognitive dysfunction, particularly as caregiver assistance may mask cognitive deficits until they become severe.

The issue of separating cognitive status from other clinical factors becomes even more difficult when multiple nonspecific screening measures or subjective appraisals of mental ability are combined to produce a global prognostic assessment. The most obvious example of this issue is the previously mentioned RTOG RPA classification system, in which patients are clustered into groups based on a flowchart consisting of a series of dichotomized branch points. In the RTOG RPA system, branch points exist for KPS (≥ 70 vs < 70), mental status (normal vs abnormal) and neurologic function (dichotomized by ability to

Table 1. Frequently used performance status classifications.

ECOG/WHO performance status		Karnofsky performance status	
Grade	Criteria	Score	Criteria
0	Fully active, able to carry on all predisease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work or office work	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self. Unable to carry out normal activity or do most active work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of their needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization is indicated, although death is not imminent
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair	20	Hospitalization necessary, very sick, active supportive treatment necessary
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

ECOG/WHO [4] and Karnofsky performance status [3] scoring systems are displayed side by side for comparison purposes. Equivalence of scores on the same level is not implied.
ECOG: Eastern Cooperative Oncology Group.

work). Similarly, a survival nomogram created from analysis of the National Cancer Institute of Canada (NCIC) trial 26981-22981/CE.3 data includes both WHO PS and Mini-Mental Status Exam (MMSE) scores [8]. This issue does not diminish the importance or utility of either of these rating scales, it simply suggests that there is ample room for further refinement based on more specific and sensitive measures of cognition.

Cognition & survival in glioblastoma

Cognitive signs and symptoms are quite common in this patient population [9,10], but are less frequently the motivating event that brings a patient with glioblastoma to medical attention. It is probable that the causes of cognitive dysfunction change throughout the disease course in patients with glioblastoma. Cognitive issues present prior to initial surgery are due in large part to the tumor itself, but the initiation of medications, such as antiepileptics and corticosteroids, may also have untoward effects

on cognitive function. Conversely, reduction of edema and improved seizure control may enhance cognitive function. At the postsurgery but preradiation time point, which is often used as the ‘baseline’ measurement in prospective adjuvant chemoradiation trials, postsurgical cognitive sequelae are also an issue. Treatment-related fatigue may contribute to cognitive issues; this may be an especially important factor during and shortly after radiation therapy. The extent to which radiation toxicity and ‘chemobrain’ cause long-term cognitive issues in patients with glioblastoma is unclear, given the difficulty in separating treatment-related cognitive decline from the effects of the tumor itself. Amongst patients who have completed their initial course of treatment, the presence or absence of tumor progression is a major predictor of cognitive decline.

■ Newly diagnosed glioblastoma

Only recently has cognitive function been studied as a potential independent predictor of survival,

apart from less specific measures of function. In 2003, Klein and colleagues published the first report linking cognitive impairment with survival in patients with newly diagnosed glioblastoma [11]. This study employed a neuropsychological test battery, which assessed cognitive functioning in the domains of perception, memory, attention and executive functioning, yielding a total of 20 test outcomes. Patients were defined as cognitively impaired if they scored 2 or more standard deviations below healthy controls on at least four of the 20 test outcomes of the neuropsychological test battery. A total of 68 consecutive patients with newly diagnosed high-grade glioma (WHO grade III and IV tumors) were evaluated. Although cognitive impairment was not associated with survival in the patient group as a whole, a statistically significant association was seen in the subpopulation of older patients with WHO grade IV gliomas. Importantly, no tests for association between survival and impairment on specific tests or within specific cognitive domains were reported.

The independent prognostic importance of cognition in newly diagnosed glioblastoma was reconfirmed in 2008 by Gorlia and colleagues in their analysis of data from the European Organization for Research and Treatment of Cancer (EORTC) and NCIC trial 26981-22981/CE.3 [8]. They modeled survival in three groups; the entire intention-to-treat population ($n = 573$); the patient subgroup assigned to temozolomide and radiotherapy ($n = 287$); and a subgroup of patients who underwent partial or complete resection and were assigned temozolomide and radiotherapy in the presence of an O^6 -methylguanine-DNA methyltransferase promoter methylation assessment ($n = 103$). In each of these models, an MMSE score of 27 or higher was associated with superior survival. This study was also the first analysis of a large randomized trial to clearly show that both clinical factors (e.g., MMSE score) and pathological factors (e.g., O^6 -methylguanine-DNA methyltransferase promoter methylation status) were independently associated with survival within the same patient group. Owing to the fact that the MMSE was used to assess cognition, rather than a battery of neuropsychological tests, this study does not provide insight into whether any specific cognitive domains are especially important.

A single-institution series of 91 patients published by Johnson and colleagues in 2012 demonstrated that the results of specific

neuropsychological tests can predict survival in newly diagnosed glioblastoma, both as continuous variables and when dichotomized by impairment [9]. Specifically, in models accounting for other clinical factors, both the Trail Making Test Part B and Controlled Oral Word Association Test were associated with survival as continuous variables and when dichotomized, while both the Similarities and Digit Span tests were associated with survival only when dichotomized by impairment. Based on the cognitive domains interrogated by the tests that proved to be associated with survival, this study provides preliminary evidence that the domains of attention and executive function are particularly relevant to survival in newly diagnosed patients with glioblastoma.

Attention and executive function rely on a distributed neural network primarily involving frontal, temporal and parietal regions. Disruption in these cognitive processes in newly diagnosed patients may reflect the extent of disease burden. Understanding cognitive function at the domain level is essential for prescribing neuropsychological interventions. It remains to be determined if interventions that improve specific aspects of cognitive function will also be associated with survival benefits. Global cognitive function as determined by insensitive screening tools (e.g., MMSE [12]) are less strongly associated with survival; however, composite variables derived by aggregating tests that are sensitive to specific cognitive functions have also shown strong associations with survival [9].

■ Recurrent glioblastoma

The first report evaluating cognition as a predictor of survival in recurrent malignant glioma (WHO grades III and IV) was that of Meyers and colleagues published in 2000 [13]. In that analysis of 80 patients evaluated with detailed neuropsychological testing at a single institution, verbal memory was strongly associated with survival, and survival models containing composite indices of multiple neuropsychological test results accounted for significantly more of the patient-to-patient variation in survival than models not including this information did. Interestingly, neither the ability to perform basic activities of daily living nor patient-rated quality of life was associated with survival time in models adjusting for other clinical covariates.

Open questions

Perhaps the most pressing current question regarding cognition and survival in glioblastoma is how cognitive status fits into larger prognostic models incorporating patient-specific markers of tumor biology. While cognition is unambiguously important in clinical prognostic models, it remains to be shown that this significance persists in models including both clinical and biological factors. For example, just in the last decade, markers such as *O*⁶-methylguanine-DNA methyltransferase methylation [14,15], *IDH* mutation [16] and tumor subtyping based on gene expression data [17] have made an important impact on the field of neuro-oncology. It could be hypothesized that tumor-related cognitive deficits are significantly associated with pathological factors in that faster-growing tumors may allow less time for plasticity/accommodation. In concept, this is similar to recent data that demonstrated that the poor prognosis of elderly patients was due, in part, to a significantly lower rate of *IDH* mutant tumors in this patient group [18]. Alternatively, patient cognition could impact prognosis by influencing physician behavior. Perhaps physicians, consciously or unconsciously, are more likely to recommend aggressive therapies at the time of diagnosis and recurrence in patients with good cognitive function. Data from the RTOG 0525 trial, a large randomized trial of two different adjuvant temozolomide chemotherapy regimens for newly diagnosed glioblastoma, will be able to provide some insight into these issues, although only a relatively small subset of patients in that trial received cognitive testing [101]. A more complete answer may be provided by ongoing trials, such as RTOG 0825, a large randomized trial of radiation and temozolomide with or without bevacizumab, as this Phase III trial included preplanned cognitive analyses [102]. Another question yet to be answered is whether the different factors impacting patient cognitive performance have different implications for survival. Intuitively, early problems due to the acute stress of diagnosis seem less likely to correlate with poor outcome than problems due to disruption of cognitive networks by the tumor itself. Other causes, such as corticosteroid-related issues, may correlate with and be confounded by tumor burden.

The path forward

In order for investigators to continue to build on recent progress, cognitive assessment must

be built into future clinical trials and this data must be collected as conscientiously as other patient-level data. Ideally, data collection should be lifelong or, at a minimum, continue to time of tumor progression. While these recommendations are uncontroversial, a number of barriers remain to be overcome before they can be fully realized.

Fundamentally, the scientific desire to capture as much data as possible is in conflict with the practicalities of clinical trial design and conduct. Comprehensive neuropsychological evaluation, the gold standard of cognitive assessment, requires considerable patient time as well as the involvement of a psychometrist to conduct testing and a neuropsychologist to clinically interview the patient and family and interpret the test results in the context of the entire clinical and psychosocial situation. This is feasible in some single-institution or multi-institution trials conducted at academic medical centers, but it is not easily achieved in the community setting. Conversely, the cognitive assessments administered as part of routine clinical care, most notably the MMSE, have insufficient sensitivity and are not able to adequately discriminate between deficits in different cognitive domains. In order for cognitive testing to be part of large clinical trials, as it must be, a battery of neuropsychological tests were identified that are psychometrically sound, measure relevant cognitive domains, can be reliably administered by non-neuropsychology staff with minimal focused training and can be completed by most patients without substantial floor or ceiling effects [19]. The International Cognition and Cancer Task Force (ICCTF) [20] and the Response Assessment in Neuro-Oncology group (RANO) [21,22] have released recommendations regarding which cognitive tests should be routinely incorporated into studies of cognition in patients with cancer (Table 2) [20]. This clinical trial battery should be thought of as a starting point from which tests can be added depending on the research question at hand, rather than a definitive list suitable for all purposes. Additionally, a number of computerized cognitive test batteries are currently being evaluated in the brain tumor patient population. While it is far too early to suggest that such tests should routinely be used to supplement traditional neuropsychological tests, pilot studies to more rigorously evaluate the performance

Table 2. Selected neuropsychological tests suggested by the International Cognition and Cancer Task Force and Response Assessment in Neuro-Oncology group for use in brain tumor clinical trials, by cognitive domain.

Cognitive domain	Test
Learning and memory	HVLT-R
Processing speed	TMT Part A
Executive function	TMT Part B COWA ^a

^aCOWA is a portion of the Multilingual Aphasia Examination.
COWA: Controlled Oral Word Association; HVLT-R: Hopkins Verbal Learning Test-Revised; TMT: Trail Making Test.

characteristics of computer-based cognitive testing are appropriate.

While test selection and battery refinement are relatively straightforward issues, a more fundamental barrier to routine use of cognitive data from large trials is suboptimum data collection practice. While patients and providers recognize the importance of collecting data regarding cognition and other aspects of clinical status, such as quality of life, this does not translate directly into action, especially with regard to long-term follow-up. There may be several reasons for this apparent disconnection. Cognitive assessment presents no notable risk to patients; however, it may be frustrating for patients as it can highlight cognitive deficits that may be masked in day-to-day life. Although patients rarely refuse cognitive testing for this reason, physicians and study personnel may stop collecting the data with the stated aim of sparing the patient distress. Even when patients perform well, data collection may lag with time. Owing to the fact that cognitive status is typically a secondary or exploratory end point, data collection and reporting is perceived to be of lesser importance than toxicity or survival data. Unfortunately, missing data cannot simply be censored or easily imputed; the reasons for patient loss are often informative, and subsequent analyses are thus inexorably confounded. To counter these trends, it would be ideal for future studies to implement and link real-time monitoring of the collection and reporting of cognitive data to study center compensation or ‘credit’, just as is done for the reporting of toxicity and survival data.

Cognitive testing should not be limited to the clinical trial setting; neuropsychological assessment should be a part of the routine care of patients with glioblastoma.

There is a growing number of neuropsychologists at major cancer centers and neuropsychologists in the community are increasingly familiar with neuropsychological issues in oncology.

Conclusion

The importance of cognitive status as a predictor of survival in glioblastoma has gone from unknown to well recognized in less than 15 years. The time has come for cognition to be routinely included as an end point in Phase III glioblastoma clinical trials. Aside from its relationship to survival, cognitive dysfunction is a serious and feared consequence of brain tumors, and it will be important to identify tumor treatments that have positive or negative effects on cognition, regardless of their abilities to prolong survival. This is especially important when evaluating targeted agents such as antiangiogenic therapies, which may impact time to progression without changing overall survival.

Future perspective

The next decade will prove the importance of cognitive evaluation in patients with brain tumors. As data from the now-completed RTOG 0525 and 0825 trials are analyzed and published, we will learn more about how the effect of cognitive function on prognosis is related to molecular factors. It is quite possible that we may identify tumor-directed therapies that improve progression-free survival and time to cognitive decline without significantly prolonging overall survival, prompting a vigorous discussion about the importance of cognitive status from the perspective of patients and third-party payers. Regardless, cognitive testing will become a part of all future Phase III trials and comprehensive neuropsychological assessment will become a routine part of the clinical care of patients with glioblastoma.

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