



Monitoring of Neurocognitive Function in the Care of Patients with Brain Tumors

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Abstract

Purpose of review A detailed characterization of the nature of neurocognitive impairment in patients with brain tumors is provided, as well as considerations for clinical practice regarding neuropsychological assessment throughout the disease course.

Recent findings Neurocognitive impairment is common in patients with brain tumors and may result from the tumor itself, as a consequence of treatment, including surgery, chemotherapy, and radiation, or in association with supportive care medications (e.g., anticonvulsant and pain medications). Serial surveillance of neurocognitive functioning in this population can facilitate medical decision-making and inform recommendations to improve patient daily functioning and quality of life.

Summary Neuropsychological assessment is increasingly recognized as a critical component of the multidisciplinary care of patients with brain tumors and has already had

practice-changing effects. Further understanding of genetic risk factors for neurocognitive decline along with the development of novel assessment and intervention strategies may further enhance functioning and general well-being in this patient population.

Introduction

Neurocognitive functioning (NCF) is a critical component of neurologic status and quality of life in patients with brain tumors. Impairment of NCF often interferes with the ability to participate in many important roles, such as work [1] and complex self-care tasks [2], and greatly reduces functional independence and quality of life [3]. In the complex medical care required for many brain tumor patients, monitoring of NCF outcomes is difficult for physicians to manage given limitations of time and available resources. Furthermore, it is well-known that brief NCF screening instruments readily available to and within the purview of physicians and

allied healthcare professionals, such as the Mini-Mental State Examination (MMSE [4];) and the Montreal Cognitive Assessment (MoCA [5];), are insensitive to clinically meaningful alterations of NCF in many brain tumor patients [6, 7]. As a result, neuropsychologists are recognized as integral members of multidisciplinary care teams for brain tumor patients [8, 9]. This review summarizes the numerous factors contributing to NCF impairment in brain tumor patients, describes the role of neuropsychological evaluation at different stages of illness/treatment, and clarifies the ways in which these evaluations improve patient care and quality of life.

Impairment of neurocognitive function in brain tumor patients

Impairment of NCF has been reported in over 90% of patients with supratentorial brain tumors and represents a common presenting symptom in this population [10, 11]. Decline in NCF is typically due to a combination of factors, including compression of neural tissue, infiltration into distributed neural networks, and edema disrupting the function of brain tissue surrounding the mass [10]. Although primary brain tumors are not common, accounting for approximately 1.4% of all cancers, there are an estimated 78,000 new cases per year in the USA [12] and NCF deficits are nearly ubiquitous in this population. Meningiomas are the most common primary brain tumor (38%), arising from the dura mater of the meninges. Although the vast majority of these tumors are classified as non-malignant by histologic criteria, they are nonetheless associated with NCF deficits [13], primarily secondary to compression of underlying brain tissue. Gliomas, which arise from glial cells, are the second most common type of primary brain tumor (26%) and are the most common type of malignant brain tumor. Prognosis varies widely among malignant gliomas and can be predicted largely by histopathological and molecular features (e.g., IDH1 mutation and MGMT methylation status [14];). NCF impairments are associated with all types of glioma [15, 7, 16]. Finally, metastatic brain tumors are far more common than primary central nervous system (CNS) tumors, occurring in 20–40% of all patients with cancer [17], and metastatic brain tumors are also associated with a high incidence of NCF morbidity [18–20].

The NCF domains affected by brain tumors can include any ability or skill. Memory and executive functioning are most frequently affected in part due to

the most common presenting location of primary brain tumors in adults (i.e., frontal and temporal lobes), but attention, processing speed, language, and visuospatial capabilities can also be impacted in many individuals. Focal neurocognitive syndromes may develop, such as aphasia with perisylvian tumors in the dominant hemisphere, but NCF changes are often more diffuse relative to the typical sequelae of other “focal” neurologic conditions, such as ischemic/embolic stroke [21]. The nature and extent of NCF deficits experienced by an individual with a brain tumor can also be influenced by demographic characteristics, such as patients pre-illness level of functioning (i.e., cognitive reserve). Additionally, tumor size, location, and genetic characteristics associated with aggressiveness of the lesion also impact the nature and extent of NCF impairment [22••, 23, 24]. Notably, more aggressive tumor growth may interfere with neuroplasticity, accounting for the finding that some individuals experience much greater NCF impairment than others with lesions of similar size and location [22••]. Additionally, infiltrating tumors are more likely to interfere with surrounding neural circuitry and can therefore produce more diffuse changes in NCF instead of more focal syndromes [25].

In addition to NCF deficits due primarily to the tumor itself, standard of care treatments can also contribute to NCF decline. Decline in NCF is often observed following surgical resection despite the implementation of strategies to protect NCF, such as preoperative functional MRI and intraoperative cognitive mapping (IOCM) [26, 27]. However, neurosurgery can also be associated with alleviation of NCF impairment in some patients due to the reduction of mass effect, such as in benign masses like meningioma [28, 29]. Nonetheless, postoperative NCF often remains below the individual’s pre-illness level of function. Chemotherapy represents an additional risk, even with relatively well-tolerated medications such as temozolomide. That is, NCF decline has been identified in about 30% of patients following temozolomide therapy, despite disease status remaining radiographically and clinically stable [30–34]. Other medications that can be used to treat neurologic sequelae of brain tumors, such as steroids, antiepileptics, and analgesics, can compound existing NCF difficulties [35]. Additionally, radiation therapy has long been associated with NCF impairment due to a variety of mechanisms, resulting in acute, subacute, and/or late effects [36•]. Because malignant brain tumors have a high rate of recurrence and can transform to a higher grade over time, patients may face additional rounds of surgery, chemotherapy, and radiation, sometimes years later, further contributing to their risk for NCF decline over time.

Neuropsychological evaluation

Neuropsychological assessment objectively quantifies specific NCF abilities by comparison of an individual’s performance to that of healthy peers that share certain demographic characteristics (e.g., age, education, gender) and/or in comparison with a patient’s own estimated pre-illness baseline. The goal of neuropsychological evaluation in the context of brain tumor populations varies but often includes elucidating the pattern and degree of NCF strengths and weaknesses, determining the presence and/or location of underlying neurologic dysfunction, and prognosticating a variety of outcomes from tolerability of treatments to survival time. Additional common roles of the neuropsychologist

include facilitating surgical decision-making through pre- and intraoperative procedures such as IOCM, identifying and treating mood, neurobehavioral changes, and other comorbidities (e.g., fatigue and sleep issues), determining need for accommodations in various important life domains (e.g., medication and financial management, driving), offering targeted NCF and neurobehavioral treatment recommendations aimed at maximizing patient functioning and well-being, and monitoring disease response/progression and/or treatment effects. Neuropsychological assessment is more sensitive and specific than bedside cognitive screening [6, 37, 36•] and can identify changes in neurologic dysfunction prior to observable effects on neuroimaging [38]. It is also non-invasive and generally well-tolerated, particularly when the evaluation is tailored to the needs of the patient and takes into consideration their limitations and medical situation [39]. Importantly, neuropsychological evaluations enable transformative feedback and inform tailored interventions to improve patient functioning.

Preoperative setting

Following the identification of a suspected brain tumor via neuroimaging, neurosurgery is often the initial intervention. The neurosurgical team is tasked with determining the optimal surgical approach to maximize resection while preserving neurologic status and NCF. The role of neuropsychological evaluation at this point is to establish the effect of the lesion on NCF and identify NCF deficits that may impact surgical planning procedures (e.g., functional MRI and intraoperative mapping). This includes identifying atypical language organization [40], as well as potential barriers to participation in fMRI and intraoperative mapping (e.g., profound aphasia, anxiety). Presurgical neuropsychological evaluation also helps to identify an individual's risk for postoperative NCF decline. Specifically, preoperative NCF is a strong predictor of postoperative outcomes in specific cognitive domains [41, 42]. Much like with epilepsy cases [43], brain tumor patients with relatively preserved preoperative memory and language skills have a higher risk of decline in those areas following surgery [26]. Neuropsychologists are also often involved in intraoperative cognitive-linguistic testing, both during brain mapping with direct cortical stimulation and continuously throughout the resection. Inclusion of neuropsychological services within the intraoperative setting is associated with higher rates of gross total resection as well as shorter duration of surgery [44••].

Postoperative setting

Over 60% of patients with brain tumors experience NCF decline immediately following tumor resection, which may be due to surgical side effects or damage to healthy tissue surrounding the tumor [26, 27]. NCF decline in the acute to subacute period following surgery tends to be more severe following left hemisphere tumor resection, but changes in NCF are not uncommon following resection of tumors in the right hemisphere [26]. These initial NCF changes may resolve relatively quickly, as in the supplementary motor area syndrome [45], although other early deficits may persist and progress. Neuropsychological evaluation following tumor resection helps to characterize postoperative functioning and identify NCF deficits that may benefit from rehabilitative services. This information can be important in practical decisions regarding functional

capacities (e.g., resuming work, academics, driving), and NCF is prognostic of overall and progression-free survival time [30, 46, 16, 47••].

Long-term follow-up

Neuropsychological evaluation is important at regular intervals during post-operative treatment and throughout survivorship. Residual or progressive tumor and related edema cause ongoing and often evolving cognitive deficits. Changes in NCF can occur secondary to tumor treatment, including chemotherapy and radiation therapy, as well as in response to supportive care therapies (i.e., steroids, antiepileptics, and analgesics). These long-term NCF deficits are associated with reduced quality of life and decline in functional independence [48]. Furthermore, NCF impairment is a stronger predictor of quality of life than other neurologic symptoms [49]. As in the near-postoperative setting, a longitudinal neuropsychological evaluation is useful in updating functional capacities and complex activities of daily living that can fluctuate widely throughout the disease course [50, 51, 2].

Late effects of chemotherapy and radiation therapy are frequently seen in brain tumor patients [20, 33, 52], including focal areas of radiation necrosis which can lead to significant symptomatology that is difficult to distinguish from recurrent tumor [53]. In some cases, widespread leukoencephalopathy can develop [54–56], gradually progressing in the months and years after radiation therapy. When this occurs, long-term NCF impairment is likely and tends to follow a course similar to neurodegenerative disease [57].

Among cancer populations, patients with glioma have the highest risk for developing depression and other forms of emotional distress [58], with estimates ranging from 20 to 90% (depending on the methods used to diagnose depression) at some point during the disease [59, 60]. The assessment of emotional distress with sensitive and validated screening tools [61] and clinical interview is a part of every neuropsychological evaluation, allowing an important opportunity to detect affective problems and facilitate treatment. This is particularly important because of not only the clear impact of depression and anxiety on quality of life [3] but also the potential impact of depression on survival duration [62, 47••].

Practical considerations in serial neuropsychological assessment

A number of practical considerations should ideally be addressed when planning serial neuropsychological surveillance in patients with a brain tumor. First, it is ideal to capture each patient's NCF at baseline prior to surgical intervention or other treatment as this will serve as the basis for longitudinal comparisons. That said, the time from tumor identification on neuroimaging to tumor resection may be quite brief. To maximize feasibility and tolerability during this understandably stressful period, neuropsychological evaluation may benefit from being tailored to the patient's presenting situation and needs of the referral source. However, as with any other neuropsychological evaluation, it is necessary to assess core NCF domains (i.e., attention, processing speed, executive functioning, memory, language, visuospatial ability, and motor skills) as well as mood and behavior (e.g., depression, anxiety, personality change). A clinical interview is also necessary to capture additional critical information regarding

symptoms and comorbidities, the impact of NCF dysfunction on the patient's daily life, and essential patient history relevant to the interpretation of NCF test results (e.g., developmental and educational history).

Because patients are typically evaluated again postoperatively and then at regular intervals throughout the disease course, test selection is vital. The use of standardized test measures with alternate forms to reduce practice effects, as well as the incorporation of statistical methods to determine the significance of test score differences over time is important (e.g., Reliable Change Index (RCI) [38]). The purpose of the evaluation will help guide the timing of repeat neuropsychological evaluations. Postsurgical re-evaluations may be needed acutely to identify the nature and extent of immediate NCF changes to help guide acute treatment and self-care decision-making. Conversely, it may be preferable to allow time for natural recovery prior to postsurgical evaluation for the identification of potentially more permanent residual NCF deficits. However, because malignant tumors typically require chemotherapy and/or radiation within weeks of tumor resection, the follow-up neuropsychological evaluation is often requested prior to these adjuvant therapies in order to facilitate treatment planning and patient monitoring. More distal longitudinal follow-up evaluations are a critical component of comprehensive multidisciplinary care and can occur at any time point throughout the disease course. These evaluations enable identification and characterization of adverse or beneficial treatment effects, potentially serving as early indicators of treatment response or tumor progression [38, 63]. In addition to identifying NCF deficits, spared skills are documented, both of which are critical in the formulation of individually tailored recommendations.

Impact of neuropsychological evaluation on patient outcome

Neuropsychological evaluation contributes to patient outcomes via personalized treatment recommendations that are a routine part of the report and feedback to the patient and treatment team. Recommendations take the form of individualized strategies that incorporate the objective findings of the evaluation within the context of an individual's goals in daily life. Recommendations may include specific compensatory strategies, use of external aids, and environmental modifications to improve NCF and performance in daily life tasks [64, 65]. Recommendations may also pertain to addressing potentially modifiable factors, such as depression and anxiety, sleep disturbance, chronic fatigue, and pain—all of which can exacerbate underlying NCF limitations. Feedback can also be therapeutic in itself [66, 67], providing an opportunity for the patient and family to gain a better understanding of NCF and neurobehavioral changes and how to manage them. Anxieties may also be allayed as patients gain a sense of control over their situation through the development and implementation of a targeted treatment plan. Another important common recommendation is for neurorehabilitative services to promote independent self-care. Additionally, home health care may be recommended in the event that return to independent functioning is less likely. Studies of the efficacy of neurorehabilitation for brain tumor patients have been mixed but generally indicate a positive impact on patient performance as well as good satisfaction on the part of patients and their families [64, 68, 69]. Sometimes, a medication

evaluation may be suggested to promote NCF, although currently used pharmacotherapies (e.g., donepezil, methylphenidate, modafinil) appear to have variable efficacy [70–74]. Non-neurologic factors contributing to NCF impairment may also be targeted in the recommendations of a neuropsychological evaluation. For example, when symptoms of depression or anxiety are identified, referral for psychological and/or psychiatric intervention is typically recommended. Participation in a professionally led support group might also be suggested. In the event of chronic insomnia or excessive daytime fatigue, the use of sleep hygiene strategies or referral for a formal sleep evaluation may be useful.

Outside of these specific areas of need, individuals with brain tumors are at increased risk of experiencing disability [75•]. Objective characterization of NCF in the context of adequate task engagement can help determine whether formal accommodations are needed in order for an individual to function adequately within his/her previous job or educational program. Typical accommodations in the academic setting include additional time to complete projects or exams, permission to take examinations in a low distraction setting, or the assistance of a note-taker in classrooms. In the workplace, obtaining permission to use noise canceling headphones if the individual works in a noisy office setting, and other accommodations, can often be justified by documentation in a neuropsychological evaluation. Neuropsychological evaluation can also identify and substantiate marked NCF deficits that compromise a patient's ability to maintain competitive employment and can serve as a critical component in supporting a disability claim.

Incorporation of neuropsychological testing into clinical trials has definitively proven the utility of such evaluations in characterizing NCF and quality of life in the brain tumor population [38]. More specifically, the inclusion of NCF assessment in clinical trials of brain tumor patients has led to changes in the standard of care, which benefit the patient population as a whole. For instance, neuropsychological evaluation of patients with brain metastases revealed that those treated via stereotactic radiosurgery plus whole brain radiation therapy (WBRT) exhibit greater memory impairment following treatment in comparison with those who undergo stereotactic radiosurgery alone [76••, 77]. That finding contributed to the implementation of hippocampal-sparing WBRT delivery techniques in an effort to preserve memory [78], as well as prescription of memantine during WBRT in an effort to preserve cognitive functioning [72].

Future directions

Genetic predictors of risk for cognitive impairment

The understanding of how molecular genetics contribute to the behavior of brain tumors has exploded in the past several years. Characterization of the genetic features of gliomas has refined diagnostic criteria and improved prediction of prognosis [14]. As noted previously, these genetic variables, specifically mutation in the IDH-1 gene, have been associated with risk of NCF impairment [79••]. Genetic variations within the individual harboring brain tumor have also been shown to be an important risk factor for NCF impairment. For example, the APOE 4 allele has been linked to vulnerability to NCF deficits in a range of medical conditions, including individuals with non-CNS cancer [80] as well as those with brain tumors [81]. Other studies have

identified associations among specific single nucleotide polymorphisms (e.g., COMT, BDNF, BTNBP1) and performance on neuropsychological measures of attention, executive functioning, and memory among individuals with brain tumors [82•, 83]. Interestingly, APOE genotype status was shown to be unrelated to brain β -amyloid deposition in glioma patients using positron emission tomography (PET) [84], suggesting that the relationship between individual genetic risk factors, neuropathology, and NCF impairment is not identical to that of neurodegenerative populations such as Alzheimer's disease. These studies suggest that as our understanding of genetic risk variation continues to grow, neuropsychological testing will be critical in determining the NCF phenotype.

Computerized assessment of cognition

Computerized cognitive assessment has been developed for use among healthy and clinical samples, with the anticipation of being more time- and cost-effective than traditional paper-and-pencil neuropsychological evaluation. There are numerous such tools on the market currently; a full review of these tests is beyond the scope of this review, though many are available [85–87]. Computerized tests have been promoted as screening measures for NCF changes, but there has been substantial criticism regarding inadequate sensitivity and reliability in some cases, raising questions about the adequacy of their psychometric properties [87]. Computerized tests have been explored for use in clinical research of patients with a brain tumor. While advocates of computerized testing assert this is more efficient than traditional paper-and-pencil testing and preferred by patients, evidence suggests that both testing methods required the same amount of time and patients liked both approaches equally well [88]. Importantly, however, the traditional paper-and-pencil tests detected cognitive impairment in patients with high-grade glioma while the computerized test was unable to identify these impairments. Recently, the Amsterdam Cognition Scan has been developed for use in adults with cancer. It consists of eight computerized subtests that assess multiple NCF abilities, clearly articulates the conditions under which these tests can be validly used, and the developers are creating stimuli for administration in multiple languages [89]. In a study of healthy adults, the software demonstrated high test-retest reliability, low multicollinearity, and expected age-related performance decrement [90•]. Additionally, in a sample of non-central nervous system cancer patients, concurrent validity related evidence was identified on all but one subtest when compared with performance on traditional neuropsychological measures [91].

Such early results provide an emerging foundation for computerized NCF testing in adults with cancer. However, critical assessment of such test platforms remains necessary at this time, as some issues specific to computerized testing have yet to be rectified. For example, Feenstra and colleagues [90•] acknowledged that some participants took notes during a computer-administered word list learning task, thereby invalidating their learning and memory performance. Additionally, participants who more routinely used computers exhibited faster responses. Computerized NCF tests completed in the home environment introduce further potential confounds, such as differences in hardware and response methods (e.g., mouse versus tracking pad), interruptions in internet access, inadequately managed distractions in the immediate environment, and

inability to confirm that the test was completed without assistance [85]. Furthermore, many computerized NCF test programs do not have a method to assess premorbid NCF capacity, which is necessary for determining whether NCF is below expectations at the time of the first testing. Objective assessment of task engagement is often not incorporated within these programs yet this information is vital regarding the validity of an examinee's results. These issues will need to be addressed if computerized testing is to become a viable method of routine NCF testing.

Conclusion

Neuropsychology is now recognized as essential to the care of patients with brain tumors. We recommend integrating neuropsychological evaluation early in the care of brain tumor patients, with longitudinal follow-up to assist with the identification of NCF changes and targets for interventions to improve quality of life. There are currently no specified guidelines for clinical neuropsychological practice in the management of brain tumor patients, though recommendations regarding NCF testing for research purposes in cancer populations have been articulated [92], including testing guidelines specific to CNS tumors [93, 94, 95, 96] and brain metastases [97]. The National Comprehensive Cancer Network (NCCN) Survivorship guidelines [98] has encouraged referral for neuropsychological evaluation and management in general for cancer patients, thereby increasing awareness of these issues and providing clear guidance on the integration of neuropsychology into this aspect of oncology practice. Although the NCCN Clinical Practice Guidelines for CNS Cancers does not currently offer similar guidance to providers taking care of this specific patient population, we anticipate future practice guidelines will be articulated and disseminated underscoring the benefits of integrating neuropsychological assessment and management into the multidisciplinary care of patients with CNS cancers.

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Compliance with Ethical Standards

Conflict of Interest

Kyle R. Noll, Mariana E. Bradshaw, Erica L. Dawson, and Jennie Rexer each declare no potential conflict of interest. Michael W. Parsons reports consulting fees from Agios Inc. and Monteris Inc. outside the submitted work. Jeffrey S. Wefel reports personal fees from Abbvie, Bayer, Blueprint Medicines, Magnolia Tejas, Novocure, and Vanquish Oncology, and reports grants from Angiochem, Juno, Novocure, and Roche outside the submitted work.

Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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