Neurocognition and health-related quality of life among patients with brain tumors

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Neurocognition and Health-Related Quality of Life Among Patients with Brain Tumors

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KEYWORDS

• Brain tumor • Neurocognitive function • Quality of life • Neuropsychology • Neuro-oncology

KEY POINTS

- Impairment of neurocognitive functioning is common in patients with brain tumors, which can lead to functional disability and handicap and/or decreased health-related quality of life.
- Contributors to impairment of neurocognitive function and decreased well-being include the lesion itself, individual and tumoral genetic characteristics, antitumoral and other treatments received, and neurologic and psychosocial comorbidities.
- Although efficacy is variable, numerous strategies exist to prevent and ameliorate neurocognitive functioning impairment and to bolster health-related quality of life in patients with brain tumors.
- Strategies include pharmacologic agents, advanced surgical planning, modification of radiation therapy, compensatory strategy training, and lifestyle modification.

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INTRODUCTION

Adults with primary or metastatic brain tumors tend to experience high symptom burden and functional impairment during their illness trajectory.[1,2] The pattern of symptoms and impairments depends on individual, tumor, and treatment factors but commonly include motor dysfunction, seizures, fatigue, and neurocognitive functioning (NCF) difficulties. These problems have the potential to impact physical and mental health and often lead to a decreased health-related quality of life (HRQoL) (**Fig. 1**).[3] Brain tumor treatments also have associated adverse effects and can result in deterioration of functioning, although stabilizing the disease and delaying tumor progression through efficacious treatment may also benefit symptom burden and patient functioning.

A well-known framework for measuring patient functioning and well-being is the World Health Organization International Classification of Functioning, Disability, and Health,[4] which includes assessments at 3 levels: (1) impairment in body function, (2) consequences of impairment in daily activities, and (3) how dysfunction affects well-being and social interactions. There are several outcome measures that measure patient functioning and well-being across these levels, referred to as clinical outcome assessments (COAs).[5] Patient-reported outcomes represent an important COA, which comprise self-report measures of functioning and well-being, including symptoms, interference with life activities, and overall quality of life. Other types of COAs include clinician-reported outcomes and observer-reported outcomes. Performance outcomes represent another essential COA tapping objective aspects of patient functioning proximal to the level of impairment in body functioning (ie, brain functioning). In the brain tumor setting, this involves objective measurement of NCF. Performance outcomes are often used in conjunction with other COAs to provide information on the net clinical benefit and/or adverse effects of brain tumors and their treatment.[6]

This review begins with a discussion of contributors to, and the consequences of, NCF impairment in patients with brain tumors. Particular focus is given to performance outcomes, although relationships with other COAs commonly used in neuropsychological practice and research are described. This is followed by discussion of factors

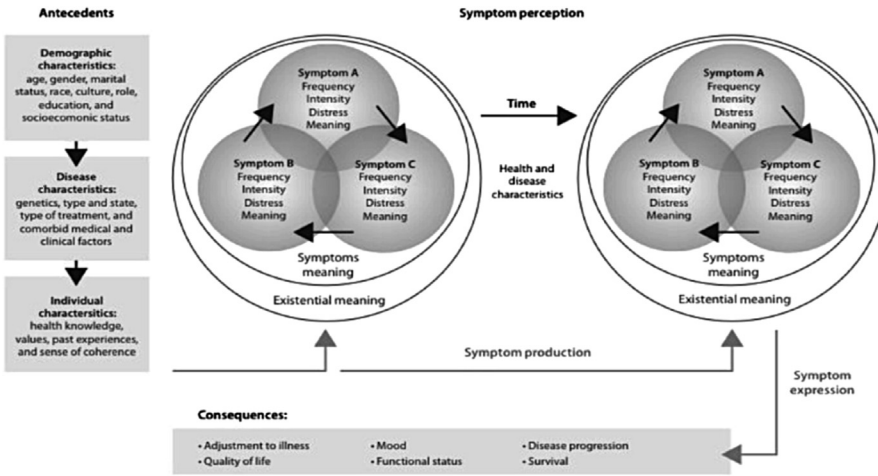

Fig. 1. Symptoms experience model.

associated with broader patient functioning, symptoms, and other aspects of HRQoL, with an emphasis on patient-reported outcome measurement methods.

NEUROCOGNITION

Although central nervous system neoplasms vary widely in malignancy and prognosis, all patients with brain tumors are at increased risk of NCF impairment. The pattern and severity of NCF dysfunction in patients with brain tumors differ across individuals according to numerous patient characteristics and tumoral features, as well as systemic therapies and adjuvant treatments received. In addition to being a primary concern of patients with brain tumors, NCF is also associated with the ability to perform daily activities and overall HRQoL.[2,7] The severity of NCF impairment predicts survival beyond clinical prognostic factors alone,[8] further supporting its usefulness in brain tumor clinical and research settings.

Clinical neuropsychological assessment involves a comprehensive multimodal–multimethod evaluation. This process includes record review and a clinical interview further assessing the presenting concerns, the functional impact of the disease, and the goals of care. During the formal assessment portion of the evaluation, patients are administered performance-based tests of NCF along with patient-reported outcomes, including measures of patient symptoms, emotional well-being, and HRQoL. Although brief screening tests exist (eg, Mini-Mental State Examination and Montreal Cognitive Assessment), comprehensive neuropsychological testing is preferred given its superior sensitivity to impairment and broader and more detailed coverage of NCF.[9] Neuropsychological testing is increasingly included as outcome measures in applied research, including large-scale clinical trials,[10] enhancing the cost–benefit analysis of various treatments for brain tumors. The results of comprehensive neuropsychological evaluation serve as the basis for diagnosing cognitive, emotional, and neurobehavioral disorders, as well as aid in developing personalized treatment plans to maximize functional independence and improve well-being.[11,12]

Unfortunately, most patients with brain tumors will exhibit objective NCF impairment at some point in the disease course, with learning, memory, and executive functioning among the most commonly impacted domains. However, considerable variability exists in the pattern and severity of NCF impairment according to numerous patient, tumor, and treatment characteristics.

PATIENT CHARACTERISTICS

Cognitive reserve differs across individuals and seems to moderate NCF outcomes in patients with brain tumors.[13] Specifically, patients with higher education tend to have better NCF, whereas older age seems to convey an increased risk of NCF impairment. Additionally, patients with brain tumors and an APOE e4 allele seem to be at increased risk of NCF impairment.[14] Various other germline genetic polymorphisms have also been associated with NCF, including those involved in neuronal health, neurotransmitter regulation, inflammation and oxidative stress response, DNA repair, and cell cycle regulation.[15,16]

TUMOR-RELATED FACTORS

Although memory and executive functions seem to be particularly vulnerable in patients with brain tumors, the pattern and severity of NCF impairment can vary by lesion location, with left hemisphere patients tending to exhibit greater deficits on testing than those with right-sided lesions.[17,18] Additionally, recent work indicates that

involvement of specific structures may cause differing patterns of alterations in structural and functional connectivity with associated impact on specific cognitive processes.[19] Despite such evidence localizing NCF impairments to focal disruptions in brain networks, other work has demonstrated more diffuse effects, even implicating structures contralateral to the brain tumor in NCF outcomes.[20,21] In other words, it seems that the relatively focal pathology of brain tumors disrupts both local and distal brain structures and functions, resulting in a mix of focal deficits and more diffuse impairments.

Although greater preoperative lesion volume is associated with greater NCF impairment,[22] baseline NCF seems to also differ according to tumor growth kinetics.[23] Patients with greater lesion momentum, as indicated by tumor grade and/or molecular characteristics, seem to be at greater risk of NCF regardless of lesion volume. More specifically, those with more aggressive, higher grade tumors exhibit worse NCF than their lower grade counterparts.[22] Similarly, patients with the more unfavorable IDH wild-type glioma show greater NCF impairment than those with IDH-mutant tumors.[23] These findings seem to be related, at least in part, to greater functional reorganization and preservation of white matter microstructure permitted by the more slowly growing tumors.[24,25]

TREATMENT-RELATED FACTORS

In addition to the lesion itself, surgical intervention may contribute to NCF impairment in patients with brain tumors, especially for those with involvement of eloquent brain regions.[26] The etiology of postoperative NCF decline is likely multifactorial and related to damage incurred to functional tissue during resection, the development of edema, and complications such as seizures and perioperative infarcts. Postoperative NCF is also associated with prognosis, because those with acquired deficits have a significantly decreased survival rate.[8] Accordingly, the neurosurgical team must balance carefully the goal of maximizing the extent of resection with the risk of acquiring NCF deficits.

Many patients with brain tumors will require radiation therapy for improved disease control and sensitization to chemotherapeutic agents. Although it is known that radiation therapy has a deleterious impact on white matter structures,[27] study of the effects of radiation therapy on objective NCF is difficult in most brain tumor populations given that many patients also receive concurrent therapies and tumors may progress, both of which impact NCF outcomes. Nonetheless, some evidence suggests that radiation dose to the hippocampus is associated with memory decline,[11] and worse NCF after radiation is associated with lower educational attainment and having received radiation to the whole brain.[28]

Patients with brain tumors often require chemotherapy for oncologic disease control, concurrently with radiation and/or as a single regimen in the adjuvant setting. Although chemotherapeutic agents can have deleterious effects on NCF in a sizable proportion of patients with cancer, most evidence comes from studies involving non–central nervous system disease. Despite this finding, a few studies have shown postchemotherapy NCF decreases in more than 30% of patients with glioma, both shortly after therapy and in the longer term survivorship period.[10,29] However, the interpretation of such studies is complicated by the fact that patients also received prior treatments (eg, radiation) that may convey a risk of delayed worsening of NCF. Accordingly, additional work is needed to understand the prevalence of and risk factors for chemotherapy-related cognitive decline in brain tumor populations.

OTHER CONTRIBUTORS

Numerous additional factors can impact NCF in patients with brain tumors, including medications for neurologic sequelae and comorbidities, such as steroids, antiepileptics, and analgesics. Fatigue and sleep problems are common in patients with brain tumors, which can exacerbate NCF deficits. Affective issues, such as depression and anxiety, also frequently occur during the glioma disease course. Recent work indicated that depressive symptoms and executive dysfunction predict survival, with worst prognosis in patients with co-occurring affective distress and impaired NCF.[8] Patients may also experience personality or neurobehavioral changes, such as the affective blunting often seen in patients with low-grade glioma. Interestingly, such emotional suppression has been associated with a decrease in aspects of executive functioning.[30]

PREVENTION AND INTERVENTION

Given the frequency of objective NCF impairment in patients with brain tumors and associated disability and decreased HRQoL, prevention of and intervention for NCF decline is paramount. Brain mapping represents an important group of invasive (eg, intraoperative direct cortical stimulation) and noninvasive (eg, functional MRI, diffusion tensor imaging tractography, transcranial magnetic stimulation) techniques that can mitigate risk of surgically acquired NCF impairment.[31] These techniques strive to identify eloquent cortical and subcortical structures underlying various NCF abilities, helping neurosurgeons to decrease risk of damage to critical structures and better preserve NCF. Regarding radiation therapy, research involving patients with brain metastases suggests that hippocampal avoidance during whole brain radiation can preserve memory functioning.[32] Importantly, recent preliminary work indicates that this technique may have similar benefits for patients with malignant glioma.[33] Additionally, radiation therapy using protons may have advantages for NCF longevity over conventional photon radiation.[34]

Pharmacologic agents have also been used, with varying degrees of efficacy, for the prevention or amelioration of NCF impairment in patients with brain tumors. Much of this work has focused on medications often used to treat Alzheimer's disease, such as memantine and donepezil. Memantine seems to slow time to cognitive decline when administered during whole brain radiation for patients with brain metastases,[35] and donepezil may benefit memory functioning and processing speed in patients with brain tumors after completion of radiation.[36] Additional work suggests that other medications typically used to treat attentional disorders, fatigue, and sleep disorders (eg, psychostimulants, hypnotics) may also benefit NCF in brain tumor populations.[37,38]

Rehabilitative approaches are commonly characterized as either compensatory strategy training or cognitive retraining. Strategy training involves teaching techniques to help compensate for NCF deficits, whereas retraining aims to improve the deficient brain function itself. A number of studies suggest that rehabilitation approaches, such as compensatory strategy training can be beneficial to NCF in patients with brain tumors.[39] In contrast, the evidence is mixed for cognitive retraining, with studies often failing to show transfer of gains beyond the trained task itself. Lifestyle interventions, including exercise, may also be part of rehabilitative programs, with some early evidence indicating usefulness in the treatment of NCF impairment in patients with brain tumors.[40]

HEALTH-RELATED QUALITY OF LIFE

As with objective NCF performance outcomes, both the tumor and its associated treatments can impact aspects of HRQoL in patients with brain tumors. Generally

speaking, the tumor has only negative effects, whereas treatment can have both positive and negative effects.[41]

Tumor-Related Factors

Postdiagnosis and pretreatment HRQoL scores for glioblastoma patients are both significantly lower than patient controls,[42,43] suggesting a direct tumor impact on functioning and well-being. Several tumor-related factors have been associated with aspects of worse HRQoL, including tumor grade, volume, and location in the brain. Patients with higher grade tumors report significantly worse HRQoL compared with those with lower grade tumors,[44,45] although this finding may reflect whether the patient has stable versus recurrent disease. Large multifocal tumors, tumors in the nondominant hemisphere, and frontal lobe tumors have been associated with worse HRQoL for brain tumor patients[44,46,47] related to problems with pain, mobility, energy, mood, sleep, and social isolation.[47]

Treatment-Related Factors

Surgical intervention can decrease tumor volume, improve symptom burden, postpone recurrence, and extend survival,[48] although surgery can also result in worsening of symptoms and functional impairments.[49] Importantly, postoperative decreases in aspects of HRQoL tend to be transient, and typically the clinical benefit of resection outweighs early adverse effects.[48,50]

Radiotherapy and chemotherapy extend survival in patients with brain tumors,[44,49] but treatment-related toxicities can result in symptoms and declines in functioning and well-being. Radiotherapy can stabilize brain tumor growth, delay time to progression, and help to maintain HRQoL, although fatigue, insomnia, and cognitive complaints are common during treatment[51] and can persist into survivorship.[52] Although there are several chemotherapeutic agents used to treat brain tumors, temozolomide is the mainstay of therapy and has been shown to extend survival and maintain HRQoL for patients with gliomas and brain metastases.[53,54] In those with high-grade glioma, the benefits from temozolomide therapy seem to persist from the stable disease period until progression, at which point there is significant deterioration in several aspects of HRQoL.[49]

Stereotactic radiosurgery is a treatment approach delivering radiation to precise targets, which may decrease the risk for adverse treatment effects and functional impairment. A recent systematic review reported HRQoL findings from 9 studies using gamma knife radiosurgery in patients with brain metastases.[55] The authors found that the majority of studies showed largely stable HRQoL scores after gamma knife across multiple domains, even up to 12 months after treatment. Studies that reported a decline in aspects of HRQoL involved older patients or HRQoL assessments further removed from treatment.[55] Results are similar for proton therapy in primary brain tumor patients, with mostly stable or improved HRQoL reported.[56] Typically, studies showing a decline in HRQoL domains after proton therapy capture the transient changes occurring during or early after treatment.[57]

Immunotherapies for solid tumors have expanded in recent years with some promising results, although trials in patients with brain tumors have demonstrated little clinical benefit.[58] Other immunotherapy trials in patients with primary and metastatic brain tumors are ongoing and include the use of checkpoint inhibitors, tyrosine kinase inhibitors, and vaccines. Several randomized phase II and III trials have evaluated use of bevacizumab, an antiangiogenic agent, in combination with cytotoxic drugs to treat newly diagnosed[59–61] and recurrent high-grade gliomas,[58,62] although this drug has largely failed to show significant survival advantage or improvements in HRQoL

compared with controls. In a phase III trial in patients with newly diagnosed glioblastoma, patients reported increased symptom burden over time, as well as a decrease in HRQoL, specifically cognitive complaints and motor dysfunction.[59] In a similar trial, HRQoL was maintained longer in the bevacizumab group and glucocorticoid requirements were lower; however, both trials reported more frequent serious adverse events in patients receiving bevacizumab.[61]

Over the last decade, the use of tumor treating fields, also known as Optune, have shown potential to improve clinical outcomes for patients with glioblastoma.[63] Early trial results showed improved progression-free and overall survival rates in those with recurrent glioblastoma who received tumor treating fields therapy versus active control chemotherapy, with only mild skin-related adverse effects reported.[64] The impact of the therapy on aspects of HRQoL were mixed, with improvements in global health and cognitive, emotional, and role functioning domains, but worsening in physical functioning.[64] Tumor treating fields have also been studied in newly diagnosed glioblastoma, randomized to temozolomide alone or in combination with tumor treating fields.[65] Results indicated that overall survival was prolonged without a negative impact on HRQoL, apart from localized pruritis, which was an expected consequence of the treatment.[66]

The use of concomitant medications is common during treatment and can impact symptom burden and functioning. Antiepileptic drugs can enhance aspects of HRQoL by decreasing seizure frequency and associated functional limitations, such as driving.[67] Although steroids and antiepileptics have the potential to improve patient functioning and well-being, they can also be associated with undesirable side effects, including drug–drug interactions, impaired cognition,[44,49] disturbed sleep, and mood changes.[68] Therefore, the judicious use and consideration of tapering these medications should be considered when medication risks outweigh benefits.

Symptom Burden and Functional Limitations

Patients with brain tumors experience both disease-specific and general cancer symptoms, both of which may contribute to a deterioration in functioning or overall HRQoL.[44,69–71] Symptoms specific to brain tumors occur as a result of elevated intracranial pressure and direct cellular damage. These symptoms include headache, seizures, and focal motor and/or cognitive complaints.[42,43] Symptoms ubiquitous across all cancers are also common and include fatigue, mood and sleep disturbance, nausea, and pain.[72] When patients with a brain tumor experience recurrence or progression of disease, they typically report a decline in overall HRQoL related to the greater symptom burden, worsening physical functioning, and work and participation limitations.[73]

Some of the most commonly reported symptoms in those with primary and metastatic brain tumors include fatigue, distress or mood disturbance, sleep disturbance and drowsiness, and cognitive symptoms, with symptoms typically occurring in clusters.[51,74] In a large study of patients with newly diagnosed glioma,[74] nearly one-half of patients reported 5 to 10 concurrent symptoms, aligning with motor, fatigue, pain, and gastrointestinal, seizure, and bladder control clusters, with the motor and fatigue clusters negatively impacting several aspects of function. Additionally, patients with moderate to severe symptoms are more likely to have a poor functional status. Further, affective and cognitive symptoms contribute to worse HRQoL in long-term survivors, specifically in activity-related and mood disturbances.[75,76] Activity-related interference, such as walking and the ability to work, has been shown to be a particularly prognostic metric, not only for its impact on life quality, but also in prediction of tumor progression and survival.[77,78]

Socioeconomic Impact

Patients with brain tumors can also experience a decrease in another important HRQoL domain, namely, financial toxicity. Patients with a brain tumor have a high prevalence of financial toxicity[79] with risk related to changes in employment status, lower socioeconomic status, higher out-of-pocket health care costs, and being on active treatment.[80] Although direct relationships between financial toxicity and HRQoL have yet to be explored, it is expected that patients who are able to continue working may experience higher levels of role and social functioning, and subsequently overall functioning and well-being.

Intervention

There are relatively few interventions available that target aspects of HRQoL in patients with a brain tumor, and the existing treatments are mostly focused on the alleviation of specific symptoms. Nonetheless, several randomized controlled trials of supportive care interventions have been conducted in brain tumor populations.[81] A number of studies have used psychostimulants[82–84] targeting fatigue, sleepiness, and overall quality of life, although they all failed to show an improvement in symptoms or well-being. Some preliminary evidence suggests that psychosocial interventions may be useful in this population, with an indication that home-based family and patient intervention may improve depressive symptoms, global HRQoL, and existential and functioning well-being.[70] Although an internet-based problem-solving intervention demonstrated post-treatment improvement in fatigue, there were no changes in depressive symptoms or other aspects of HRQoL.[69] Other novel interventions that aim to enhance HRQoL include acupuncture and virtual reality to target functional and cognitive deficits, with promising improvements reported in self-care ability, sensorimotor function, symptom burden, and several HRQoL domains.[85,86]

DISCUSSION AND FUTURE DIRECTIONS

Patients with brain tumors frequently experience NCF impairment with a multifactorial etiology. However, the patterns and severity NCF impairment and its functional impact can differ greatly according to tumor and patient characteristics, as well as prevention and intervention strategies used. Unfortunately, the NCF difficulties common to these patients can profoundly impact autonomy and well-being, with an indication that even survival can vary in relation to NCF outcomes. Neuropsychologists are uniquely positioned to evaluate the NCF sequelae of brain tumors and can facilitate implementation of existing interventions and the development of novel management strategies moving forward. Further, neuropsychological methods such as performance-based testing have already proven usefulness as important outcomes in clinical trials and should remain among the forefront of patient-centered outcomes in future clinical trials.

In brain tumor clinical trials, the benefits of a new treatment strategy should continue to be weighed against the associated adverse effects, not only in terms of overall and progression-free survivals and NCF, but also with regard to relevant aspects of HRQoL. However, measurement heterogeneity for HRQoL outcomes continues to be an issue when comparing clinical trial findings; thus, further work must strive for an alignment of outcome measures to accurately assess the impact of new treatment strategies on patient functioning and well-being. Additionally, understanding the natural history and trajectory of symptoms and functional limitations are critical to understanding and potentially mitigating risk for poor patient outcomes. Finally, there is a need for the development of novel interventions to target single or multiple aspects

of HRQoL, which could improve symptom burden, tolerance of antitumor therapies, and potentially prolong progression-free survival for patients with brain tumors.

SUMMARY

Despite decades of pharmaceutical and clinical research, brain tumors remain incurable and management is directed at maximizing survival while maintaining functioning and well-being. NCF and HRQoL have become key outcome measures included in brain tumor clinical trials facilitating determination of the net clinical benefit for new treatment options. Additionally, routine assessment of NCF and HRQoL is clinically informative, aiding in the identification of functional problems and symptoms that may be targeted with interventions that ultimately improve patient well-being during an often all-too-brief survivorship period.

CLINICS CARE POINTS

- The measurement of patient functioning should incorporate objective and subjective assessment techniques to determine the extent of impairment in brain function, the consequences of impairment in daily activities, and how dysfunction affects the patient's well-being and social interactions.
- Comprehensive neuropsychological evaluation is superior to brief cognitive screening measures for the assessment of neurocognitive function in patients with brain tumors.
- Neurocognitive impairment is associated strongly with patient functional independence and characterization of a patient's neurocognitive profile can help to facilitate interventions, such as targets for rehabilitation.
- Patient perception of functioning and well-being can be captured through various patient-reported outcome measures, which can be useful in determining the tolerability and effectiveness of various antineoplastic therapies.
- Interventions aimed at improving overall patient functioning may be better informed by assessing patient HRQoL in various domains.
- Long-term survivorship owing to more effective therapies will require careful attention to patient-reported outcomes and performance outcomes, such as HRQoL and NCF, to assess the net clinical benefit for patients.

DISCLOSURE

J.S. Wefel, has consulting/advisory board relationships with Bayer, GT Medical Technologies, Juno, Novocure, and Vanquish Oncology.

REFERENCES

1. Liu R, Page M, Solheim K, et al. Quality of life in adults with brain tumors: current knowledge and future directions. Neuro Oncol 2009;11(3):330–9.
2. Noll KR, Bradshaw ME, Weinberg JS, et al. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. Neurooncol Pract 2018;5(3):184–93.
3. Reijneveld J, Armstrong T. Psycho-oncology. In: Aminoff MJ, Boller F, Swaab DF, editors. Handbook of clinical neurology. vol. 134. 3rd edition. New York: Elsevier B.V.; 2016. p. 1–9.

4. World Health Organization. International classification of functioning, disability, and health. Geneva: World Health Organization; 2001.
5. US Food & Drug Administration. Clinical outcome assessment (COA) 2020. Available at: https://www.fda.gov/about-fda/clinical-outcome-assessment-coa. Accessed April 24, 2021.
6. Armstrong T, Dirven L, Arons D, et al. Glioma patient-reported outcome assessment in clinical care and research: a response assessment in neuro-oncology collaborative report. Lancet Oncol 2020;21:E97–103.
7. Noll KR, Bradshaw ME, Weinberg JS, et al. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. Psychooncology 2017;26(5):617–24.
8. Noll KR, Sullaway CM, Wefel JS. Depressive symptoms and executive function in relation to survival in patients with glioblastoma. J Neurooncol 2019;142(1):183–91.
9. Meyers CA, Wefel JS. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. J Clin Oncol 2003;21(19):3557–8.
10. Armstrong TS, Wefel JS, Wang M, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. J Clin Oncol 2013;31(32):4076.
11. Gondi V, Hermann BP, Mehta MP, et al. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys 2012;83(4):e487–93.
12. Coomans MB, van der Linden SD, Gehring K, et al. Treatment of cognitive deficits in brain tumour patients: current status and future directions. Curr Opin Oncol 2019;31(6):540.
13. van Kessel E, Snijders TJ, Baumfalk AE, et al. Neurocognitive changes after awake surgery in glioma patients: a retrospective cohort study. J Neurooncol 2020;146(1):97–109.
14. Correa D, Kryza-Lacombe M, Zhou X, et al. A pilot study of neuropsychological functions, APOE and amyloid imaging in patients with gliomas. J Neurooncol 2018;136(3):613–22.
15. Altshuler DB, Wang L, Zhao L, et al. BDNF, COMT, and DRD2 polymorphisms and ability to return to work in adult patients with low-and high-grade glioma. Neurooncol Pract 2019;6(5):375–85.
16. Correa DD, Satagopan J, Martin A, et al. Genetic variants and cognitive functions in patients with brain tumors. Neuro Oncol 2019;21(10):1297–309.
17. Noll KR, Ziu M, Weinberg JS, et al. Neurocognitive functioning in patients with glioma of the left and right temporal lobes. J Neurooncol 2016;128(2):323–31.
18. van Kessel E, Emons MA, Wajer IH, et al. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a retrospective cohort study prior to antitumor treatment. Neurooncol Pract 2019;6(6):463–72.
19. Liu Y, Yang K, Hu X, et al. Altered rich-club organization and regional topology are associated with cognitive decline in patients with frontal and temporal gliomas. Front Hum Neurosci 2020;14:23.
20. Hu G, Hu X, Yang K, et al. Restructuring of contralateral gray matter volume associated with cognition in patients with unilateral temporal lobe glioma before and after surgery. Hum Brain Mapp 2020;41(7):1786–96.

21. De Baene W, Rutten GJM, Sitskoorn MM. Cognitive functioning in glioma patients is related to functional connectivity measures of the non-tumoural hemisphere. Eur J Neurosci 2019;50(12):3921–33.
22. Noll KR, Sullaway C, Ziu M, et al. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. Neuro Oncol 2015;17(4):580–7.
23. Wefel JS, Noll KR, Rao G, et al. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. Neuro Oncol 2016;18(12):1656–63.
24. Derks J, Kulik S, Wesseling P, et al. Understanding cognitive functioning in glioma patients: the relevance of IDH-mutation status and functional connectivity. Brain Behav 2019;9(4):e01204.
25. Jütten K, Mainz V, Gauggel S, et al. Diffusion tensor imaging reveals microstructural heterogeneity of normal-appearing white matter and related cognitive dysfunction in glioma patients. Front Oncol 2019;9:536.
26. Noll KR, Weinberg JS, Ziu M, et al. Neurocognitive changes associated with surgical resection of left and right temporal lobe glioma. Neurosurgery 2015;77(5):777–85.
27. Tringale KR, Nguyen T, Bahrami N, et al. Identifying early diffusion imaging biomarkers of regional white matter injury as indicators of executive function decline following brain radiotherapy: a prospective clinical trial in primary brain tumor patients. Radiother Oncol 2019;132:27–33.
28. Wong SS, Case LD, Avis NE, et al. Cognitive functioning following brain irradiation as part of cancer treatment: characterizing better cognitive performance. Psychooncology 2019;28(11):2166–73.
29. Habets EJ, Taphoorn MJ, Nederend S, et al. Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors. J Neurooncol 2014;116(1):161–8.
30. Aerts H, Van Vrekhem T, Stas L, et al. The interplay between emotion regulation, emotional well-being, and cognitive functioning in brain tumor patients and their caregivers: an exploratory study. Psychooncology 2019;28(10):2068–75.
31. Rossi M, Nibali MC, Torregrossa F, et al. Innovation in neurosurgery: the concept of cognitive mapping. World Neurosurg 2019;131:364–70.
32. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol 2014;32(34):3810.
33. Jayaprakash KT, Wildschut K, Jena R. Feasibility of hippocampal avoidance radiotherapy for glioblastoma. Clin Oncol 2017;29(11):748–52.
34. Sherman JC, Colvin MK, Mancuso SM, et al. Neurocognitive effects of proton radiation therapy in adults with low-grade glioma. J Neurooncol 2016;126(1):157–64.
35. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013;15(10):1429–37.
36. Rapp SR, Case LD, Peiffer A, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. J Clin Oncol 2015;33(15):1653.
37. Chang MC, Chun MH. The effect of hypnotics on sleep quality and cognitive function in patients with brain tumors. J Korean Neurosurg Soc 2020;63(2):261.

38. Gehring K, Patwardhan S, Collins R, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. J Neurooncol 2012;107(1):165–74.
39. van Lonkhuizen PJ, Klaver KM, Wefel JS, et al. Interventions for cognitive problems in adults with brain cancer: a narrative review. Eur J Cancer Care 2019; 28(3):e13088.
40. Gehring K, Stuiver MM, Visser E, et al. A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. Neuro Oncol 2020;22(1):103–15.
41. Dirven L, Reijneveld JC, Taphoorn MJB. Health-related quality of life or quantity of life: a difficult trade-off in primary brain tumors? Semin Oncol 2014;41(4):541–52.
42. Taphoorn M, Stupp R, Coens C, et al. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. Lancet Oncol 2005;6:937–44.
43. Taphoorn M, van den Bent M, Mauer M, et al. Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: results of a European Organisation for Research and Treatment of Cancer randomised clinical trial. J Clin Oncol 2007;25:5723–30.
44. Dirven L, Aaronson NK, Heimans JJ, et al. Health-related quality of life in high-grade glioma patients. Chin J Cancer 2014;33(1):40–5.
45. Giovagnoli A, Silvani A, Colombo E, et al. Facets and determinants of quality of life in patients with recurrent high-grade glioma. J Neurol Neurosurg Psychiatr 2005;76(4):562–8.
46. Baker P, Bambrough J, Fox J, et al. Health-related quality of life and psychological functioning in patients with primary malignant brain tumors: a systematic review of clinical, demographic and mental health factors. Neurooncol Pract 2015; 3(4):211–6.
47. Salo J, Niemala A, Joukamaa M, et al. Effect of brain tumour laterality on patients' perceived quality of life. J Neurol Neurosurg Psychiatry 2002;72:373–7.
48. Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. J Neurooncol 2016;130(2):269–82.
49. Taphoorn MJ, Sizoo EM, Bottomley A. Review on quality of life issues in patients with primary brain tumors. Oncologist 2010;15(6):618–26.
50. Tunthanathip T, Madteng S. Factors associated with the extent of resection of glioblastoma. Precis Cancer Med 2020;3:12.
51. Armstrong T, Shade M, Breton G, et al. Sleep-wake disturbance in patients with brain tumors. Neuro Oncol 2017;19(3):323–35.
52. Rogers J, Vera E, Acquaye A, et al. Living with a central nervous system (CNS) tumor: findings on long-term survivorship from the NIH natural history study. Neurooncol Pract 2021;8(4):1–15.
53. Liu R, Solheim K, Polley M, et al. Quality of life in low-grade glioma patients receiving temozolomide. Neuro Oncol 2009;11:59–68.
54. Lv Y, Zhang J, Liu Z, et al. Quality of life and efficacy of temozolomide combined with whole-brain radiotherapy in patients with brain metastases from non-small-cell lung cancer. Mol Clin Oncol 2018;9(1):70–4.
55. Verhaak E, Gehring K, Hanssens PEJ, et al. Health-related quality of life in adult patients with brain metastases after stereotactic radiosurgery: a systematic, narrative review. Support Care Cancer 2020;28(2):473–84.
56. Dutz A, Agolli L, Butof R, et al. Neurocognitive function and quality of life after proton beam therapy for brain tumour patients. Radiother Oncol 2020;143:108–16.

57. Langegard U, Fransson P, Bjork-Eriksson T, et al. Health-related quality of life in patients with primary brain tumors during and three months after treatment with proton beam therapy. Tech Innov Patient Support Radiat Oncol 2021;17:5–17.
58. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 2017;377(20):1954–63.
59. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370(8):699–708.
60. Taphoorn MJ, Henriksson R, Bottomley A, et al. Health-related quality of life in a randomized phase iii study of bevacizumab, temozolomide, and radiotherapy in newly diagnosed glioblastoma. J Clin Oncol 2015;33(19):2166–75.
61. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370(8):709–22.
62. van den Bent MJ, Klein M, Smits M, et al. Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. Lancet Oncol 2018;19(9):1170–9.
63. The Brain Tumour Charity. TTF (tumour treating fields, or optune). 2021. Available at: https://www.thebraintumourcharity.org/brain-tumour-diagnosis-treatment/treating-brain-tumours/emerging-treatments/ttf-tumour-treating-fields/. Accessed March 19, 2021.
64. Stupp R, Wong E, Kanner A, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer 2012;48:2192–202.
65. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA 2017;318(23):2306–16.
66. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: a secondary analysis of a randomized clinical trial. JAMA Oncol 2018;4(4):495–504.
67. Tanti MJ, Marson AG, Chavredakis E, et al. The impact of epilepsy on the quality of life of patients with meningioma: a systematic review. Br J Neurosurg 2016;30(1):23–8.
68. Arvold ND, Armstrong TS, Warren KE, et al. Corticosteroid use endpoints in neuro-oncology: response assessment in neuro-oncology working group. Neuro Oncol 2018;20(7):897–906.
69. Armstrong TS, Vera-Bolanos E, Acquaye A, et al. The symptom burden of primary brain tumors: evidence for a core set of tumor- and treatment-related symptoms. Neuro Oncol 2016;18(2):252–60.
70. Randazzo D, Peters K. Psychosocial distress and its effects on the health-related quality of life for primary brain tumor patients. CNS Oncol 2018;5(4):241–9.
71. Marotta D, Tucker Z, Hayward EN, et al. Relationship between cognitive functioning, mood, and other patient factors on quality of life in metastatic brain cancer. Psychooncology 2020;29(7):1174–84.
72. Basch E, Abernethy A, Mullins C, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol 2012;30(34):4249–55.
73. Bosma I, Reijneveld J, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. Neuro Oncol 2009;11:51–8.

74. Coomans M, Dirven L, Aaronson N, et al. Symptom clusters in newly diagnosed glioma patients: which symptom clusters are independently associated with functioning and global health status. Neuro Oncol 2019;21(1):1447–57.
75. Armstrong T, Vera-Bolanos E, Acquaye A, et al. The symptom burden of primary brain tumors: evidence for a core set of tumor- and treatment-related symptoms. Neuro Oncol 2015;18(2):252–60.
76. Rogers J, Vera E, Acquaye A, et al. Living with a central nervous system tumor: findings on long-term survivorship from the NIH Natural History Study. Neurooncol Pract 2021;8(4):460–74.
77. Vera E, Acquaye AA, Mendoza TR, et al. Relationship between symptom burden and health status: analysis of the MDASI-BT and EQ-5D. Neurooncol Pract 2018;5(1):56–63.
78. Armstrong T, Vera-Bolanos E, Gning I, et al. The impact of symptom interference using the MD Anderson Symptom Inventory-Brain Tumor module (MDASI-BT) on prediction of recurrence in primary brain tumor patients. Cancer 2011;117(14):3222–8.
79. Kalra D, Menon N, Singh G, et al. Financial toxicities in patients receiving systemic therapy for brain tumors: a cross-sectional study. Cancer Res Treat 2020;3:724–9.
80. Mols F, Tomalin B, Pearce A, et al. Financial toxicity and employment status in cancer survivors. A systematic literature review. Support Care Cancer 2020;28(12):5693–708.
81. Pan-Weisz TM, Kryza-Lacombe M, Burkeen J, et al. Patient-reported health-related quality of life outcomes in supportive-care interventions for adults with brain tumors: a systematic review. Psychooncology 2019;28(1):11–21.
82. Boele F, Douw L, de Groot M, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. Neuro Oncol 2013;15(10):1420–8.
83. Page B, Shaw E, Lu L, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. Neuro Oncol 2015;17(10):1393–401.
84. Butler JJ, Case L, Atkins J, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. Int J Radiat Oncol Biol Phys 2007;69(5):1496–501.
85. Yang S, Chun M, Son Y. Effect of virtual reality on cognitive dysfunction in patients with brain tumor. Ann Rehabil Med 2014;38(6):726–33.
86. Yu H, Schroder S, Liu Y, et al. Hemiparesis after operation of astrocytoma grade II in adults: effects of acupuncture on sensory-motor behavior and quality of life. Evid Based Complement Alternat Med 2013;1–13.