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Clinical Investigation

Quality of Life Is Independently Associated With Neurocognitive Function in Patients With Brain Tumors: Analysis of a Prospective Clinical Trial

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Purpose: We conducted the first prospective longitudinal study examining the independent association between patient-reported health-related quality of life (hrQoL) (physical, social/family, emotional, functional, and brain cancer-specific) and neurocognitive function (NCF), while controlling for mood symptoms in patients with primary brain tumors.

Methods and Materials: Patients with primary brain tumors (n = 59) receiving brain radiation therapy underwent hrQOL (Functional Assessment of Cancer Therapy-Brain), mood (Beck Depression and Anxiety Inventories), and neurocognitive evaluation at baseline and 3, 6, and 12 months postradiation therapy in a prospective clinical trial. Neurocognitive assessments measured attention/processing speed, memory, and executive function, including the Delis-Kaplan Executive Function System Verbal Fluency, Hopkins Verbal Learning Test Revised (HVLT-R), and Brief Visuospatial Memory Test. Subjects underwent neurocognitive, mood, and hrQoL assessments in the same testing session. Multivariable linear mixed-effects models assessed associations between hrQOL and NCF over time, controlling for patient, tumor, and treatment characteristics as well as timepoint-specific patient-reported mood (ie, anxiety and depression symptoms). *P* values were adjusted for multiple comparisons.

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Results: Higher physical hrQoL was associated with better verbal memory (HVLT-R Total Recall, $P = .047$), and higher functional hrQoL was associated with better executive function (Delis-Kaplan Executive Function System Verbal Fluency Switching Total, $P = .009$) and verbal memory (HVLT-R Delayed Recall, $P = .006$). Higher brain tumor-specific hrQoL was associated with better verbal and nonverbal memory (HVLT-R Total, $P = .004$ and Delayed Recall, $P = .030$; Brief Visuospatial Memory Test Total, $P = .049$ and Delayed Recall, $P = .049$). There was no association between social/family or emotional hrQoL and NCF after controlling for mood.

Conclusions: Higher physical, functional, and brain tumor-specific hrQoL were associated with better executive function and memory among patients with primary brain tumors. Physical and functional impairments are correlated with cognitive performance. Interventions to maximize quality of life after treatment may influence neurocognition and vice versa.

Introduction

Mood, health-related quality of life (hrQoL), and neurocognitive function (NCF) are the most important patient-relevant outcomes other than survival in the brain tumor population.[1] These outcomes are assessed and regarded independently in the clinical and research settings[2,3]; however, it is in fact the *intersection between* these 3 components that contributes to patients' overall functioning. Indeed, in a previous study, we found that patients' mood correlates with how patients think,[4] suggesting that efforts to address anxiety and depression symptoms may improve neurocognitive performance. Although hrQoL and mood are highly linked,[5,6] hrQoL encompasses important aspects of the patient experience not captured by assessment of mood alone, including physical symptoms and functional status. These represent crucial aspects of patient well-being and may thus additionally contribute to NCF.

Explorations of the relationship between hrQoL and NCF in the primary brain tumor population have been limited. Two retrospective cross-sectional studies[5,7] of patients with primary brain tumors at a single timepoint and one longitudinal study of patients with metastatic brain tumors[8] have demonstrated a link between NCF and hrQoL. Yet, to our knowledge, no prospective longitudinal studies of this association in patients with primary brain tumors have been conducted. In particular, previous studies have failed to parse the relationship between NCF and hrQoL independent of depression and anxiety symptoms. Although mood has been shown to correlate with neurocognitive performance,[4] it comprises only one segment of well-being. The additional facets of patients' experiences captured within hrQoL may share a different relationship with NCF that is also important to explore. We present the first prospective clinical trial examining the association between patient-reported hrQoL and domain-specific NCF while controlling for mood symptoms in a diverse group of high-functioning patients with primary brain tumors, for whom NCF and hrQoL preservation is especially pertinent. We hypothesized that diminished multidimensional hrQoL would be associated with reduced executive function, attention and processing speed, and memory assessed at the same timepoint, highlighting the significance of collecting both mood and hrQoL outcomes when evaluating NCF in this patient population.

Methods and Materials

Study design and participants

This study was approved by our institutional review board. All enrolled patients provided written informed consent. Adult patients (n = 63) with primary brain tumors treated with partial-brain radiation therapy (RT) with protons or photons were enrolled in this ongoing prospective, observational clinical trial from 2014 to 2019. Eligibility criteria included age >18 years, Karnofsky Performance Status ≥70, ability to undergo neurocognitive testing in English, and life expectancy >1 year. Patients who received prior brain RT were excluded. Subjects underwent neurocognitive, mood, and hrQoL assessments in the same testing session at baseline (pre-RT) and at 3, 6, and 12 months after RT.

Quality of life assessments

The Functional Assessment of Cancer Therapy-Brain (FACT-Br) is a validated, self-report, 53-item questionnaire evaluating symptoms associated with primary and metastatic brain malignancies over the past 7 days. This covers 5 subscales of well-being: physical, social/family, emotional, functional, and brain tumor-specific. The FACT-Br has been used in other studies of patients with brain tumors.[9,10] Greater hrQoL is reflected by a higher score on each subscale. Mean scores on each hrQoL subscale among a reference population of patients with brain tumors have been described elsewhere.[11] Scores were classified as average, below/above average, and well below/above average (within 1, 1-2, and 2-3 standard deviations of the subscale mean, respectively).

Mood assessments

The Beck Depression Inventory-II[12] (BDI) and Beck Anxiety Inventory[13] (BAI) are validated, self-report

questionnaires that assess the number and severity of depression and anxiety symptoms in the past 1 to 2 weeks. A higher score on each of these tests indicates a greater number and/or severity of depression and anxiety symptoms. These are robust assessments that have been used in other studies of patients with cancer.[4,5]

Neurocognitive assessments

Neurocognitive assessment consisted of 6 tests (12 test indices) measuring executive function, attention and processing speed, and memory. Executive function was measured by the Delis-Kaplan Executive Function System[14] Verbal Fluency (DKEFS-VF) Letter Fluency and Category Switching subtests and the Wisconsin Card Sorting[15] Test Perseverative Errors score. Attention and processing speed were evaluated by the DKEFS Trail Making Visual Scanning, Number Sequencing, and Letter Sequencing tests and the Weschler-Adult Intelligence Scale-IV[16] Digit Span and Coding subtests. Memory was assessed with the Hopkins Verbal Learning Test-Revised[17] (HVLT-R) Total Recall and Delayed Recall tests and the Brief Visuospatial Memory[18] (BVMT) Total Recall and Delayed Recall tests. To avoid increasing familiarity with tests at subsequent testing sessions, alternate forms of the DKEFS-VF test were used at 3 and 12 months. Alternate forms of the HVLT-R and BVMT tests were used at each testing session. Raw neurocognitive test scores were converted to t scores (mean = 50, standard deviation = 10) and corrected for age, sex, and education when appropriate.[19]

Statistical analysis

Associations between patient and clinical factors and baseline and longitudinal hrQoL

Statistics were performed in R Studio. First, univariable linear and linear mixed-effects (LME) models were fit to assess the association of baseline and longitudinal FACT-Br scores, respectively, with patient characteristics (shown in Table 1). All LME models were fit using the lme4 package for R.[20] LME models are well-suited for longitudinal analyses because they account for within-subject correlation between repeated measures and allow for incomplete outcome data.[21] Covariates with a P value < .2 on initial univariable analysis were then included in multivariable linear and LME models for stepwise backward selection. All covariates with a likelihood ratio test (LRT) P value < .05 on backward selection were included in the final, multivariable models. The association between FACT-Br and BAI/BDI scores assessed at the same timepoint was also assessed on univariable LME analysis. All LME models of FACT-Br scores additionally included baseline FACT-Br score and time (categorical) as fixed effects and subject-specific random intercepts.

Associations between hrQoL and NCF

We fit multivariable LME models of the association between each raw FACT-Br score (fixed effect) and each neurocognitive test t score (dependent variable) assessed at

Table 1 Patient, treatment, and tumor characteristics

Study population characteristics at baseline, n = 59	n (%) or median (range)
Age, y	47 (20-75)
Sex	
Male	36 (61.0)
Female	23 (39.0)
Race/ethnicity	
Hispanic	6 (10.2)
Non-Hispanic	
Asian/Pacific Islander	3 (5.1)
Black/African American	1 (1.7)
White	49 (83.1)
Highest education achieved	
High school	12 (22.6)
College	26 (49.1)
Graduate school	15 (28.3)
Marital status	
Married	42 (71.2)
Single	17 (28.8)
Handedness	
Left-handed	8 (14.0)
Right-handed	49 (86.0)
Tumor diagnosis	
Glioma	
Low-grade (WHO grade I-II)	9 (15.3)
High-grade (WHO grade III-IV)	26 (44.1)
Pituitary adenoma	5 (8.5)
Meningioma	13 (22.0)
Other*	6 (10.2)
Tumor side	
Left	32 (54.2)
Right	23 (39.0)
Central	4 (6.8)
Tumor region	
Frontal	18 (30.5)
Temporal	15 (25.4)
Suprasellar	9 (15.3)
Parietal	6 (10.2)
Base of skull	4 (6.8)
Cerebellar	3 (5.1)
Cavernous sinus	3 (5.1)
Sphenoid wing	1 (1.7)
Baseline Karnofsky Performance Status score	
80	4 (6.8)
90	36 (61.0)
100	19 (32.2)
Radiation therapy type	
IMRT/VMAT	44 (74.6)
Protons	15 (25.4)

(*Continued*)

Table 1 (*Continued*)

Study population characteristics at baseline, n = 59	n (%) or median (range)
Radiation dose, Gy (median, 59.4; range, 50.4-70)	
<54	8 (13.6)
≥54	51 (86.4)
Planning target volume, cc	144.6 (3.32-579.1)
Surgery	
Gross total resection	13 (22.0)
Subtotal resection	36 (61.0)
Biopsy	3 (5.1)
None	7 (11.9)
Chemotherapy during or after radiation therapy	34 (57.6)
Seizures during study period	26 (44.1)
Antiepileptic drug use during study period	31 (52.5)

Abbreviations: IMRT/VMAT = intensity modulated radiation therapy/volumetric arc therapy; WHO = World Health Organization.
* Includes craniopharyngioma (2), schwannoma (3), and low-grade chondrosarcoma (1)

the same timepoint. Covariates listed in Table 1 were included in these models via stepwise backward selection to account for variability in patient characteristics within our sample. We also included BAI and BDI scores in the backward selection process if they were found to be significantly associated with FACT-Br scores assessed at the same timepoint. Clinical and mood covariates with an LRT P value < .10 on backward selection were included in the final, multivariable models. LRT P values for FACT-Br subscale estimates of neurocognitive test scores in multivariable models were corrected for multiple comparisons using the false discovery rate.[22]

Results

Patient cohort

Of the 63 patients enrolled in this study, 59 underwent baseline neurocognitive and hrQoL assessment and were included in the analysis. At 3, 6, and 12 months post-RT, 38, 40, and 33 patients underwent neurocognitive and hrQoL assessment, respectively. Patient characteristics are summarized in Table 1. This cohort was predominantly non-Hispanic white (78%) and highly educated (49.1% college-educated, 28.3% with graduate-level education).

Analysis of HrQoL subscales

Baseline FACT-Br outcomes are demonstrated in Table E1. At baseline, the majority of patients had average hrQoL across all subscales. FACT-Br Total and subscale scores over the study period are shown in Figure 1. Only FACT-Br Social scores significantly decreased with time (P < .001).

Association between patient and clinical factors and baseline FACT-Br scores

Multivariable associations between patient characteristics and FACT-Br scores at baseline are illustrated in Figure 2a with significant (P < .05) predictors shown in blue and yellow. Multivariable associations with P values are shown in Table E2. Patients receiving protons had higher baseline FACT-Br Total (P = .012), Functional (P = .036), and Brain (P = .015) scores. Lower baseline FACT-Br Emotional scores were observed in patients with right-sided tumors (P = .013). Lower baseline FACT-Br Brain scores correlated with a history of seizures (P = .008).

Association between patient and clinical factors and longitudinal FACT-Br scores

Multivariable LME analysis of longitudinal FACT-Br scores with clinical predictors are demonstrated in Figure 2b, with significant (P < .05) predictors shown in blue and yellow. Multivariable associations with P values are shown in Table E3. Patients with a history of seizures had lower longitudinal FACT-Br (P = .017) Total, and Brain (P < .001) scores. Reduced longitudinal FACT-Br Emotional scores correlated with left-handedness (P = .003). Lower education level (P = .027) was associated with worse longitudinal FACT-Br Brain scores.

Univariable longitudinal associations between BAI/BDI scores and FACT-Br scores are demonstrated in Table E4. Mean BAI/BDI scores at each timepoint in the same cohort have been published elsewhere.[4] Longitudinal BAI and BDI scores were associated with all FACT-Br subscales assessed at the same timepoint (P < .001); therefore, BAI and BDI were included as covariates in the backward selection process of multivariable LME models of neurocognitive outcomes. Planning target volume was not included in the stepwise backward selection process given that it was highly correlated with glioma diagnosis (t test P < .001).

Association between FACT-Br scores and NCF

Twelve measures of 3 neurocognitive domains (executive function, attention and processing speed, and memory) were assessed. Changes in these neurocognitive outcomes over time in the same cohort have been described previously.[23-25]

Association between FACT-Br Total, Physical, Functional, and Brain and NCF

Univariable LME analysis of the association between clinical covariates and longitudinal neurocognitive test

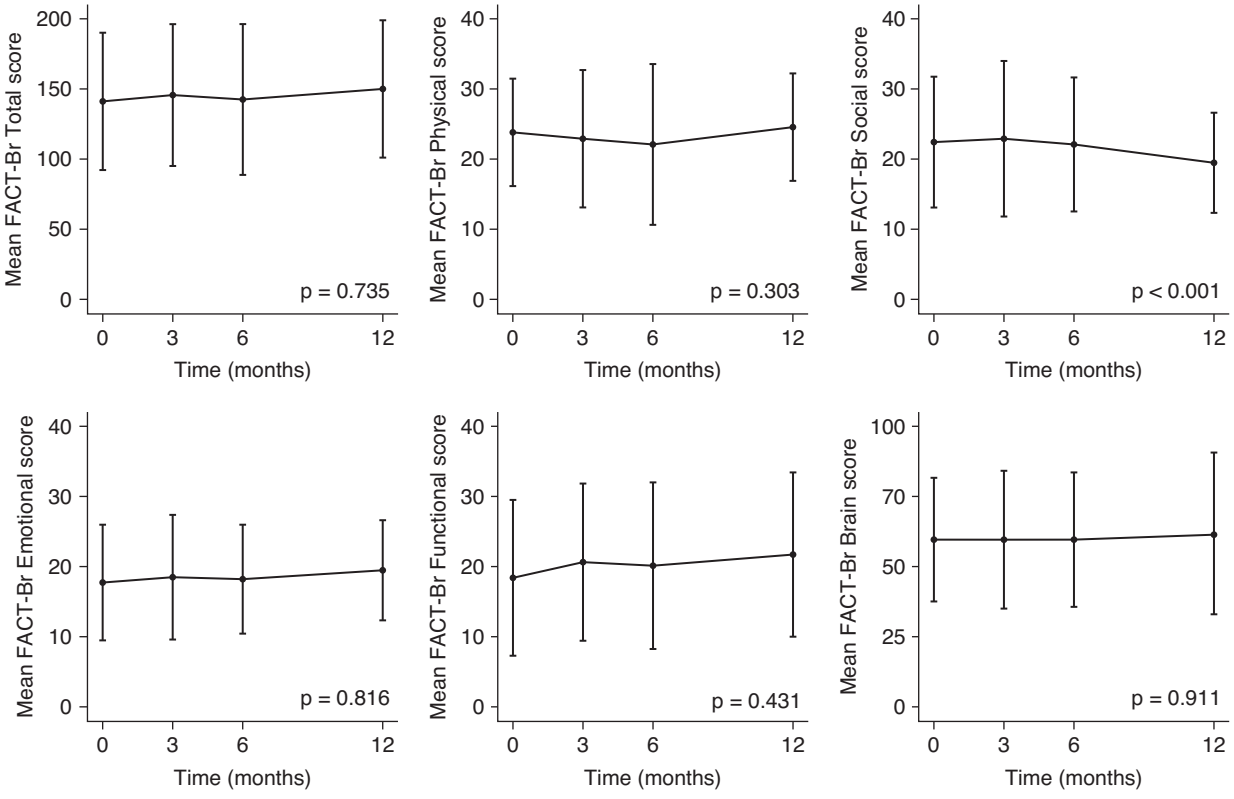

Fig. 1. Mean Functional Assessment of Cancer Therapy-Brain (FACT-Br) Total and subscale scores over time. Line plots for raw FACT-Br Total and subscale scores over time. Line plots are mean scores over time with error bars representing the 95% confidence intervals. Mean FACT-Br Social scores significantly decreased over time (likelihood ratio test P value $< .001$).

outcomes is shown in Table E5. Multivariable LME analysis of the association between FACT-Br Total, Physical, Functional, and Brain and each neurocognitive test controlling for mood symptom scores is shown in Figure 3. Higher FACT-Br Total scores were associated with better DKEFS-VF Switching Total ($\beta = 0.162$, $P < .001$) and HVLT-R Total ($\beta = 0.141$, $P = .047$) and Delayed ($\beta = 0.124$, $P = .004$) Recall performance. Higher FACT-Br Physical scores correlated with higher HVLT-R Total Recall scores ($\beta = 0.198$, $P = .047$). Higher FACT-Br Functional scores were associated with better DKEFS-VF Switching Total ($\beta = 0.527$, $P = .009$) and HVLT-R Delayed Recall ($\beta = 0.527$, $P = .006$) performance. Higher FACT-Br Brain scores correlated with higher HVLT-R Total ($\beta = 0.266$, $P = .004$), HVLT-R Delayed ($\beta = 0.191$, $P = .030$), BVMT Total ($\beta = 0.159$, $P = .049$), and BVMT Delayed ($\beta = 0.150$, $P = .049$) Recall scores.

Association between FACT-Br Social and Emotional and NCF

Multivariable LME models of the association between FACT-Br Social and Emotional scores and each neurocognitive domain are represented in Figure 4. After controlling for depression and anxiety symptom scores, there were no associations between FACT-Br Social and Emotional scores and any neurocognitive tests.

Discussion

Mood, hrQoL, and NCF are critical outcomes in the brain tumor population[1] and together contribute to patients' overall sense of well-being. Nevertheless, the interplay between these components is often overlooked in the research and clinical settings. Clarification of the relationship between how patients *subjectively feel* and *objectively think* may highlight the multifactorial nature of patients' cognitive impairments and facilitate the development of interventions that improve NCF and well-being. Our previous work[4] demonstrated an association between NCF and depression and anxiety symptoms, suggesting that concurrent mood symptoms should be accounted for in clinical trials measuring NCF. However, assessment of mood fails to capture physical symptoms and functional status, both of which are encompassed within hrQoL and may also correlate with cognitive performance. In this prospective longitudinal study, we identified associations between executive function and memory and physical, functional, and brain tumor-specific hrQoL independent of mood in patients with primary brain tumors. Future studies of patients with brain

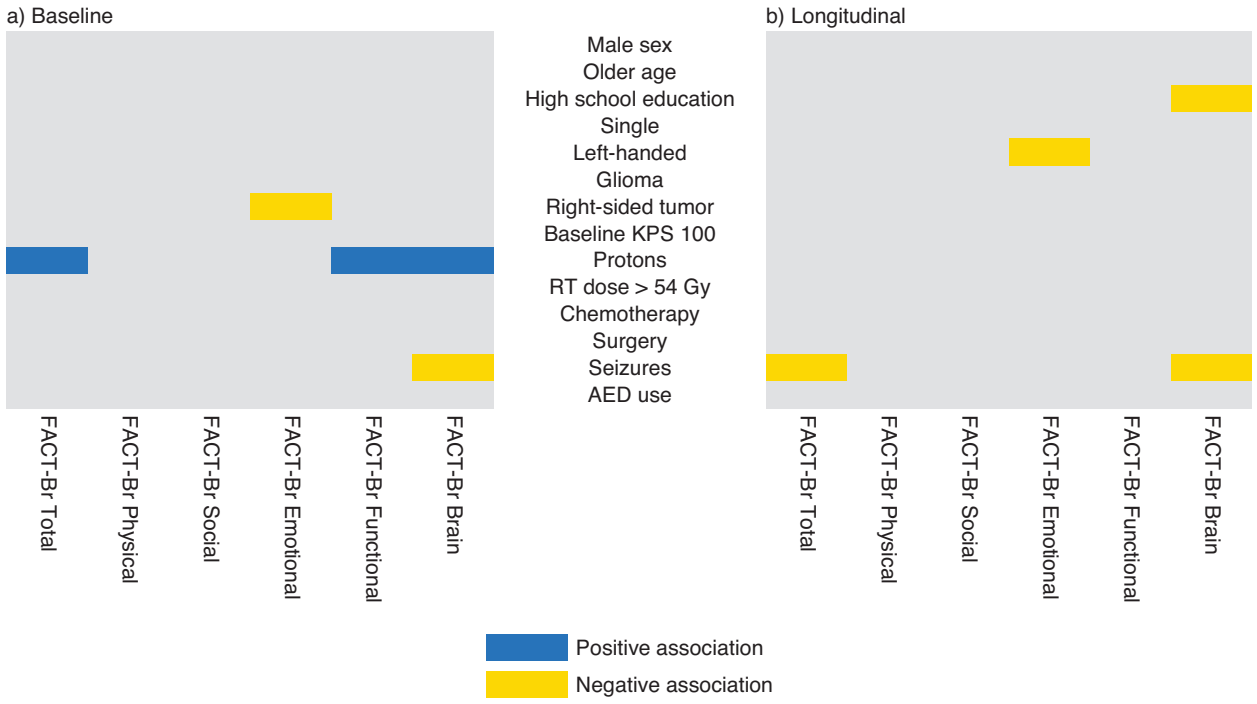

Fig. 2. Multivariable associations between patient and clinical factors and baseline and longitudinal Functional Assessment of Cancer Therapy-Brain (FACT-Br) scores. Baseline (a) and longitudinal (b) multivariable associations between patient, tumor, and treatment characteristics and FACT-Br scores. Only significant ($P < .05$) associations are shown in color. Blue squares indicate significant positive association; yellow squares indicate significant negative association. Gray squares indicate no significant association.

tumors should therefore control for both mood *and* hrQoL when assessing NCF, especially given that these outcomes are routinely gathered in prospective clinical trials.[2,3] This also suggests that physical symptoms and functional impairment may influence cognitive performance and vice versa, paving the way for novel interventions to improve patient well-being.

Physical function and cognitive status are often regarded as separate domains in patients with primary brain tumors. We found that physical hrQoL and memory were associated; however, it is unclear which one affects the other. In the FACT-Br Physical subscale, patients report symptoms including nausea, pain, and fatigue. Lower short-term memory scores have been observed in patients with chronic pain[26] and fatigue syndromes,[27] likely because these symptoms interfere with information consolidation and effort during testing, which may manifest as memory deficits.[28] Additionally, although exercise has been shown to result in cognitive benefits via improved blood flow,[29] physical impairments may limit the ability of patients to engage in these activities.

We also uncovered correlations between functional hrQoL and executive function and memory. The FACT-Br Functional subscale assesses patients' ability to work and participate in hobbies. These allow patients to engage in purposeful activity, which contributes to neuroplasticity and cognitive reserve.[30] Previous studies of patients with primary brain tumors have demonstrated associations between functional hrQoL and executive function, attention and processing speed, and memory; however, these outcomes were assessed at a single timepoint.[5,31] Here, we demonstrate longitudinal correlations between NCF and functional hrQoL before and after RT, both of which may vary significantly over time. Moreover, these prior studies did not adjust for mood symptoms, which we demonstrate to be highly correlated with hrQoL.

Brain tumor-specific hrQoL was associated with memory. Patients report brain tumor-specific symptoms, including visual and hearing impairments, in the FACT-Br Brain subscale. These deficits have been reported in over half of patients with brain tumors[32] and have been linked to NCF decline.[33,34] A secondary analysis of a phase III trial found correlations between FACT-Br Brain scores and memory, verbal fluency, motor coordination, and executive function among patients with metastatic brain tumors.[8] However, these results may not be generalizable to patients with primary brain tumors, who may differ with regards to brain tumor symptoms and treatment.[35] This study also did not adjust for mood symptoms, making it difficult to measure the independent relationship between brain tumor symptoms and cognition.

Alternatively, posttreatment cognitive decline may portend reduced hrQoL. Of the 3 cognitive domains assessed in this study, only memory and executive function correlated with physical and functional hrQoL. These cognitive domains have been shown to predict future functional

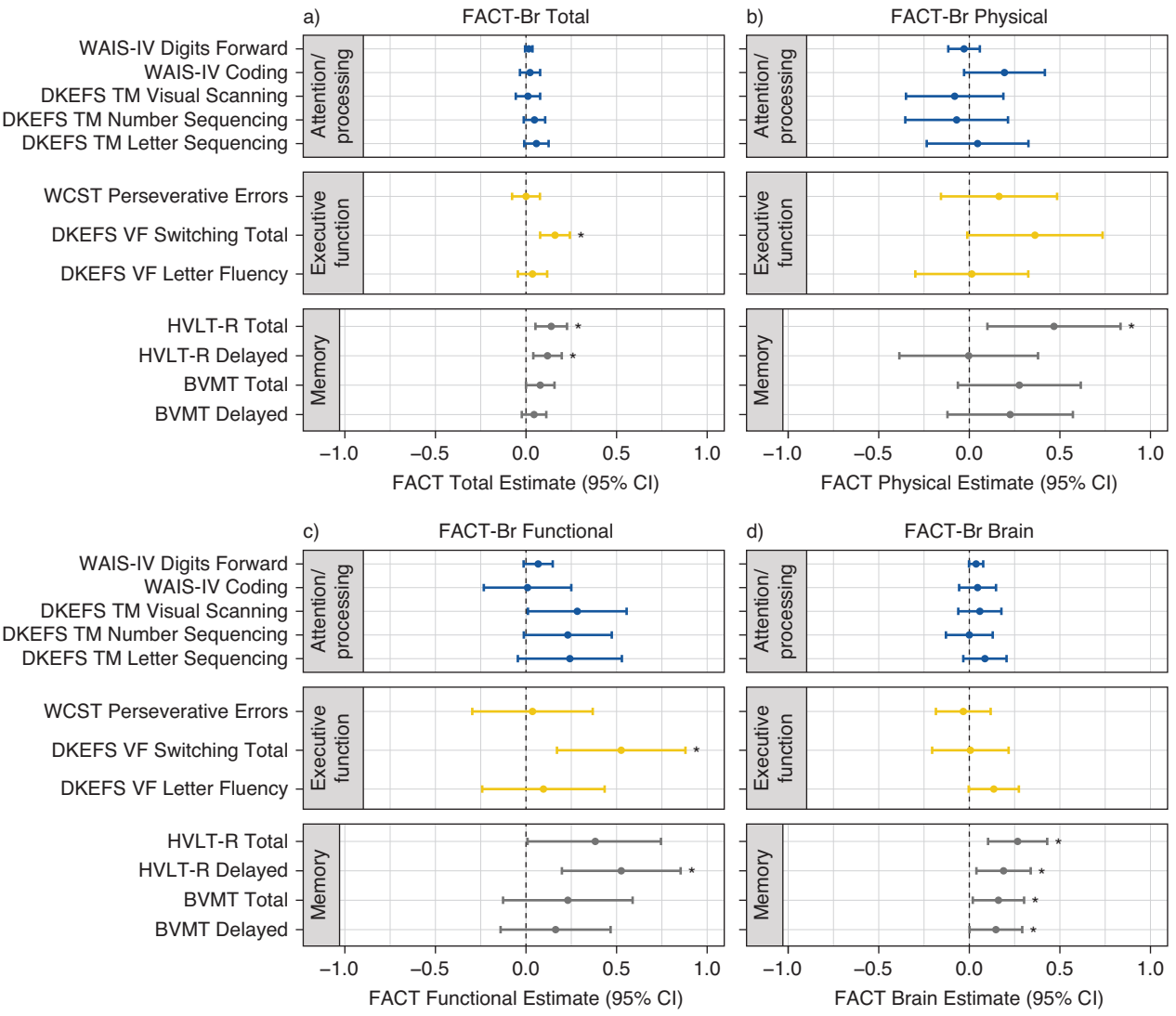

Fig. 3. Multivariable linear mixed-effects regression of cognitive function on total, physical, functional, and brain tumor-specific health-related quality of life (hrQoL). Multivariable linear mixed-effects analyses of (a) Functional Assessment of Cancer Therapy-Brain (FACT-Br) Total, (b) FACT-Br Physical, (c) FACT-Br Functional, and (d) FACT-Br Brain as predictors of neurocognitive functioning. Assessments of attention/processing (5 tests), executive functioning (3 tests), and memory (4 tests) are shown. Each assessment was investigated with a unique model. Beta estimates are shown by dot. Whiskers reflect 95% confidence interval (CI) of the estimate. Significant associations after correction for multiple comparisons are reflected by a 95% CI that does not cross the 0.0 reference line. *Indicates associations that remained significant after correcting for multiple comparisons.

ability in older adult populations.[36] Cognition plays a vital role in facilitating communication among the biological, social, and behavioral systems involved in the execution of physical tasks.[37] Moreover, memory and executive function are critical in instrumental activities of daily living such as financial management, transportation, and shopping.

We did not identify associations between social/family and emotional hrQoL and NCF after controlling for mood. Information captured by these FACT-Br subscales, which assess patients' level of social support, worry, and sadness, likely overlaps considerably with that measured by the BAI and BDI surveys. This may also explain why we did not observe associations between any hrQoL subscales and attention and processing speed. In a previous study examining mood and similar cognitive domains, we only found correlations between mood and attention and processing speed.[4] This suggests that mood and hrQoL may have different relationships with NCF in patients with brain tumors, with depressed or anxious mood primarily associated with attention and processing speed and physical functioning principally associated with executive function and memory.

Only social hrQoL significantly declined over the study period. This trend has been observed in patients with breast cancer[38] but has not yet been described in patients with brain tumors to our knowledge. Patients with cancer often describe an outpouring of social support upon initial

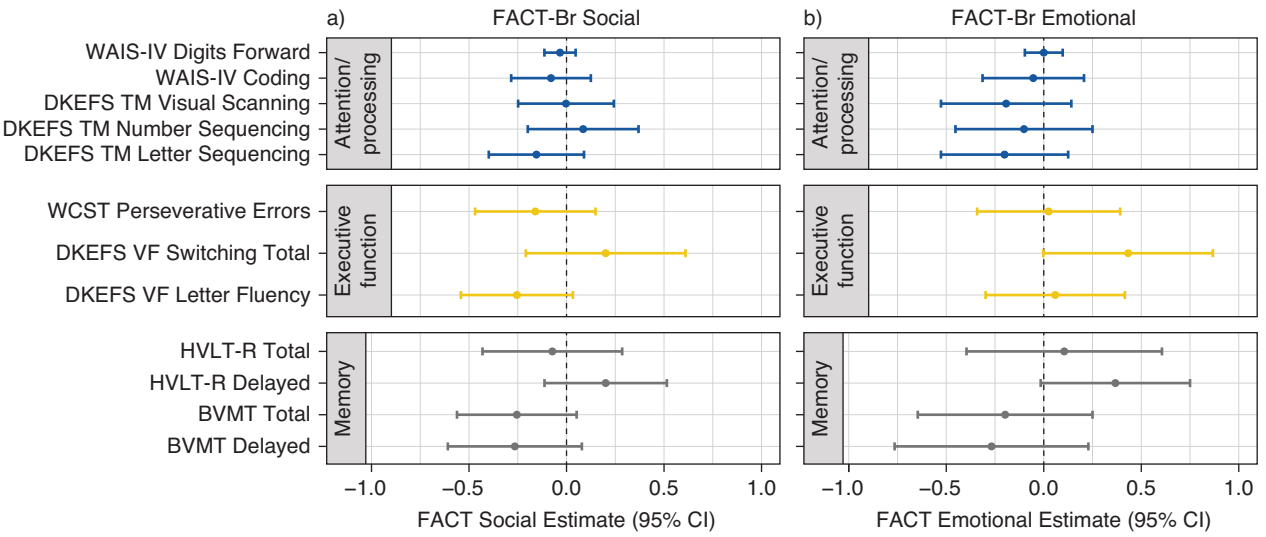

Fig. 4. Multivariable linear mixed-effects regression of cognitive function on social and emotional health-related quality of life (hrQoL). Multivariable linear mixed-effects analyses of (a) Functional Assessment of Cancer Therapy-Brain (FACT-Br) Social and (b) FACT-Br Emotional as predictors of neurocognitive functioning. Assessments of attention/processing (5 tests), executive functioning (3 tests), and memory (4 tests) are shown. Each assessment was investigated with a unique model. Beta estimates are shown by dot. Whiskers reflect 95% confidence interval (CI) of the estimate. There were no significant associations between FACT-Br Social/Family and FACT-Br Emotional hrQoL and neurocognition after correcting for multiple comparisons.

diagnosis and treatment that declines over time as they begin to "look fine" again.[39] This may reflect the experience of patients in our cohort.

We also identified demographic and clinical characteristics associated with reduced pre- and post-RT hrQoL. Patients with right-sided tumors and those who were left-handed reported worse baseline and longitudinal emotional hrQoL, respectively. Right-sided tumors have been associated with worse emotional functioning in patients with primary brain tumors[40]; this may be related to hemispheric specialization in emotional processing and neurotransmitter concentrations.[41] Additionally, higher rates of anxiety and depression have been reported among left-handed individuals.[42,43] Patients with more aggressive tumors had reduced hrQoL in multiple domains at baseline and after RT. This included patients who underwent chemotherapy, received higher radiation doses, underwent intensity modulated RT/volumetric-modulated arc therapy versus proton therapy, and had gliomas. These patients likely experienced greater anxiety, future uncertainty, and brain tumor- and treatment-related symptoms throughout the study.

Our results suggest that interventions to maximize hrQoL may influence cognition and vice versa. The relationships and significant associations among these outcomes are shown in the Venn diagram of Figure E2. Although neurocognitive preservation strategies in patients undergoing brain RT have increasingly focused on complex dose-avoidance techniques[44] and proton therapy,[45] our findings reinforce the notion that patient-specific factors, such as hrQoL, may also influence NCF. Importantly, our findings imply that efforts to improve posttreatment physical symptoms and functional status, such as with structured exercise interventions,[46] may hold additional cognitive benefits on top of correcting mood symptoms alone. Alternatively, more widespread use of cognitive-sparing RT planning, directed at memory preservation for example, may improve posttreatment physical and functional well-being. Ultimately, a combination of these strategies will produce the greatest improvement in patient experience after brain tumor treatment.

This study has several limitations. Our cohort was relatively small and consisted of mostly white, highly educated patients; however, patients underwent extensive NCF, hrQoL, and mood testing in the same sitting at multiple time points. There was some drop-off in FACT-Br and NCF test completion between baseline and 12 months post-RT. This study was part of an ongoing clinical trial and some patients had therefore not yet reached later time-points. Although our cohort included patients with benign tumors and gliomas, our models adjusted for glioma histology. Moreover, this heterogeneous sample allowed us to assess the relationship between hrQoL and NCF in a diverse group of high-functioning patients with brain tumors, for whom NCF and hrQoL preservation is particularly relevant. HrQoL may have been overestimated in this study given that participation in a clinical trial requires a high level of functioning. There may be additional associations between NCF and hrQoL in patients with reduced hrQoL

that we could not detect in this cohort of relatively high-functioning and highly educated patients. Although our results demonstrate an association between neurocognition and hrQoL, they do not provide evidence of a causal link between these outcomes. Future studies exploring the directionality of this relationship may lend insight into potential hrQoL- and cognitive-sparing interventions in this population. Additionally, radiation treatment details, such as planning target volume and dose to brain structures important for cognition, likely influence hrQoL and NCF. Future studies investigating these relationships in an normal tissue complication probability analysis are of great interest.

We present the first prospective evidence of an independent association between hrQoL and NCF in patients with primary brain tumors, while accounting for mood. Our results demonstrate an important, often overlooked, association between physical functioning and NCF and demonstrate the importance of accounting for hrQoL in neuro-oncologic clinical trials assessing NCF. This may represent a bidirectional influence. We also identify patient subgroups at increased risk of hrQoL decline that may benefit from targeted hrQoL interventions. Future investigation of the cognitive benefits of hrQoL-directed programs and implications of cognitive-sparing interventions for hrQoL may yield novel methods for mitigating decline in these outcomes.

References

1. Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: Neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol* 2013;14:e407–e416.
2. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases a randomized clinical trial. *JAMA* 2016;316:401–409.
3. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:699–708.
4. Tibbs MD, Huynh-Le M-P, Reyes A, et al. Longitudinal analysis of depression and anxiety symptoms as independent predictors of neurocognitive function in primary brain tumor patients. *Int J Radiat Oncol* 2020;108:1229–1239. https://doi.org/10.1016/j.ijrobp.2020.07.002.
5. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. *Psychooncology* 2017;26:617–624.
6. Lin L, Chiang HH, Acquaye AA, Vera-Bolanos E, Gilbert MR, Armstrong TS. Uncertainty, mood states, and symptom distress in patients with primary brain tumors: Analysis of a conceptual model using structural equation modeling. *Cancer* 2013;119:2796–2806.
7. Giovagnoli AR, Silvani A, Colombo E, Boiardi A. Facets and determinants of quality of life in patients with recurrent high grade glioma. *J Neurol Neurosurg Psychiatry* 2005;76:562–568.
8. Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys* 2008;71:64–70.
9. Kvale EA, Murthy R, Taylor R, Lee JY, Nabors LB. Distress and quality of life in primary high-grade brain tumor patients. *Support Care Cancer* 2009;17:793–799.
10. Huang ME, Wartella JE, Kreutzer JS. Functional outcomes and quality of life in patients with brain tumors: A preliminary report. *Arch Phys Med Rehabil* 2001;82:1540–1546.
11. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *J Clin Oncol* 1993;11:570–579.
12. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation; 1996.
13. Beck A, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psychol* 1988;56:893–897.
14. Delis D, Kaplan E, Kramer J. *Delis-Kaplan Executive Function System (D-KEFS)*. United Kingdom: Pearson; 2001.
15. Heaton R, Chelune G, Talley J, Kay G, Curtiss G. *Wisconsin Card Sorting Test*. Lutz, FL: Par Inc.; 1993.
16. Weschler D. *Manual for the Weschler Adult Intelligence Scale*. 3rd ed United Kingdom: Pearson; 1997.
17. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test - Revised: Normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychol* 1998;12:43–55.
18. Benedict RHB, Groninger L, Schretlen D, Dobraski M, Shpritz B. Revision of the brief visuospatial memory test: Studies of normal performance, reliability, and, validity. *Psychol Assess* 1996;8:145–153.
19. Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. *J Clin Oncol* 2006;24:1305–1309.
20. Bates D, Machler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2016;67:1–48.
21. Bernal-Rusiel JL, Greve DN, Reuter M, Fischl B, Sabuncu MR. Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *Neuroimage* 2013;1:249–260.
22. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Ser B* 1995;57:289–300.
23. 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.
24. Tringale KR, Nguyen TT, Karunamuni R, et al. Quantitative imaging biomarkers of damage to critical memory regions associated with post-radiotherapy memory performance in brain tumor patients. *Int J Radiat Oncol* 2019;105:773–783.
25. Huynh-Le M-P, Tibbs MD, Karunamuni R, et al. Microstructural injury to corpus callosum and intra-hemispheric white matter tracts correlate with attention and processing speed decline after brain radiation. *Int J Radiat Oncol* 2021;110:337–347.
26. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. *JAMA Intern Med* 2017;177:1146–1153.
27. Grafinan J, Schwartz V, Dale JK, Scheffers M, Houser C, Straus SE. Analysis of neuropsychological functioning in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 1993;56:684–689.
28. Sandman CA, Barron JL, Nackoul K, Goldstein J, Fidler F. Memory deficits associated with chronic fatigue immune dysfunction syndrome. *Biol Psychiatry* 1993;33:618–623.
29. Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF, Greenough WT. Exercise, experience and the aging brain. *Neurobiol Aging* 2002;23:941–955.
30. Vance DE, Bail J, Enah CC, Palmer JJ, Hoenig AK. The impact of employment on cognition and cognitive reserve: Implications across

diseases and aging. *Nursing: Research and Reviews* 2016;6:61–71. https://doi.org/10.2147/NRR.S115625.
31. Boele FW, Zant M, Heine EC, et al. The association between cognitive functioning and health-related quality of life in low-grade glioma patients. *Neuro-Oncology Pract* 2014;1:40–46. https://doi.org/10.1093/nop/npu007.
32. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. *Am J Phys Med Rehabil* 2001;80:346–350.
33. Golub JS, Brickman AM, Ciarleglio AJ, Schupf N, Luchsinger JA. Association of subclinical hearing loss with cognitive performance. *JAMA Otolaryngol* 2019;10032:57–67.
34. Uhlmann RF, Larson EB, Koepsell TD, Rees TS, Duckert LG. Visual impairment and cognitive dysfunction in Alzheimer's disease. *J Gen Intern Med* 1991;6:126–132. https://doi.org/10.1007/BF02598307.
35. Burt Nabors L, Ahluwalia M, Baehring J, et al. NCCN guidelines version 1.2019: Anaplastic gliomas/glioblastoma. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns_blocks.pdf. Accessed August 5, 2019.
36. Ford K, Sowers M, Seeman TE, Greendale GA, Sternfeld B, Everson-Rose SA. Cognitive functioning is related to physical functioning in a longitudinal study of women at midlife. *Gerontology* 2010;56:250–258.
37. Tabbarah M, Crimmins EM, Seeman TE. The relationship between cognitive and physical performance: MacArthur studies of successful aging. *J Gerontol - Ser A Biol Sci Med Sci* 2002;57:228–235.
38. Fong AJ, Scarapicchia TMF, Mcdonough MH, Wrosch C, Sabiston CM. Changes in social support predict emotional well-being in breast cancer survivors. *Psychooncology* 2017;26:664–671. https://doi.org/10.1002/pon.4064.
39. Courtens AM, Stevens FC, Crebolder HFJM, Philipsen H. Longitudinal study on quality of life and social support in cancer patients. *Cancer Nurs* 1996;19:162–169.
40. Salo J, Niemelä A, Joukamaa M, Koivukangas J. Effect of brain tumour laterality on patients' perceived quality of life. *J Neurol Neurosurg Psychiatry* 2002;72:373–377.
41. Cummings JL. Neuropsychiatric manifestations of right hemisphere lesions. *Brain Lang* 1997;37:22–37.
42. Wright L, Hardie SM. Are left-handers really more anxious? *Laterality* 2012;17:629–642.
43. Denny K. Handedness and depression: Evidence from a large population survey. *Laterality* 2009;14:246–255.
44. Brown PD, Gondi V, Pugh S, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III trial NRG Oncology CC001. *J Clin Oncol* 2020: JCO1902767.
45. NRG Oncology. Proton beam or intensity-modulated radiation therapy in preserving brain function in patients with IDH mutant grade II or III glioma: NCT03180502. Available at: https://clinicaltrials.gov/ct2/show/NCT03180502?term=BN005&draw=2&rank=1. Accessed January 17, 2021.
46. Galiano-Castillo N, Cantarero-Villanueva I, Fernandez-Lao C, et al. Telehealth system: A randomized controlled trial evaluating the impact of an internet-based exercise intervention on quality of life, pain, muscle strength, and fatigue in breast cancer survivors. *Cancer* 2016;122:3166–3174.