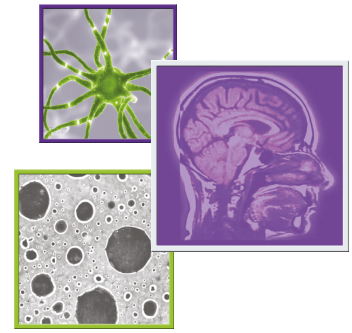
Preliminary Communication

CNS Oncology



Daily functioning in glioma survivors: associations with cognitive function, psychological factors and quality of life

Kathleen Van Dyk*[1,2], Lucy Wall[1], Brandon F Heimberg[1], Justin Choi[3], Catalina Raymond[4,5], Chencai Wang[4,5], Albert Lai[2,3], Timothy F Cloughesy[2,3], Benjamin M Ellingson[1,2,4,5] & Phioanh Nghiemphu[2,3]

[1]Department of Psychiatry & Biobehavioral Sciences, Semel Institute for Neuroscience & Human Behavior, University of California Los Angeles, Los Angeles, CA 90024, USA

[2]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA 90024, USA

[3]Department of Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90024, USA

[4]UCLA Brain Tumor Imaging Laboratory (BTIL), Center for Computer Vision & Imaging Biomarkers, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90024, USA

[5]Department of Radiological Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90024, USA

*Author for correspondence: KVanDyk@mednet.ucla.edu

Aim: Understanding and supporting quality of life (QoL) and daily functioning in glioma patients is a clinical imperative. In this study, we examined the relationship between cognition, psychological factors, measures of health-related QoL and functioning in glioma survivors. **Materials & methods:** We examined neuropsychological, self-reported cognition, mood and QoL correlates of work and non-work-related daily functioning in 23 glioma survivors, and carried out linear models of the best predictors. **Results & conclusion:** A total of 13/23 participants were working at the time of enrollment. The best model for worse work-related functioning (R^2 = .83) included worse self-reported cognitive function, depression, loneliness and brain tumor symptoms. The best model for worse non-work-related functioning (R^2 = .61) included worse self-reported cognitive functioning, anxiety, sleep disturbance and physical functioning. Neuropsychological variables were not among the most highly correlated with function. Worse cognitive, particularly self-reported and psychosocial outcomes may compromise optimal functioning in glioma survivors.

First draft submitted: 5 January 2022; Accepted for publication: 7 April 2022; Published online: 18 May 2022

Keywords: cancer • daily functioning • employment • function • glioma • quality of life • survivorship

Malignant gliomas are neuroepithelial tumors with recent US incidence rates of approximately 4.8 per 100,000 [1]. Lower grade glioma (LGG) survivors in particular benefit from more favorable outcomes compared with other tumor types and comprise approximately 40% of all glioma diagnoses [2]. LGG tends to occur in younger ages compared with other brain tumors and have better overall survival rates with some reports of survival up to 20 years [2,3]. Given the relatively higher likelihood of survival for years after treatment, understanding how to support quality of life (QoL) and daily functioning in glioma survivors, especially LGG, is a clinical imperative receiving growing attention [4–7].

Resuming normal activities in glioma survivorship is critical to QoL [8]. Unfortunately, the survivorship phase is often etched with disruptive cognitive and functional impairments; 30–50% of survivors encounter significant cognitive and functional impairment after treatment and it is one of the most concerning outcomes for patients [9–12]. Even though it is less likely that patients will suffer from more severe cognitive impairment seen in faster growing tumors, even mild cognitive changes can have a profound impact on higher-level functional goals [13,14]. For instance, approximately half of LGG survivors return to work after treatment [15]. Cognitive and other changes

Future Medicine

threaten glioma survivors ability to carry out complex daily life activities and limit the ability to return to work and fill meaningful and important roles [4–7,16,17].

To help elucidate key factors related to functioning in glioma survivorship, including LGG, we conducted a study of cognition, psychological factors, QoL and functioning in glioma survivors. We grounded our approach in the more developed extant literature available in the parallel field of non-CNS cancer survivors and assembled an extensive neuropsychological and psychosocial battery of measures. In this preliminary report of the first sample of recruited patients, we aimed to understand contributing factors to work and non-work-related daily functioning.

Materials & methods

Sample & study design

This is a cross-sectional observational study of cognitive and psychosocial functioning in glioma survivors. Participants with a history of glioma were recruited from the UCLA Neuro-Oncology clinic. Eligible participants were over the age of 18, had at least 5th grade proficiency in English, and had completed treatments (i.e., surgery, radiation and/or chemotherapy) at least 6 months prior to enrollment. They also must have had a Karnofsky performance status >60%, be able to undergo MRI and pregnant women were excluded.

Enrolled participants underwent same-day research evaluations added on to clinical follow-up appointments. Participants completed a self-report questionnaire framed in biopsychosocial theory, as well as a targeted battery of neuropsychological tests, detailed below. This study also involved extended neuroimaging with fMRI in addition to clinical structural scans, which are not included in the current report. This study was approved by the UCLA Institutional Review Board and all participants signed informed consent.

Neuropsychological & psychosocial measures

Dependent variables

Daily functioning was measured using the work productivity and activity impairment (WPAI) instrument [18], which yields continuous scores for how much the participant's brain tumor affected: work productivity; and non-work ability or functioning outside the workplace. Scores range from 1 to 10 and are converted into percentages, with higher scores indicating more functional impairment.

Independent variables

The neuropsychological test battery was selected in consideration of expert recommendations for assessment patients with a primary brain tumor, International Cognition and Cancer Task Force recommendations and authors' clinical experience [19,20]. The battery included the following measures: test of premorbid functioning [21]; The Hopkins Verbal Learning Test – Revised [22]; The Brief Visuospatial Memory Test – Revised [23]; The Trail-Making [24,25]; Wechsler Adult Intelligence Scale-IV [26] Coding and Digit Span subtests; The Connor's Continuous Performance Test-II [27]; The Golden Stroop [28]; Verbal fluency – FAS and animal naming [29]; The Boston Naming Test [30]; and The Rey–Osterrieth complex figure [31]. Raw scores were transformed into standard scores using published normative data.

Subjective cognitive functioning was assessed using the functional assessment of cancer therapy-cognitive function (FACT-Cog) version 3 [32,33]. The FACT-Cog yields four sub scores derived from items using a 5-point Likert scale to rate impairment: perceived cognitive impairment; perceived cognitive ability; comments from others; and impact on QoL. Depression symptoms were assessed using the Beck depression inventory-2nd edition [34], anxiety using the Beck Anxiety Inventory [35] and trauma symptoms were evaluated using the revised Impact of Event Scale [36]. We measured sleep disturbance using the Pittsburgh Sleep Quality Index [37], with missing values replaced by the mean of completed items [38]. Fatigue was assessed using the multidimensional fatigue symptom inventory – short form [39].

Health-related QoL was measured using the FACT-brain, a global QoL measure for cancer survivorship that also incorporates items specific to the brain tumor population [40]. This scale yields the subscales physical well-being, social/family well-being, emotional well-being, functional well-being, the brain cancer subscale and a total. In order to avoid confounds with the outcome (i.e., functioning), we did not include the functional well-being or total in analyses.

Analytic approach

Simple demographic information was summarized for the sample (see Table 1). We also compared those who

Table 1. Demographic characteristics of study population.

Characteristic		Total sample (n = 23)	
		n	Percent
Age, years			
Mean	44.26		
SD	12.24		
Education			
Mean	16.04		
SD	1.77		
Time since surgery, years			
Mean	7.60		
SD	(5.06)		
Intelligence quotient (IQ)			
Mean	104.96		
SD	12.33		
Gender			
Male		15	34.8
Female		8	65.2
Race			
White, non-Hispanic		21	91.3
African–American		1	4.3
Asian		1	4.3
Employment status			
Full or part-time		10	43.5
Not employed		13	56.5
Tumor location			
Left frontal		5	21.7
Left occipital		1	4.3
Left parietal		1	4.3
Left temporal		4	17.4
Right frontal		6	26.1
Right frontal temporal		1	4.3
Right occipital		1	4.3
Right parietal		2	8.7
Right temporal		1	4.3
Subcortical		1	4.3
IDH mutant			
Yes		15	65.2
No		3	13
N/A		4	17.4
Missing		1	4.3
Radiation therapy			
Yes		21	91.3
No		2	8.7
Chemotherapy			
Yes		21	91.3
No		2	8.7
Chemotherapy type			
PCV, tamoxifen		1	4.3
TMZ/PCV/CCNU/procarb/vincristine		1	4.3

AA: Anaplastic astrocytoma; AOA: Anaplastic oligoastrocytoma; AOG: Anaplastic oligodendroglial gliomas; CCNU: Lomustine; GBM: Glioblastoma; LA: Low grade astrocytoma; LO: Low grade oligodendroglioma; PCV: Procarbazine + lomustine + vincristine chemotherapy; PPA: Pilocytic astrocytoma; PXA: Pleomorphic xanthoastrocytoma; SD: Standard deviation; TMZ: Temozolomide (Temodar).

10.2217/cns-2022-0002

Table 1. Demographic characteristics of study population (cont.).

Characteristic	Total sample (n = 23)	
	n	Percent
TMZ, adjuvant	18	78.3
Velcade/TMZ, adjuvant	1	4.3
N/A	2	8.7
Cancer diagnosis, revised		
AA	5	21.7
AOA	3	13
AOG	2	8.7
Anaplastic mixed glioma	1	4.3
GBM	4	17.4
LA	4	17.4
LO	2	8.7
PPA	1	4.3
PXA	1	4.3

AA: Anaplastic astrocytoma; AOA: Anaplastic oligoastrocytoma; AOG: Anaplastic oligodendroglial gliomas; CCNU: Lomustine; GBM: Glioblastoma; LA: Low grade astrocytoma; LO: Low grade oligodendroglioma; PCV: Procarbazine + lomustine + vincristine chemotherapy; PPA: Pilocytic astrocytoma; PXA: Pleomorphic xanthoastrocytoma; SD: Standard deviation; TMZ: Temozolomide (Temodar).

were still working to those who stopped working on neuropsychological and self-report outcomes using *t*-tests (see Table 2). For descriptive purposes, we identified those with cognitive impairment defined as having more than two tests >-2 z-score compared with normative data, consistent with International Cognition and Cancer Task Force guidelines accounting for the number of tests in the battery [19,41]. We took a two-step approach toward modeling WPAI work productivity (among those still working) and WPAI non-work ability (among the entire sample. First, preliminary correlations were conducted to identify relevant correlates to include in the models (see Table 3). We then conducted two exploratory linear regression models of WPAI Work Productivity and WPAI non-work ability to evaluate the magnitude of effects (see Table 4). Since this is a small sample we minimized the number of predictors to four in each model [42]. We also examined model diagnostics to ensure <5% of standardized residuals were greater than 1.96. All analyses were conducted using IBM SPSS Statistics for Mac software, v. 24. (IBM Corp., NY, USA).

Results

We recruited 24 gliomas survivors for the study. Participants had various glioma diagnoses, predominantly lower grade, including anaplastic astrocytoma ([AA]; 5/23), anaplastic oligoastrocytoma ([AOA]; 3/23), anaplastic oligodendroglial liomas ([AOG]; 2/23), anaplastic mixed glioma (1/23), glioblastoma ([GBM]; 4/23), low grade astrocytoma ([LA]; 4/23), low grade oligodendroglioma ([LO]; 2/23), pilocytic astrocytoma ([PPA]; 1/23) and pleomorphic xanthoastrocytoma ([PXA]; 1/23). Broadly, participants were more likely to be positive for the IDH mutation, with nearly half of participants with frontal tumor location (11/23). Participants were also likely to have received radiation therapy (21/23) and chemotherapy (21/23), with TMZ adjuvant as the most common type (18/23). One participant was excluded for low English fluency detected during testing. The analytic sample included 23 participants, demographic and clinical characteristics displayed in Table 1. In general, the sample was mostly male, White, with an average estimated verbal IQ. At the time of this study, 13 participants were currently working; 11 reported no change in employment and two had reduced their time at work. Ten participants were not working, of which seven reported they had stopped working due to the brain tumor. Table 2 displays comparisons on neurocognitive and psychosocial factors between those currently working and those not working (neuropsychological scores are summarized in Supplementary Table 1). No differences were observed on neurocognitive outcomes between those working and those not working. Compared with working survivors, those not currently working reported higher levels of anxiety, worse perceived cognitive impairment, worse emotional well-being, worse symptoms related to brain cancer and lower sense of self-efficacy ($p < .05$). Mean WPAI work productivity scores were 18.46% (±23.75) among the 13 working and mean WPAI non-work ability scores were 22.17% (±27.13%), with higher percentages indicating greater impairment.

Table 2. Psychosocial factors between diffuse glioma survivors currently working or not working.

Variable	Working (n = 13)	Not working (n = 10)	Total sample (n = 23)
Employment change post brain tumor, n (%)			
No	11 (85)	3 (30)	14 (61)
Yes (reduced, personal time, stopped)	2 (15)	7 (70)	9 (39)
Age, mean (SD)	42.85 (14.69)	46.10 (8.49)	44.26 (12.24)
Gender, n (%)			
Male	10 (77)	5 (50)	15 (65)
Female	3 (23)	5 (50)	8 (35)
Years of education, mean (SD)	16.23 (1.301)	15.80 (2.30)	16.04 (1.77)
IQ, mean (SD)	105.08 (14.69)	104.8 (9.16)	104.96 (12.33)
Time since surgery (years), mean (SD)	8.08 (5.78)	6.96 (4.14)	7.60 (5.06)
Impaired on two or more neuropsychological tests ≤-2 z-score, n (%)	7 (54)	5 (50)	12 (52)
BDI-II, mean (SD)	8.08 (8.751)	11.6 (9.08)	9.61 (8.87)
BAI, mean (SD)	5.15 (5.94)	12.3 (9.61)	8.26 (8.38)†
FACT-Br, mean (SD)			
Physical well-being	24.92 (4.07)	23.6 (4.74)	24.35 (4.32)
Social/family well-being	21. 69 (6.41)	20.7 (5.06)	21.26 (5.75)
Emotional well-being	21 (2.92)	17.9 (3.9)	19.65 (3.65)†
Functional well-being	20.15 (8.05)	18.7 (5.06)	19.52 (6.81)
Brain cancer subscale (n = 22)	74.96 (14.75)	59.78 (17.98)	68.75 (17.49)†
Total (n = 22)	162.73 (26.35)	139.11 (29.85)	153.07 (29.62)
FACT-Cog, mean (SD)			
Perceived cognitive impairments	54.38 (18.19)	37.5 (18.05)	47.04 (19.67)†
Comments from others	13.92 (2.93)	13 (3.53)	13.52 (3.16)
Perceived cognitive abilities	18.08 (7.66)	12.1 (7.23)	15.48 (7.91)
Impact of quality of life (n = 22)	14.42 (2.43)	10.3 (5.31)	12.55 (4.43)†
MFSI-SF, mean (SD)			
General scale	6.27 (7.12)	5.1 (4.47)	5.76 (6.01)
Physical scale	2.54 (3.97)	5.1 (5.08)	3.65 (4.57)
Emotional scale	3.69 (3.90)	5.75 (5.63)	4.59 (4.73)
Mental scale	5.58 (5.17)	10.1 (6.83)	7.54 (6.24)
Vigor scale	15.08 (5.42)	12.8 (6.22)	14.09 (5.76)
Total score	3 (22.06)	13.25 (23.43)	7.46 (22.74)
PSQI, mean (SD)			
Global (n = 18)	4.86 (4.11)	6.71 (3.45)	5.58 (3.87)
Global with avg missing items (n = 22)	5.73 (5.59)	6.58 (3.27)	6.08 (4.71)
Loneliness scale total (n = 22), mean (SD)	4.23 (1.42)	5.11 (1.96)	4.59 (1.68)
Self-efficacy scale total, mean (SD)	50.92 (10.02)	39.1 (17.07)	45.78 (14.49)†
Impact of event scale total, mean (SD)	10.92 (10.5)	20.8 (15.12)	15.22 (13.37)

†$p < 0.05$.
BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory – second edition; FACT-Br: The functional assessment of cancer therapy – brain; FACT-Cog: The functional assessment of cancer therapy – cognitive function; IQ: Intelligence quotient; MFSI-SF: Multidimensional fatigue symptom inventory – short form; PSQI: The Pittsburg Sleep Quality Index; SD: Standard deviation.

Preliminary bivariate correlations identified several associations with both WPAI work productivity and WPAI non-work ability scores, see Table 3. Among demographic and clinical variables, none were associated with WPAI work productivity or WPAI non-work ability. Few neuropsychological test scores were significantly correlated with either measure except better learning was associated with higher WPAI work productivity and better attention was associated with higher WPAI non-work ability (p's <.05). In contrast, several self-report correlates emerged for both measures including mood, physical well-being, brain tumor symptoms, perceived cognitive impairment, loneliness and sleep disturbance. Given the small sample and relatively large effects, we selected the four strongest relationships for each measure for exploratory regression models; of note, we selected the highest of the two

10.2217/cns-2022-0002

Table 3. Correlations with work productivity and activity impairment productivity and work productivity and activity impairment ability.

Demographic and clinical variables	WPAI productivity (n = 13)	WPAI ability (n = 23)
Age	0.236	-0.074
Gender	-0.357	-0.147
Education, years	-0.311	0.329
IQ	-0.269	0.036
Time since surgery§	0.364	-0.002
Chemotherapy (yes/no)	0.345	0.193
Neuropsychological tests, normed		
Letter fluency total	-0.447	0.124
Animal naming total	-0.421	-0.132
BNT-2 total	-0.366	-0.163
BVMT-R total recall	-0.394	0.029
BVMT-R delayed recall	-0.368	0.049
Coding total	-0.261	-0.426†
Digit span total	-0.325	-0.273
HVLT-R total recall	-0.624†	-0.276
HVLT-R delayed recall	-0.467	-0.151
HVLT-R recognition§	-0.367	-0.198
Rey-O copy§	-0.401	-0.409
Stroop word reading	-0.360	-0.128
Stroop color naming	-0.263	-0.223
Stroop color-word	-0.391	-0.308
Stroop interference§	-0.451	-0.114
TOPF	-0.269	0.036
Trails A time	0.131	-0.068
Trails B time	-0.144	-0.346
Impaired on two or more neuropsychological tests ≤-2 z-score, n (%)	0.479	0.374
Self-report measures		
BDI-II raw	0.827‡	0.576‡
BAI Raw	0.468	0.609‡
FACT-Br physical well-being§	-0.621†	-0.583‡
FACT-Br social/family well-being§	-0.469	-0.446†
FACT-Br emotional well-being	-0.269	-0.469†
FACT-Br functional well-being§	-0.250	-0.533‡
FACT-Br brain cancer subscale	-0.612†	-0.506†
FACT-Cog perceived cognitive impairments	-0.760‡	-0.542‡
FCAT-Cog perceived cognitive abilities	-0.851‡	-0.564‡
PSQI global§	0.587†	0.721‡
Loneliness scale total	0.818‡	0.414
Impact of event scale total§	0.607†	0.527‡

†$p < 0.05$.
‡$p < 0.01$.
§Variable significantly skewed (Z >1.96), Spearman's rank correlation coefficient.
BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory – second edition; BNT-2: Boston naming test, 2nd edition; BVMT-R: Brief visuospatial memory test-revised; FACT-Br: The functional assessment of cancer therapy – brain; FACT-Cog: The functional assessment of cancer therapy – cognitive function; HVLT-R: Hopkins verbal learning test-revised; IQ: Intelligence quotient; PSQI: The Pittsburg Sleep Quality Index; Rey-O: Rey–Osterrieth complex figure test; Stroop: Stroop golden; TOPF: Test of premorbid functioning; WPAI: Work productivity and activity impairment questionnaire.

Table 4. Linear regression models of work productivity and activity impairment productivity and ability.

DV	Variable	R^2	$R^2_{adjusted}$	β	Standard error	Standardized beta	Partial correlation	Part correlation	Variance inflation factor
WPAI productivity		0.832	0.748						
	FACT-Cog perceived cognitive abilities			-0.302†	0.120	-0.974	-0.665	-0.365	7.128
	FACT-br physical well-being			-0.209	0.172	-0.359	-0.395	-0.176	4.152
	BDI-II raw			0.075	0.076	0.277	0.329	0.143	3.756
	Loneliness scale total			-1.072	0.717	-0.643	-0.467	-0.216	8.816
WPAI ability		0.610	0.518						
	FACT-Cog perceived cognitive abilities			-0.158†	0.073	-0.448	-0.465	-0.328	1.861
	FACT-br physical well-being			-0.238	0.139	-0.386	-0.383	-0.259	2.223
	BAI raw			0.078	0.066	0.246	0.277	0.180	1.861
	PSQI global			-0.085	0.147	-0.146	-0.139	-0.087	2.792

†$p < 0.05$.
BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory – second edition; FACT-Br: The functional assessment of cancer therapy – brain; FACT-Cog: The functional assessment of cancer therapy – cognitive function, v.3; PSQI: The Pittsburg Sleep Quality Index; WPAI: Work productivity and activity impairment questionnaire.

mood measures highly correlated with WPAI non-work ability (i.e., the BAI). We also examined part and partial correlations in the models for further scrutiny of unique effects since the strongest associations were in self-report measures.

The model statistics for both WPAI Work Productivity and WPAI non-work ability are presented in Table 4. For WPAI Work Productivity, 83% of the variance was explained by the BDI-II, Loneliness, the FACT-Cog Perceived Cognitive Abilities, and the FACT-Brain Physical Well-Being, $F(4,8) = 9.92$, $p < .01$. The FACT-Cog Perceived Cognitive Abilities score was the strongest and only significant predictor in the model, but given the small sample size we also examined the partial and part correlations of the other predictors, which each seem to carry some unique predictive value to the model with small to moderate effect sizes after accounting for the other predictors. The model of WPAI non-work ability was also significant, $F(4,17) = 6.65$, $p < .01$, explaining 61% of the variance with measures of subjective cognitive functioning (FACT-Cog Perceived Cognitive Abilities), anxiety (the BAI), sleep disturbance (PSQI) and physical functioning (FACT-brain physical well-being). Again, the FACT-Cog Perceived Cognitive Abilities score was the strongest and only significant factor. Examining partial and part correlations revealed some small to moderate unique effects of the BAI and FACT-brain physical well-being, but the PSQI dropped to negligible effects in the presence of the other factors.

Discussion

Functioning in brain tumor survivorship is an important factor to promote QoL in these patients, a critical clinical mandate [43]. The present study is a preliminary report of functional outcomes among glioma survivors participating in a comprehensive QoL study. Our goal in this report was to begin understanding factors that contribute to work and non-work related daily functioning in glioma survivors, including LGG, which comprised the majority of our sample. In our sample, roughly half of the survivors were not currently employed, consistent with others' findings [15]. Rates of impairment in work productivity and non-work ability were comparable to those reported in other samples of patients with chronic conditions (i.e., multiple sclerosis) [44]. The majority of those no longer working reported that it was due to the impact a brain tumor has had on their life. At the bivariate level, we found a range of psychological factors associated with both work and non-work related functioning, including objective and subjective cognitive measures, mood, self-reported physical functioning and self-reported loneliness. Linear models of work and non-work related functioning both highlighted perceived cognitive functioning, physical well-being and mood as unique predictors.

Surprisingly, neuropsychological outcomes were not strongly associated with functional outcomes. We found no differences on individual neurocognitive test scores between those currently working and those not working, nor different rates of cognitive impairment. Further, no neurocognitive measure was as strongly associated with self-reported cognition for either work or non-work-related daily functioning. There are high rates of cognitive

impairment in glioma patients across their trajectory of treatment and into survivorship, and even in lower grade tumors [14,45,46]. Cognitive impairment is a significant risk to QoL and functioning in patients with glioma [43]. Noll and colleagues' reported that neuropsychological functioning significantly predicted independent functioning among newly diagnosed patients with temporal lobe tumors of mixed type [47]. They found specifically memory and executive function measures predicted functional independence, although self-reported cognition measures were not included. By comparison, our study employed several of the same neuropsychological measures, but our sample was smaller and comprised mostly of glioma survivors well after completing treatment, with varying tumor locations. Our results do not frankly contradict their conclusion about the ecological validity of neuropsychological measures: we did observe some relationships during preliminary correlational analyses consistent with their findings, and the correlation coefficients in many instances are relatively high and of a similar magnitude to the Noll *et al.* study, if non significant – notably the cognitive impairment variable and memory and executive function measures. Since, this was a small preliminary study, further research will be critical to more fully understand neuropsychological predictors of functioning.

Even in this small sample, though, our preliminary findings do point to a few important lines of inquiry that will require further pursuit with larger samples. Our results highlight a unique role of perceived cognitive function. The significance of perceived cognitive impairment on function in the non-CNS cancer survivorship literature is also gaining attention. Cognitive changes in glioma patients, including LGG, may be more mild than those experienced by patients with other types of brain tumor, as seen in our sample [48]. Even if mild, can significantly compromise higher-level functional goals such as returning to work or resuming family roles [16,17]. While objective neuropsychological testing is critical to characterizing deficits, self-reported cognitive functioning may provide a unique window into the patient's experience and priorities that can help signal need for attention and intervention, such as cognitive rehabilitation.

The rich literature in non-CNS cancer populations similarly portrays functioning be complex, shaped by multiple factors including, but not limited to, cognitive impairment [10,19,49] and emphasizes the importance of self-reported cognitive function [50]. Our findings from this preliminary study are well-aligned with this position, suggesting a cluster of influences on daily functioning including cognitive function and psychological factors. Overall, the results of our study adds a new dimension of appreciating self-reported cognitive challenges in brain tumor survivors as well as the likely contributions of psychological factors and highlights the need for more study.

The need to address psychological needs in brain tumor survivors is intensifying [51,52]. We know that cognitive and functional changes often manifest in the setting of psychosocial risk factors such as the well-described increases in anxiety and depression symptoms in brain tumor and other cancer patients [53–55]. Similar to our findings, Feuerstein and colleagues examined contributing factors to work productivity in brain tumor survivors and also found depressive symptoms to independently contribute [56]. Others have similarly found mood to be a predictor of health-related QoL in recently diagnosed glioma patients [57]. Furthermore, patients' functional goals and sense of meaning can be altered by brain tumor diagnosis and an anticipated shortened survival [51]. Loughan and colleagues recently found high rates of death-related distress in primary brain tumor patients irrespective of tumor grade [58]. Given the complexity of needs, it is critical to incorporate a biopsychosocial framework in developing models of optimal functioning for these patients, as also advocated by others [5,8,51].

This study has limitations. First, we acknowledge the restrictions of small sample size in terms of statistical power and generalizability. Glioma survivors, especially LGG, are a fraction of all brain tumor survivors, which are a small fraction of all cancer survivors in general. There is also substantial heterogeneity in our study sample including cognitive impairment, time since treatment and tumor location, which could be influencing outcomes and limiting our ability to detect relationships with factors such as cognitive function. Importantly, we also primarily focused on cognitive, psychological and QoL outcomes – it remains important to understand the full nature of potential contributing factors to functioning in this population, such as specific physical impairments and type of work. Despite the limitations of size of the population from which we sampled, UCLA is a tertiary center and draws patients from a wide region, permitting accrual of relatively larger samples than seen in general oncology clinics. Thus, while small by statistical standards, the collected sample is a unique aggregate of data from this population. Additionally, our sample was predominantly White with higher levels of educational attainment and more study in more diverse samples is imperative.

Conclusion

This study lends preliminary evidence to support a multi-factorial approach to providing supportive care in glioma survivorship. Despite favorable outcomes in terms of longevity for LGG survivorship, the cognitive and psychological toll of this experience compromises optimal functioning and it is critical to further study and develop interventions for optimizing functioning and QoL for these patients.

Summary points

- Survival among glioma survivors, especially lower grade, is improving.
- However, 30–50% of survivors experience significant functional impairment.
- To better support glioma survivors, it is important to understand factors contributing to functional impairment.
- This preliminary study examines cognitive, psychological and quality of life predictors of work and non-work-related functional impairment in 23 glioma survivors. A total of 13/23 survivors in our sample were currently working.
- Linear models of the strongest correlates of work productivity included self-reported cognitive function, depression, loneliness and brain tumor symptoms, explaining 83% of the variance.
- Linear models of the strongest correlates of non-work-related ability included self-reported cognitive function, anxiety, sleep disturbance and brain tumor symptoms.
- The results of our preliminary study highlight a multifactorial approach to supporting functioning in glioma survivorship including cognitive, both objective and self-report and psychological factors. Further research in this area with larger samples will be important for developing targeted and effective supportive interventions in this population.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cns-2022-0002

Financial & competing interests disclosure

This research was supported by the National Cancer Institute at the National Institutes of Health grant K08CA241337 to KVD, grant P50CA211015 to BE, UCLA Neuro-Oncology Program Brain Cancer Research Fund, IGN foundation and donations in memory of David Hanneman and Jeri Weiss. KVD is also supported in part by R35CA197289 and R01AG068193. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest

1. Surveillance Research Program, National Cancer Institute. SEER*Explorer: an interactive website for SEER cancer statistics. https://seer.cancer.gov/explorer/
2. Ostrum QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018. *Neuro-Oncol.* 23(S3), iii1–iii105 (2021).
3. Youland RS, Schomas DA, Brown PD *et al.* Changes in presentation, treatment, and outcomes of adult low-grade gliomas over the past fifty years. *Neuro-Oncol.* 15(8), 1102–1110 (2013).

• **Demonstrates improved overall survival in lower grade glioma over a 50 year period.**

4. Leeper H, Milbury K. Survivorship care planning and implementation in neuro-oncology. *Neuro-Oncol.* 20(Suppl. 7), vii40–vii46 (2018).

5. Leeper HE. Survivorship and caregiver issues in neuro-oncology. *Curr. Treat. Options Oncol.* 20(11), 80 (2019).
6. Leeper HE, Acquaye AA, Bell S *et al.* Survivorship care planning in neuro-oncology. *Neuro-Oncol. Pract.* 5(1), 3–9 (2018).
7. Aaronson NK, Taphoorn MJB, Heimans JJ *et al.* Compromised health-related quality of life in patients with low-grade glioma. *J. Clin. Oncol.* 29(33), 4430–4435 (2011).
8. Ownsworth T, Hawkes AL, Chambers S, Walker DG, Shum D. Applying a biopsychosocial perspective to investigate factors related to emotional adjustment and quality of life for individuals with brain tumour. *Brain Impair.* 11(3), 270–280 (2010).
9. Prabhu RS, Won M, Shaw EG *et al.* Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J. Clin. Oncol.* 32(6), 535–541 (2014).
10. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J. Clin.* 65(2), 123–138 (2015).
11. Locke DEC, Cerhan JH, Wu W *et al.* Cognitive rehabilitation and problem-solving to improve quality of life of patients with primary brain tumors: a pilot study. *J. Support Oncol.* 6(8), 383–391 (2008).
12. Douw L, Klein M, Fagel SS *et al.* Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neuro* 8(9), 810–818 (2009).

- **Demonstrates cognitive decline in lower grade glioma following low-dose radiotherapy.**

13. Duffau H. Diffuse low-grade gliomas and neuroplasticity. *Diagn. Interv. Imaging* 95(10), 945–955 (2014).
14. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-Oncol.* 17(4), 580–587 (2015).

- **Demonstrates worse cognitive deficits among those with higher grade compared to lower grade tumors irrespective of tumor size.**

15. Rydén I, Carstam L, Gulati S *et al.* Return to work following diagnosis of low-grade glioma: a nationwide matched cohort study. *Neurology* 95(7), e856–e866 (2020).
16. Lombardi G, Bergo E, Del Bianco P *et al.* Quality of life perception, cognitive function, and psychological status in a real-world population of glioblastoma patients treated with radiotherapy and temozolomide. *Am. J. Clin. Oncol.* 41(12), 1263–1271 (2018).
17. Mugge L, Mansour TR, Crippen M, Alam Y, Schroeder J. Depression and glioblastoma, complicated concomitant diseases: a systemic review of published literature. *Neurosurg. Rev.* 43(2), 497–511 (2020).
18. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 4(5), 353–365 (1993).
19. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol.* 12(7), 703–708 (2011).

- **Landmark paper outlining methodology to improve consistency among cancer-related cognitive impairment studies.**

20. Reijneveld JC, Sitskoorn MM, Klein M, Nuyen J, Taphoorn MJB. Cognitive status and quality of life in patients with suspected versus proven low-grade gliomas. *Neurology* 56(5), 618–623 (2001).
21. Wechsler D. Test of premorbid functioning. Psych Corp., TX, USA (2009).
22. Brandt J, Benedict RHB. Hopkins verbal learning test – revised. Psychological Assessment Resources, FL, USA (2001).
23. Benedict RH. Brief visuospatial memory test – revised. Psychological Assessment Resources, FL, USA (1997).
24. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept. Mot. Skills* 8, 271–276 (1958).
25. Heaton RK, Miller SW, Taylor MJ, Grant I. Revised comprehensive norms for an expanded Halstead–Reitan battery: demographically adjusted neuropsychological norms for African American and Caucasian adults. Psychological Assessment Resources, FL, USA (2004).
26. Wechsler D. Wechsler adult intelligence scale – Fourth Edition (WAIS–IV). Pearson, TX, USA (2008).
27. Conners CK, Staff MHS. Conners' continuous performance test II (CPT II V. 5). Multi-Health Syst Inc., NY, USA (2000).
28. Golden CJ, Freshwater SM. Stroop Color and Word Test: Revised examiner's manual. Stoelting Co., IL, USA (2002).
29. Strauss E, Sherman EMS, Spreen O. In: *A Compendium of Neuropsychological Tests (3rd Edition).* Oxford University Press, NY, USA (2006).
30. Kaplan EF, Goodglass H, Weintraub S. In: *The Boston Naming Test (2nd Edition).* Lippincott Williams & Wilkins, PA, USA (2001).
31. Meyers JE, Meyers KR. In: *Rey complex figure test and recognition trial professional manual.* Psychological Assessment Resources, FL, USA (1995).
32. Wagner LI, Lai JS, Cella D, Sweet J, Forrestal S. Chemotherapy-related cognitive deficits: development of the FACT-Cog instrument. *Ann. Behav. Med.* 27, S10 (2004).
33. Wagner LI, Sweet J, Butt Z, Lai J, Cella D. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. *J. Support Oncol.* 7(6), W32–39 (2009).
34. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. Pearson, TX, USA (1996).

35. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J. Consult. Clin. Psychol.* 56(6), 893–897 (1988).
36. Weiss DS. The impact of event scale: revised. In: *Cross-Cultural Assessment of Psychological Trauma and PTSD.* Wilson JP, So-kum Tang C (Eds). Springer, MA, USA, 219–238 (2007).
37. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28(2), 193–213 (1989).
38. Guo S, Sun W, Liu C, Wu S. Structural validity of the Pittsburgh Sleep Quality Index in Chinese undergraduate students. *Front. Psychol.* 7, 1126 (2016).
39. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. *J. Pain Symptom Manag.* 27(1), 14–23 (2004).
40. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Levin VA, Cella DF. The functional assessment of cancer therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. *Cancer* 75(5), 1151–1161 (1995).
41. Ingraham LJ, Aiken CB. An empirical approach to determining criteria for abnormality in test batteries with multiple measures. *Neuropsychology* 10(1), 120 (1996).
42. Jenkins DG, Quintana-Ascencio PF. A solution to minimum sample size for regressions. *PLoS ONE* 15(2), e0229345 (2020).
43. Klein M. Quality of life in patients with diffuse low-grade glioma. In: *Diffuse Low-Grade Gliomas in Adults.* Duffau H (Ed.). Springer International Publishing, Cham, Switzerland, 235–252 (2017).
44. Glanz BI, Dégano IR, Rintell DJ, Chitnis T, Weiner HL, Healy BC. Work productivity in relapsing multiple sclerosis: associations with disability, depression, fatigue, anxiety, cognition, and health-related quality of life. *Value Health* 15(8), 1029–1035 (2012).
45. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J. Neurooncol.* 134(1), 9–18 (2017).
46. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-Oncol.* 17(4), 580–587 (2015).
47. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. *Neuro-Oncol. Pract.* 5(3), 184–193 (2018).
48. Bartolo M, Springhetti I. *Neurorehabilitation in Neuro-Oncology.* Bartolo M, Soffietti R, Klein M (Eds). Springer Nature Switzerland, Cham, Switzerland (2019).
49. Lange M, Joly F, Vardy J *et al.* Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 30(12), 1925–1940 (2019).
50. Henneghan AM, Van Dyk K, Kaufmann T *et al.* Measuring self-reported cancer-related cognitive impairment: recommendations from the Cancer Neuroscience Initiative Working Group. *JNCI J. Natl Cancer Inst.* 113(12), 1625–1633 (2021).
51. Ownsworth T, Hawkes A, Steginga S, Walker D, Shum D. A biopsychosocial perspective on adjustment and quality of life following brain tumor: a systematic evaluation of the literature. *Disabil. Rehabil.* 31(13), 1038–1055 (2009).

- **Key literature review supporting multifactor approach to supporting brain tumor survivors.**

52. Johnson DR. A focus on psychological needs of brain tumor patients and leveraging epidemiology. *Neuro-Oncol. Pract.* 7(5), 463–464 (2020).
53. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. *Psychooncology* 10(1), 19–28 (2001).
54. Inhestern L, Beierlein V, Bultmann JC *et al.* Anxiety and depression in working-age cancer survivors: a register-based study. *BMC Cancer* 17(1), 347 (2017).
55. Arnold SD, Forman LM, Brigidi BD *et al.* Evaluation and characterization of generalized anxiety and depression in patients with primary brain tumors. *Neuro-Oncol.* 10(2), 171–181 (2008).
56. Feuerstein M, Hansen JA, Calvio LC, Johnson L, Ronquillo JG. Work productivity in brain tumor survivors. *J. Occup. Environ. Med.* 49(7), 803–811 (2007).
57. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. *Psychooncology* 26(5), 617–624 (2017).
58. Loughan AR, Aslanzadeh FJ, Brechbiel J *et al.* Death-related distress in adult primary brain tumor patients. *Neuro-Oncol. Pract.* 7(5), 498–506 (2020).