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Research Paper

Evaluation of the key geriatric assessment constructs in primary brain tumor population - a descriptive study

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ABSTRACT

Introduction: Despite an increasing aging population, older adults (≥ 65 years) with primary brain tumors (PBTs) are not routinely assessed for geriatric vulnerabilities. Recent reports of geriatric assessment (GA) in patients with glioblastomas demonstrated that GA may serve as a sensitive prognosticator of overall survival. Yet, current practice does not include routine evaluation of geriatric vulnerabilities and the relevance of GA has not been previously evaluated in broader cohorts of PBT patients. The objective of this descriptive study was to assess key GA constructs in adults with PBT dichotomized into older versus younger groups.

Materials and Methods: A cross-sectional analysis of data collected from 579 participants with PBT recruited between 2016 and 2020, dichotomized into older (≥ 65 years, $n = 92$) and younger (≤ 64 years, $n = 487$) from an ongoing observational trial. GA constructs were evaluated using socio-demographic characteristics, Charlson Comorbidity Index (CCI), polypharmacy (>5 daily medications), Karnofsky Performance Status (KPS), Neurologic Function Score (NFS), and patient-reported outcome assessments including general health, functional status, symptom burden and interference, and mood. Descriptive statistics, *t*-tests, chi-square tests, and Pearson correlations were used to evaluate differences between age groups.

Results: Older participants were more likely to have problems with mobility (58% vs. 44%), usual activities (64% vs 50%) and self-care (38% vs 26%) compared to the younger participants (odds ratios [ORs] = 1.3–1.4, ps < 0.05), while older participants were less likely to report feeling distressed (OR = 0.4, $p < 0.05$). Older participants also had higher CCI and were more likely to have polypharmacy (OR = 1.7, ps < 0.05). Increasing age strongly correlated with worse KPS score ($r = -0.232$, OR = 1.4, $p < 0.001$) and worse NFS ($r = 0.210$, OR = 1.5, $p < 0.001$). No differences were observed in overall symptom burden, symptom interference, and anxiety/depression scores.

Discussion: While commonly used GA tools were not available, the study employed patient- and clinician-reported outcomes to identify potential future research directions for the use of GA in the broader neuro-oncology population. Findings illustrate missed opportunities in neuro-oncology practice and underscore the need for incorporation of GA into routine care of this population. Future studies are warranted to further evaluate the prognostic utility of GA and to better understand functional aging outcomes in this patient population.

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1. Introduction

The incidence of primary brain tumors (PBT) is higher in adults older than 40 years, with a median age of 60 years for all PBTs and 65 years for glioblastomas and meningiomas [1–3]. Cancer and cancer treatments accelerate functional aging phenotypes compounded with normal aging processes, leading to increased morbidity and mortality [4,5]. Efforts to date in neuro-oncology have focused on evaluating tumor response and tolerance of standard treatment and its modifications based on chronological age and performance status scores alone [6]. While past studies demonstrated that older adults (≥ 65 years) diagnosed with glioblastoma may benefit from temozolomide monotherapy, hypofractionated radiotherapy with concurrent temozolomide [7–9], or hypofractionated radiotherapy alone [10,11], there is currently no standard approach to guide treatment in older adults with PBTs.

Extant literature demonstrates that some older patients with PBTs may be at higher risk of toxicity due to overtreatment, whereas others eligible for treatment may receive less aggressive treatments or remain untreated, which may further contribute to earlier mortality [6,12]. Moreover, a recent study demonstrated that older patients with malignant gliomas experience geriatric vulnerabilities, such as falls, polypharmacy, and comorbidities, not captured by performance status scales [13].

In recent years, geriatric assessment (GA) has been increasingly used as set forth by the International Society of Geriatric Oncology and American Society for Clinical Oncology, aimed at identifying older adults at greatest risk for mortality and adverse events [14,15]. Several recent studies demonstrated that GA or specific GA domains may serve as significant prognosticator of overall survival in patients with glioblastoma [16–18]. However, these studies excluded patients with non-glioblastoma tumors and did not capture the impact of treatment on patient-centered outcomes, such as symptom burden and overall health status. Greater symptom burden is associated with functional impairment in older patients with cancer [19] and both symptom burden and poor performance status were previously shown to be associated with functional limitations in patients with glioblastoma [20].

To our knowledge, no studies have evaluated age-related differences using GA in adults across multiple PBT other than glioblastoma. To fill this gap and assess the relevance within the broader neuro-oncology population, we evaluated GA constructs in a large cohort of adults with diverse PBT types. Leveraging patient- and clinician-reported outcomes, the constructs assessed encompassed comorbidities, polypharmacy, functional status, neurologic function, patient-reported health status, mood, symptom burden, and symptom interference. We hypothesized that older adults will have higher comorbidities, polypharmacy, greater functional impairment, lower neurologic function score, and higher mood disturbances, symptom burden, and interference compared to younger adults.

2. Materials and Methods

2.1. Study Design and Setting

This is a cross-sectional analysis of an ongoing observational IRB-approved Natural History Study conducted at the Neuro-Oncology Branch, National Cancer Institute (NCI), National Institutes of Health (NIH) (NCT02851706, PI: TS Armstrong). Details of the study procedures have been previously described [21]. Briefly, participants diagnosed with PBT who completed patient-reported outcomes (PROs) measures and enrolled between September 21, 2016 and January 31, 2020 were included in analyses. Clinician-reported outcomes (CROs) and demographic data were collected using standardized forms by the clinicians evaluating the patient. Tumor diagnoses and grading were based on the 2016 World Health Organization Classification of Tumors of the Central Nervous System. Older age was defined as ≥65 years, consistent with prior neuro-oncology studies [16–18]. The cohort was dichotomized into older (≥ 65 years) and younger groups (≤ 64 years) using the age recorded at the last clinic visit prior to analysis. Informed consent was obtained prior to data collection.

2.2. Clinician-Reported Outcomes Instruments

Karnofsky Performance Status (KPS) scale was used to evaluate functional status [22]. This non-linear scale includes eleven categories with scores ranging from 0 (dead) to 100 (normal, no complaints; no evidence of disease). The scores were dichotomized as good (KPS ≥ 90) and poor (KPS ≤ 80) [23].

Comorbidities were assessed using the Charlson Comorbidity Index (CCI), which consists of nineteen items of different medical comorbid conditions [24] and both unadjusted and age-adjusted CCI were included. Age-adjusted CCI was weighed to adjust for age with 40 years considered as lowest with each subsequent decade adding 1 point [25]. Seizure incidence ("at least one seizure") was collected in addition to CCI. Self-reported medication lists were collected during clinic visits and polypharmacy was calculated as more than five daily medications [26].

Lastly, neurological function was assessed using the Neurologic Function Score (NFS), which has five distinct categories ranging from zero(no neurologic symptoms; fully active at home/work without assistance) to four (severe neurologic symptoms; totally inactive requiring complete assistance; unable to work). Scores were dichotomized as good (0–1) and poor (2–4), as previously established [27,28].

2.3. Patient-Reported Outcome Instruments

The EQ-5D-3L instrument was used to measure self-reported general health status along the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [29]. Each dimension consists of three levels: "no problems," "some problems," and "extreme problems." We dichotomized each dimension into (i) "reporting impairment," which included "some problems," "unable to perform," "confined to bed," and "extreme problems" and (ii) "no impairment," which included only "no problems." An EQ-5D-3L global index score was calculated using population-based preference weights with final scores ranging from 0 (health described death-like) to 1 (perfect health) [30].

Patient-Reported Outcomes Measurement Information System (PROMIS)-Anxiety Short Form 8a and -Emotional Distress-Depression Short Form 8a were used to assess anxiety and depressive symptoms over the past seven days, respectively [31]. PROMIS-Anxiety and -Depression use an 8-item Likert scale ranging from "never" to "always" with established validity and reliability ($r > 0.80$). Mean *t*-scores centered on the general US population are 50 ± standard deviation (SD) of 10 for both measures [32].

The MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT), a self-reported measure of symptom burden and interference with established validity and reliability, was used to capture symptom experiences within the last 24 h [33]. The questionnaire includes 22 symptom burden items and uses a Likert scale ranging from 0 ("not present") to 10 ("as bad as you can imagine") and six symptom interference items rated from 0 ("did not interfere") to 10 ("interfered completely"). The symptom burden items were categorized into six primary factors (affective, cognitive, neurologic, treatment-related, general disease, and gastrointestinal) and interference items were categorized into two interference subscales (activity-related and mood-related) [33]. Symptoms rated as ≥5 were considered moderate-severe while interference mean scores of ≥2 were considered moderate-severe.

2.4. Statistical Analyses

Descriptive statistics, together with frequency distributions, were used to characterize clinical and demographic variables. All statistical analyses were conducted using IBM SPSS Statistics Version 28.0 (IBM

Corporation, Armonk, NY) and figures were created using GraphPad Prism version 8.4.3 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). Pearson bivariate correlation analysis was run between the continuous variable of age and measures of functional status (i.e., KPS) and neurologic function (i.e., NFS). Differences between older (≥ 65 years) and younger (≤ 64 years) patient groups in demographic, clinical, patient-reported, and clinician-reported variables were analyzed by running 2 × 2 contingency tables with Pearson chi-square tests, Fisher's tests for categorical variables, and independent samples *t*-tests for continuous variables. A value of $p < 0.05$ was considered statistically significant and False Discovery Rate (FDR) was applied for multiple comparison corrections using the RStudio version 1.4.1717 statistical package version 4.1.1. (RStudio, Boston, MA, https://www.rstudio.com). Odds ratios (ORs) were calculated for variables with two categories. Several CROs and demographic variables had missing data with exact numbers outlined in Supplementary Table 1.

Table 1
Clinical and demographic characteristics.

		Total sample $N = 579$	Older adults n = 92	Younger adults n = 487	*p*
Age	Mean [SD]	50 [14]	70 [4]	46 [11]	NA
	Median [min, max]	50 [18, 85]	70 [65, 85]	47 [18, 64]	
BMI (kg/m^2)	Mean [SD]	28 [10]	29 [15]	28 [9]	0.507
	Median [min, max]	26 [16, 64]	26 [18, 51]	26 [16,64]	
Time since diagnosis (months)	Mean [SD]	68 [72]	73 [89]	67 [69]	0.494
	Median [min, max]	35 [403]	29 [376]	36 [403]	
		n (%)			
Sex	Female	243 (42)	35 (38)	208 (43)	0.422
	Male	336 (58)	57 (62)	279 (57)	
Race/Ethnicity	White	433 (75)	71 (77)	362 (74)	0.191
	Black/African American	38 (7)	9 (10)	29 (6)	
	Asian/Native Hawaiian/Pacific Islander	30 (5)	6 (7)	24 (5)	
	Missing/Other	25 (4)	2 (2)	23 (5)	
	Hispanic/Latino	53 (9)	4 (4)	49 (10)	
Marital status^	Single	113 (21)	6 (7)	107 (23)	0.349
	Married	375 (69)	69 (81)	306 (67)	
	Divorced/Separated/Widowed	57 (10)	10 (12)	47 (10)	
Lives alone^^	No	282 (92)	41 (89)	241 (93)	0.379
	Yes	24 (8)	5 (11)	19 (7)	
Education^	High school or below	77 (14)	14 (16)	63 (13)	0.705
	Some college	88 (16)	12 (14)	76 (16)	
	Bachelor's degree	192 (34)	25 (29)	167 (36)	
	Professional/Graduate degree	201 (36)	35 (41)	166 (35)	
Annual Household Income^^	< $25,000	32 (11)	3 (7)	29 (11)	**0.046***
	$25,000-$49,999	34 (11)	2 (5)	32 (13)	
	$50,000–$149,999	125 (42)	19 (44)	106 (42)	
	≥$150,000	59 (20)	15 (35)	44 (17)	
	Missing	46 (16)	4 (9)	42 (17)	
Work status^	Employed/Homemaker/Student	284 (51)	17 (20)	267 (57)	**<0.001***
	Retired	99 (18)	60 (71)	39 (8)	
	Disabled/Medical leave/Unemployed due to tumor	126 (23)	7 (8)	119 (25)	
	Unemployed	47 (9)	1 (1)	46 (10)	
Tumor Diagnosis	Astrocytoma	361 (62)	56 (61)	305 (63)	0.706
	Oligodendroglioma	76 (13)	8 (9)	68 (14)	
	Ependymoma	39 (7)	7 (8)	32 (7)	
	Other*	88 (15)	18 (19)	70 (14)	
	No tissue diagnosis	15 (3)	3 (3)	12 (2)	
Tumor Grade	WHO grade I-II	130 (22)	23 (25)	107 (22)	0.795
	WHO grade III-IV	427 (74)	66 (72)	361 (74)	
	No tissue/none assigned	22 (4)	3 (3)	19 (4)	
Surgery**	Gross total resection	191 (33)	30 (33)	161 (33)	0.692
	Subtotal resection	186 (32)	25 (28)	161 (33)	
	Biopsy	124 (21)	20 (22)	104 (21)	
	Resection NOS	62 (11)	13 (14)	49 (10)	
	No surgery	15 (3)	3 (3)	12 (3)	
Prior radiation**	Yes	477 (82)	70 (76)	407 (84)	0.098
	No	101 (18)	22 (24)	79 (16)	
Prior chemotherapy**	Yes	417 (72)	55 (60)	362 (74)	**0.005***
	No	161 (28)	37 (40)	124 (26)	
Recurrence	0	235 (41)	37 (40)	198 (41)	0.091
	1	142 (24)	30 (33)	112 (23)	
	≥2	202 (35)	25 (27)	177 (36)	
Polypharmacy^ (> 5 medications)	Yes	246 (44)	61 (68)	185 (39)	**<0.001***
	No	315 (56)	29 (32)	286 (61)	
At least 1 seizure**	Yes	210 (37)	19 (22)	191 (40)	0.001
	No	357 (63)	69 (78)	288 (60)	

Abbreviations: BMI = body mass index, SD = standard deviation, WHO = World Health Organization, NOS = not otherwise specified.
Missing data: variables that had lower sample sizes due to missing data are denoted as following:**missing 1–12, ^ missing 18–34, ^^missing 273–283 participants' responses (Supplementary Table 1).
* Atypical Teratoid Rhabdoid Tumor, atypical meningioma, central neurocytoma, diffuse midline glioma, dysembryoplastic neuroepithelial tumor, ganglioglioma, glial neoplasm, hemangiopericytoma, high grade glioma, high grade neuroepithelial tumor, low grade glioma, medulloblastoma, meningioma, multinodular and vacuolating neuronal tumors, papillary glioneuronal tumor, papillary tumor of pineal region, pineal parenchymal tumor (intermediate differentiation), pineoblastoma, pituitary carcinoma, rosette-forming glioneuronal tumor, rhabdoid meningioma, undifferentiated pleomorphic sarcoma.

3. Results

3.1. Sociodemographic and Clinical Characteristics

A total of 579 PBT participants were included in this cohort, dichotomized into the older group ($n = 92$, 16%) and the younger group ($n = 487$, 84%) (Table 1). Participants were predominately White/Non-Hispanic (75%) males (58%). Importantly, no significant differences were identified in the sex, education, race, ethnicity, marital status, or "lives alone" variables. Older participants were more likely to be retired and have an annual income of ≥ $150,000. Astrocytomas were the most common tumor diagnosis (61% older and 63% younger) with the majority having a high grade (III-IV) lesion. Additionally, there was no difference in the percentage of patients undergoing a gross total resection; however, older participants were less likely to have had upfront chemotherapy ($p = 0.005$) or radiation therapy ($p = 0.098$) after surgery.

3.2. Clinician-Reported Outcomes

3.2.1. Comorbidities

Experiencing at least one seizure was reported by 22% of older participants compared to 40% of younger participants ($X^2(1) = 10.66$, OR = 0.5, $p = 0.001$) (Table 1). In addition, older participants had higher CCI (mean = 0.94, range 0–6) compared to their younger counterparts (mean = 0.14, range = 0–2, t (65.7) = −4.596, $p < 0.001$). Similarly, for age-adjusted CCI, older participants had significantly higher CCI (mean = 3.45, range = 2–9) compared to younger participants (mean = 0.64, range = 0–4, $t(72.1) = -14.612$, $p < 0.001$) (Fig. 2A and B).

3.2.2. Polypharmacy

Regarding medications, older participants reported taking a mean of eight (range 1–25) medications daily, while younger participants had a mean of five (range 1–21). When categorized into polypharmacy (> 5 daily medications), older participants (68%) were 1.7 times more likely to report taking more than five medications compared to younger participants (39%) ($X^2(1) = 24.9$, OR = 1.7, $p < 0.001$) (Table 1).

3.2.3. Body Mass Index (BMI)

There were no differences in BMI between the two age groups. Both older and younger participants had similar percentages in underweight (1% vs. 1%), normal weight (38% vs. 35%), overweight (35% vs. 36%), and obese (26% vs. 28%) categories, respectively.

3.2.4. Functional Status

KPS scores ranged from 40 to 100 in both groups. As age increased, KPS scores significantly decreased ($r = -0.232$, $p < 0.001$) (Fig. 1A). Older patients were 1.4 times more likely to have a poor KPS (≤ 80) than younger patients ($X^2(1) = 8.7$, $p = 0.003$, OR = 1.4) (59% versus 43%) (Fig. 1C).

3.2.5. Neurologic Function

NFS ranged from 0 to 4 in both age groups. As age increased, NFS scores also significantly increased ($r = 0.210$, $p < 0.001$) (Fig. 1B). Older patients were 1.5 times more likely to have a poor NFS (2–4) than younger patients ($X^2(1) = 7.7$, $p = 0.007$, OR = 1.5) (42% versus 27%, respectively) (Fig. 1D).

3.3. Patient-Reported Outcomes

3.3.1. General Health Status

Older participants reported greater functional impairment in the EQ-5D-3L dimensions of mobility, usual activities, and self-care (ORs = 1.3–1.4, $p = 0.035$), after adjusting the significance for multiple comparisons (Table 2). Specifically, older participants were 1.3 times more likely to have problems with mobility (58% vs. 44%) and usual activities (64% vs 50%), and 1.4 times more likely to have problems with self-care (38% vs 26%) compared to the younger participants. No significant differences were found in the pain/discomfort or anxiety/depression dimensions (Table 2). Notably, there was no significant difference in the perception of overall health status (EQ-5D index score) between older

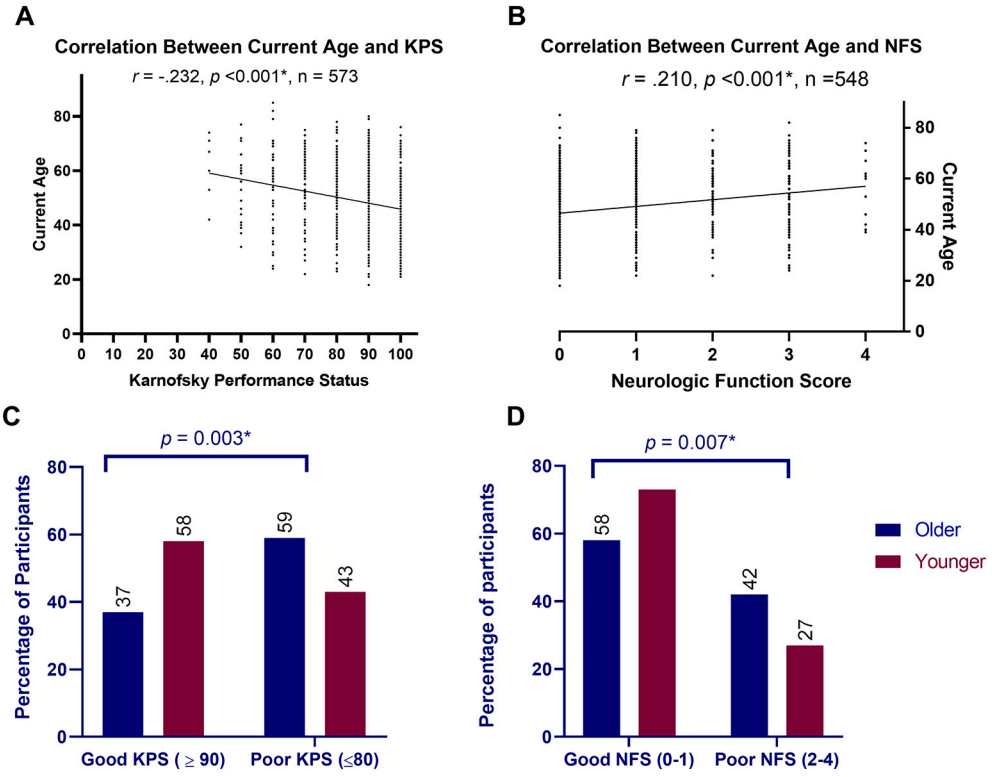

Fig. 1. Older age associated with worse functional status and neurological function. (A) KPS scores negatively correlated with age (r = −0.232, $p < 0.001$, $n = 573$), (B) NFS scores positively correlated with age (r = 0.210, $p < 0.001$, $n = 548$); (C) Chi-square test found that older patients were more likely to have a poor KPS (≤80) than younger patients ($X^2(1) = 8.7$, $p = 0.003$, OR = 1.4), (D) Chi-square test found that older patients were more likely to have a poor NFS (2–4) than younger patients ($X^2(1) = 7.7$, $p = 0.006$, OR = 1.5).
*$p < 0.05$.

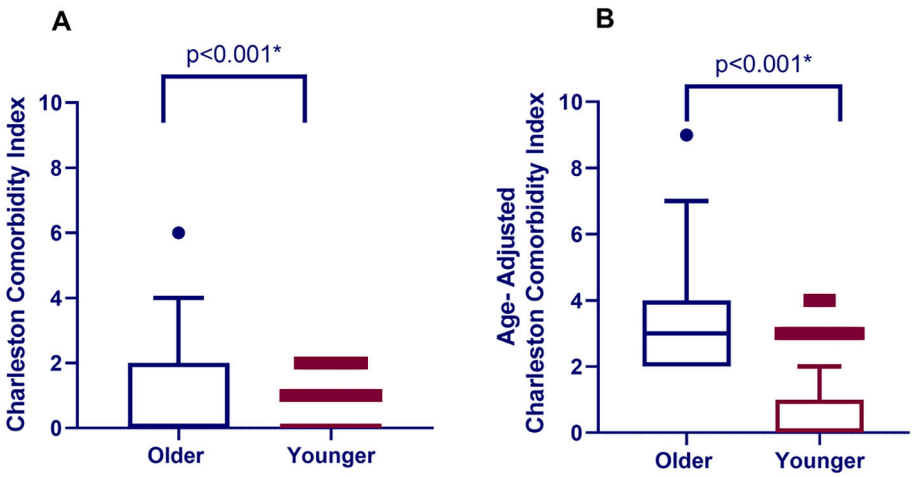

Fig. 2. Charlson Comorbidity Index(CCI)**. (A) Higher unadjusted CCI was found in older group (mean = 0.94, SD = 1.36, range = 0–6) compared to younger group (mean = 0.14, SD = 0.45, range = 0–2, $t(65.7) = -4.596$, $p < 0.001$). (B) Higher age-adjusted CCI was found in older group (mean = 3.45, SD = 1.5, range = 2–9) compared to younger group (mean = 0.64, SD = 1.9, range = 0–4, $t(72.1) = -14.612$, $p < 0.001$).
**CCI had complete data of 64 older and 334 younger participants.

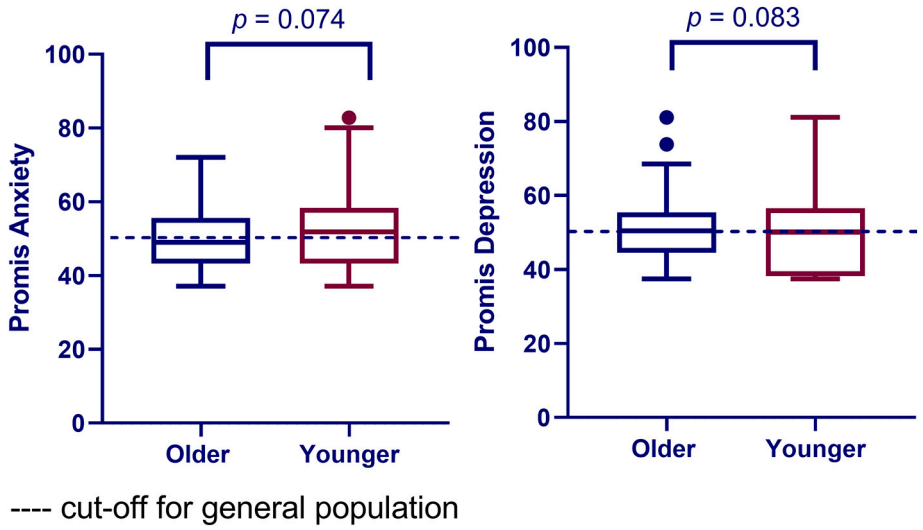

Fig. 3. Mood. No significant differences ($p = 0.074$) were found in anxiety measured by PROMIS-Anxiety between older (mean = 49.2, SD = 9.02) and younger (mean = 51.2, SD = 10.12) adults. PROMIS-Depression did not differ between older (mean = 50.1, SD = 9.08) and younger adults (mean = 50.3, SD = 9.69, $p = 0.083$).

Table 2
EQ-5D-3L dimensions.

Primary domains	Levels of impairment	Older patients ($n = 92$)		Younger patients ($n = 487$)		p	Adj. p	OR [a]
		n	%	n	%			
Mobility	No problems walking about	39	42%	275	56%	0.013	**0.035***	1.3
	Some problems or confined to bed	53	58%	212	44%			
Usual activities	No problems with usual activities	33	36%	242	50%	0.015	**0.035***	1.3
	Some problems or unable to perform	59	64%	245	50%			
Self-care	No problems with self-care	57	62%	359	74%	0.021	**0.035***	1.4
	Some problems or unbale to perform	35	38%	128	26%			
Anxiety/Depression	Not anxious or depressed	55	60%	243	50%	0.089	0.111	0.8
	Moderately or severely anxious or depressed	37	40%	244	50%			
Pain/Discomfort	No pain or discomfort	58	63%	303	62%	0.907	0.907	1.0
	Moderate or extreme pain or discomfort	34	37%	184	38%			

All p-values are calculated using Fisher's Exact test. False Discovery Rate (FDR) was used for multiple comparison corrections.
Abbreviations: OR = odds ratio, adj. = adjusted.
* $p < 0.05$.
[a] Older group is the reference for odds ratio.

and younger participants' scores (0.73 vs. 0.77, respectively, $p = 0.237$).

3.3.2. Mood

Mean anxiety scores were 49.2 (SD = 9.02) for older and 51.2 (SD = 10.12) for younger participants. Mean depression scores were 50.1 (SD

= 9.08) for older and 50.3 (SD = 9.69) for younger participants (Fig. 3). No significant differences were found in either PROMIS-Anxiety or -Depression scores.

3.3.3. Symptom Burden and Interference

MDASI-BT mean symptom burden scores for older and younger participants ranged from zero to six and zero to eight, respectively. No significant differences were found in symptom burden scores between older (mean = 1.8, SD = 1.5) and younger (mean = 2, SD = 1.7) participants. The top three moderate-severe symptoms in both groups were (1) fatigue (44% older, 41% younger), (2) feeling drowsy (29% older, 30% younger), and (3) difficulty remembering (28% older, 29% younger) (Table 3). Fewer older participants reported feeling distressed compared to younger participants (11% vs. 27%, respectively, OR = 0.4, p = 0.022) after a false discovery rate (FDR) correction was applied (Table 3). Among the six symptom factors, older participants had only a lower affective symptom factor score compared to younger participants (mean = 2.3 vs. 2.9, respectively, p = 0.011); however, after applying a FDR correction, the difference was no longer statistically significant (p = 0.066).

Table 3
Comparison of patients with moderate - severe symptoms (MDASI-BT) between older and younger cohorts.

Symptoms	Older patients (n = 92)		Younger patients (n = 487)		p	Adj. p	OR[a]
	count	%	count	%			
Affective							
Fatigue	40	44	200	41	0.729	1.000	1.1
Disturbed sleep	14	15	140	29	**0.007***	0.077	0.5
Feeling distressed	10	11	132	27	**0.001***	**0.022***	0.4
Feeling sad	14	15	117	24	0.077	0.34	0.6
Irritability	12	13	106	22	0.066	0.363	0.6
Cognitive							
Difficulty understanding	18	20	82	17	0.548	1.000	1.2
Difficulty remembering	26	28	140	29	1.000	1.000	1.0
Difficulty speaking	23	25	80	16	0.054	0.396	1.5
Difficulty concentrating	17	19	92	19	1.000	1.000	1.0
Neurologic							
Seizures	2	2	31	6	0.142	0.52	0.3
Weakness on one side of body	20	22	116	24	0.789	1.000	0.9
Numbness/tingling	14	15	76	16	1.000	1.000	1.0
Pain	12	13	86	18	0.363	0.89	0.7
Treatment-related							
Dry mouth	16	17	71	15	0.524	1.000	1.2
Feeling drowsy	27	29	145	30	1.000	1.000	1.0
Lack of appetite	8	9	51	11	0.709	1.000	0.8
General Disease							
Change in appearance	12	13	56	12	0.724	1.000	1.1
Vision	21	23	100	21	0.675	1.000	1.1
Change in bowel pattern	9	10	79	16	0.153	0.480	0.6
Shortness of breath	6	7	43	9	0.546	1.000	0.7
GI							
Nausea	7	8	58	12	0.282	0.78	0.6
Vomiting	5	5	23	5	0.79	1.000	1.2

Note: [a] Older group is the reference for odds ratio. * $p < 0.05$. A rating of 5 or higher on a 0–10 scale is considered moderate - severe.
Abbreviations: OR = odds ratio, adj. = adjusted, GI = gastrointestinal.

Interference scores ranged from 0 to 10, with a mean of 2.9 for both age groups. Although not statistically significant, older participants were 1.2 times (55% vs. 45%, OR = 1.2, p = 0.067) more likely to report moderate-severe interference of their walking compared to younger participants (Table 4). There were no significant differences in the activity-related and mood-related interference subscale scores between groups.

4. Discussion

The world's aging population is growing at an accelerated rate, with adults aged 65 years and above expected to reach 83.7 million by the year 2050 [34]. This, coupled with the fact that cancer, including brain tumors, occurs more commonly in older adults, contributes to a substantial increase in cancer numbers in an aging population. The GA can potentially identify vulnerabilities, guide interventions, assist in clinical treatment decisions, predict toxicity and prognosticate survival in oncology patients [35,36]. To our knowledge, this is the first study using patient- and clinician- reported outcomes along with standard clinical assessments and characteristics to assess key GA constructs between age groups in a large PBT cohort. We found that older participants were more likely to be retired, have higher annual income, higher comorbidities, worse performance status and neurological function, and more impairments in mobility, usual activities, and self-care. Older participants also reported significantly less distress; however, both age groups had comparable overall symptom burden, symptom interference, and mood disturbance.

The GA starts with careful review for demographic and social vulnerabilities of older adults [14,36]. In our cohort, the majority in both age groups were married and did not live alone, suggesting a lower likelihood of social loneliness and isolation, two critical geriatric vulnerabilities [37,38]. Additionally, older participants were more likely to be retired and have higher income than younger participants. This is congruent with other studies showing that increasing age is a risk factor for an early retirement [39] and younger age is a predictor of higher likelihood of financial hardship [40,41] among cancer survivors.

The measurement of comorbidities, aggregation of two or more co-occurring medical diagnoses in the same individual [42], using indices such as the CCI has been demonstrated to have high prognostic value of survival among cancer survivors [43]. Consistent with prior oncology reports [44], the older group had higher comorbidity index demonstrated by both age-adjusted and unadjusted CCI. The presence of

Table 4
Severity of interference items between older and younger groups.

Interference items	Levels of impairment	Older patients (n = 92)		Younger patients (n = 487)		p	OR[a]
		n	%	n	%		
Activity-Related							
General Activity	None-Mild	37	40	215	44	0.486	1.1
	Moderate-Severe	55	60	272	56		
Work	None-Mild	44	48	215	44	0.515	0.9
	Moderate-Severe	48	52	272	56		
Walking	None-Mild	41	45	266	55	0.067	1.2
	Moderate-Severe	51	55	218	45		
Mood-Related							
Mood	None-Mild	49	53	220	45	0.154	0.9
	Moderate-Severe	43	47	267	55		
Enjoyment	None-Mild	40	43	238	49	0.342	1.2
	Moderate-Severe	52	57	249	51		
Relations	None-Mild	56	61	272	56	0.373	0.8
	Moderate-Severe	36	39	215	44		

Note: [a] Older group is the reference for odds ratio. * $p < 0.05$. Interference items 0–1 are coded as none-mild and ≥ 2 are coded as moderate- severe.
Abbreviations: OR = odds ratio.

comorbidities diminishes receipt of chemotherapy [44,45], which is on par with our finding that older participants were less likely to receive chemotherapy, a finding not observed in the younger group. Conversely, while seizures are not a factor in CCI, they are prevalent in the PBT population. We, therefore, evaluated the incidence of seizures and, as anticipated, fewer older participants reported seizures compared to younger adults, who tend to have slower-growing tumors [46].

Polypharmacy is common in older patients with cancer and leads to additional toxicities, drug interactions, and increased costs [47]. Decreased renal and hepatic function alters drug pharmacology, typically decreasing drug clearance, and is associated with biological aging [48]. Decline in these functions can be further accelerated by cancer and its treatment. In our cohort, polypharmacy was 1.7 times more likely in the older group. Polypharmacy is associated with moderate-to-severe drug-drug interactions and therapeutic duplication [49]. Therefore, inclusion of GA tools, such as Beers criteria, in older PBT patients may help mitigate adverse outcomes.

Nutritional status represents an additional oncogeriatric parameter related to decreased performance status and worse overall survival [14,50]. Although nutritional status or weight loss were not assessed, comparison of BMI and BMI categories between age groups revealed no significant differences. BMI, albeit a straightforward clinical tool, is limited in its ability to discern between fat versus muscle and a one-time measure does not capture weight loss [51], making it a poor proxy of malnutrition. However, in a recent review of nutritional measures in all malignancies, BMI was included in 21 studies. No association between BMI and patient outcomes was found in thirteen studies and an association between low BMI and poor cancer-related outcomes was found in eight studies [51].

Functional status is the most significant GA domain because it is intended to capture early functional decline, a significant prognosticator of early morbidity and mortality [5,37,52]. Consistent with previous studies in PBT patients [53,54], using CROs we found that age significantly correlated with worse functional status scores and older adults were more likely to have poor functional status. While KPS is frequently used in oncology practice, contemporary evidence demonstrates that it does not capture functional deficits that may be revealed by GA and is a poor prognosticator of functional decline [37,55]. In support of this are studies that found 47% of people with glioblastoma and good KPS (70–100) were diagnosed as frail using the comprehensive GA [17], and older age was associated with mobility impairment measured by Timed Up and Go test and Times Sit-to-Stand (TSS) in a PBT cohort [56].

We investigated differences in functional status between age groups using PROs, the EQ-5D-3L and MDASI-BT, and found that older participants had significantly greater impairments in mobility, usual activities, and self-care. In addition, while not statistically significant, older adults were more likely to report greater walking interference. Notably, about half of the participants in both age groups reported activity-related interference, with older participants more frequently reporting moderate-severe interference with walking. Similarly, in a cohort of 903 cancer survivors, older age was associated with greater symptom interference with walking [57]. These findings suggest a relationship between activity-related symptom interference with functional impairment [20], and, as previously reported by our group, greater activity-related interference may be related to tumor progression in patients with glioblastomas [58]. These findings highlight the need for gait assessment, fall risk, and potentially rehabilitation and assistance needs in this patient population.

Although we did not observe differences in cognitive or neurologic factors of the MDASI-BT, increasing age correlated with worsening NFS scores and older participants were more likely to have poor NFS. NFS reflects clinician-assessed impact of neurologic symptoms (e.g., aphasia, seizures, and weakness) of participants in PBTs. Poor NFS indicates greater impairment of function. Notably, there was a lower incidence of seizures found among the older group compared to the younger group, and fewer older participants received chemotherapy with no group differences in tumor diagnoses, tumor grade, or history of tumor recurrence. The observed age differences in NFS may be related to brain aging processes previously reported in glioblastomas (i.e., senescence-associated secretory phenotype (SASP), neuroinflammation, and indoleamine 2,3-dioxygenase [IDO]) [59,60]. Moreover, given the higher CCI scores and presence of polypharmacy among older participants, NFS findings may be related to the synergistic effects of comorbidities and polypharmacy together with brain aging and effects of the tumor itself.

Lastly, we found that older participants were less likely to report feeling distressed or to report disturbed sleep, a finding that is consistent with prior reports [61,62] of cancer survivors. In contrast, a study by Mohile et al. [57] found that older adults had greater distress and sleep disturbances in the last week of radiation therapy, compared to younger adults. These differences between our studies may be related to the timing of assessments, which were more acute in the Mohile et al. [57] study compared to ours. In addition, Mohile et al. [57] had equal doses of therapy delivered in both age groups in contrast to our cohort, which reported a lower incidence of chemotherapy in older participants. Additionally, anxiety and depression symptom scores were found to be comparable between age groups. In contrast, distress, anxiety, and depression, are frequently reported to be higher among younger cancer survivors across all cancer types [57,63,64]. This generational difference may be related to younger participants viewing cancer as a greater threat to their phase of life and work, greater cancer fatalism, or fear of inevitable death due to cancer [65], while older participants are thought to assess their health status in comparison to their chronological age peers [63].

Although this study includes a large cohort of participants with PBT, which were demographically and clinically well-matched, and leveraged concurrent use of PROs and CROs, there are several key limitations worth noting. First, the older participants' sample size was small compared to younger participants, which limited the statistical power of analyses. Second, the study is cross-sectional in nature, thus limiting the ability to evaluate changes in the GA constructs over time. It is important to note our study employed CROs (KPS, NFS) and PROs (EQ-5D-3L, MDASI-BT) to assess functional status rather than commonly used GA tools such as ADLs or iADLs. Further, data on cognition, falls and geriatric syndromes such as frailty and dementia were not collected. Thus, future GA studies in the broader neuro-oncology patient population would benefit from incorporating GA constructs [14]. Additionally, although the comparison groups are unbalanced, our sample had a mean age of 50 (SD 14), consistent with the higher incidence of PBT in adults older than 40 years of age and represents the diversity of neuro-oncologic diagnoses rather than the high grade gliomas alone. Lastly, we acknowledge a limitation of this study may be a referral bias of patients enrolling into the Natural History Study at the National Institutes of Health and older group ($\geq$ 65 years) may be particularly susceptible to the selection bias as evidenced by the smaller number of participants.

In summary, our findings highlight that older participants living with a PBT may have more vulnerabilities in functional aging parameters, such as functional and neurological function status, comorbidities, and polypharmacy, compared to younger participants. Functional impairments were more evident in the older group across both PROs and CROs, highlighting this as a vulnerability and an important opportunity for future research. Additionally, both age groups were similar in overall symptom burden, severity of symptom interference, mood and overall health status, suggesting that further assessments encompassing all age groups would be informative in uncovering functional aging impairments related to PBT.

Findings highlight several important future directions in advancing the science in the PBT population. Specifically, systematic inclusion of geriatric vulnerability assessments, such as frailty, malnutrition, and dementia, using the tools previously outlined by GA researchers [14]. Future prospective studies should also incorporate longitudinal designs with comprehensive GA across the disease trajectory with measures of emotional and caregiver support, in addition to the items noted above

and greater inclusion of gender, racial, and ethnic minorities to fully understand geriatric vulnerabilities across the entire diverse PBT patient population.

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Author Contributions

Conceptualization: DS, EV, TSA, HL, MRG; Supervision: TSA, HL, EV; Data curation: EV, AC, AA, NB, AC, EG, VJ, JL, ML, JR, KR, JR, MT, LB, EB, NL, MP, MPP, VP, LP, BJT, JW, MRG, TSA, HL; Formal analysis: DS, EV, TSA, HL; Writing-original draft: DS, TSA, HL; Writing- editing: DS, EV, AC, AA, NB, AC, EG, VJ, JL, ML, JR, KR, JR, MT, LB, EB, NL, MP, MPP, VP, LP, BJT, JW, MRG, TSA, HL; Writing- review: DS, EV, AC, AA, NB, AC, EG, VJ, JL, ML, JR, KR, JR, MT, LB, EB, NL, MP, MPP, VP, LP, BJT, JW, MRG, TSA, HL.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2022.08.013.

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