ISSN: 2641-1911
DOI: 10.33552/ANN.2021.11.000758
Archives in Neurology & Neuroscience
Iris Publishers

Research Article

Cognitive Dysfunction in Non-Brain Metastatic Cancer

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Received Date: August 16, 2021

Published Date: September 13, 2021

Abstract

Background: Cognitive impairment in primary cancer and brain metastatic (BM) cancer has been well-documented. There is a dearth of research comparing the cognitive profiles of people with BM and non-brain metastatic cancer (NBM), as well as base rates of such impairment.

Objective: The present study addressed this gap in the literature by comparing the cognitive profiles of participants with BM and NBM.

Method: This cross-sectional study consisted of 61 BM, 40 NBM, and 37 healthy control (HC) participants. Participants completed the same neuropsychological battery, including tests of processing speed, attention, working memory, expressive language, auditory-verbal memory, and executive functioning.

Results: Both clinical groups showed reduced processing speed, verbal learning/memory, and executive functions. BM participants performed below HC participants across all neuropsychological tests, while NBM participants performed below control participants on tests of processing speed and executive functioning. The clinical groups differed in semantic verbal fluency (NBM>BM). Fifty-seven percent of BM participants had ≥3 impaired scores (i.e., ≤5th%ile), and 25% of NBM participants had the same level of cognitive impairment.

Conclusion: Over half of BM participants were cognitively impaired on at least three neuropsychological tests, and one-quarter of NBM participants demonstrated this same level of cognitive impairment. The elevated rate of cognitive dysfunction in the BM group may be associated with the greater neurologic disease burden posed by brain metastases in conjunction with treatment effects, while the cognitive deficits among NBM participants are possibly attributable to systemic illness and treatment effects. Clinical implications and areas for future study are discussed.

Introduction

The National Cancer Institute estimates that over 38% of all Americans will be diagnosed with cancer in their lifetimes. This translates to over 1.7 million newly diagnosed cases per year [22]. Roughly half will present with evidence of metastasis, and of this population, 10% will present with brain metastasis (BM) [20,22,27,29]. Where and when metastasis develops depends largely on the primary tumor location, genetic markers, and metabolic characteristics [29]. Metastases are difficult to treat and are estimated to be responsible for 90% of cancer deaths [13]. BMs are associated with significant morbidity and mortality, and an overall median survival time of just over 7 months, although some people with BM will live for years after diagnosis depending on the type of primary cancer [13]. BMs are associated with significant cognitive impairments which adversely affects quality of life (QoL), functional independence, and caregiver burden. In a randomized Phase III clinical trial of heterogeneous primary cancer patients with brain metastases, 90% of BM participants displayed cognitive impairment on at least one neurocognitive test, with the majority of

impairments observed in memory, executive functioning, and fine motor control [26]. Similar rates of baseline cognitive impairment among people with BM have been demonstrated, with memory deficits present in over half of individuals [4,5,12,14]. Additionally, those with BM have increased susceptibility to depression and anxiety [7], which can also affect cognition and QoL [19,23].

Even among cancer patients without BM, cognitive impairment can be present before chemotherapy [16,31,32,43], occurring in up to 33% of people with breast cancer [43]. A recent review of longitudinal research in people with breast cancer found impairments in memory, executive function, processing speed, and attention [15]. High rates of cognitive impairment in pre-chemotherapy cancer participants suggests that chemotherapy is not the sole cause of cancer related cognitive impairment (CRCI), and even rates of subjective and objective cognitive changes post-chemotherapy vary greatly in the literature ranging months to decades [1,40]. However, the literature on pre-chemotherapy cognitive impairment is scarce. There are also sparse CRCI studies in individuals with non-brain related metastatic cancer (NBM), which is important for developing coping and treatment strategies, and improving overall QoL. One such study [41] compared cognition and rates of impairment among localized colorectal cancer (n=281), metastatic colorectal cancer (n=66), and healthy controls (n=72) across 10 clinical tests, and 47% of their patients with metastatic cancer had deficits in two or more domains compared to 15% of their healthy controls. Common domains with deficits included processing speed, attention, working memory, and verbal learning [41]. This study aims to characterize the pattern and prevalence of cognitive impairment of BM and NBM using neuropsychological tests. We hypothesized that both cancer groups will display cognitive impairment in multiple domains compared to healthy controls, with BM participants having more severe cognitive impairment, and at a higher frequency, due to the presence of brain tumor(s). We also expected both BM and NBM groups to show a similar profile of cognitive impairment as previously reported [12].

Methods

Participants

Newly diagnosed BM (n=61) and NBM (n=40) participants were recruited from the Department of Radiation Oncology and the Division of Hematology Oncology between 2013 and 2018. All diagnoses were made by a board-certified radiation oncologist. Eligible participants were age 19 years or older. All BM participants had supratentorial lesions. Clinical participants with any history of one or more primary brain tumors, cranial radiation, leptomeningeal disease, neurological or psychiatric illness, substance abuse, or serious coexisting medical illness adversely affecting cognition were excluded from this study. Clinical participants were assessed within one week of starting radiation therapy to the brain for brain metastasis.

The HC group was comprised of healthy adult volunteers (n=37) recruited in a prior study [38]. The HC group met the same eligibility requirements, except no history of cancer was permitted. They were recruited from the community through advertisements and were screened via telephone structured interviews to assess study appropriateness. None of the HC participants reported any cognitive symptoms. The following treatments for brain metastases were used: surgical resection, single fraction radiosurgery with Gamma Knife or LINAC technology (15-24 Gy) for tumors ≤ 4 cm, hypofractionated focal radiation with LINAC for tumors > 3-4 cm (5-6 Gy x 5 fractions for 25-30 Gy total), and whole-brain radiation therapy (with LINAC; 30Gy in 10 fractions to 37.5 Gy in 15 fractions). Off-study guidelines for radiosurgical treatment followed maximum tolerated doses outlined in RTOG 9005 (Shaw et al., 2000) [37]. The majority of participants in the cancer groups did not have any surgical history—only 7 BM (11%) and 2 NBM patients (5%) had prior resective surgery. This study was approved by the University of Alabama at Birmingham Institutional Review Board (IRB 141023002) and was in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Measures

Commonly used neuropsychological tests were administered (see Table 1), including digit span [42], digit symbol subtest [42], verbal fluency (CFL/Animals) [34], Trail Making Test (TMT) Parts A and B [33], and the Hopkins Verbal Learning Test-Revised (HVLT-R) [3]. The Karnofsky Performance Status (KPS) scale was used to measure functional status [18]. The Hospital Anxiety and Depression Scale [45], and Beck Depression Inventory-II [2] were used to measure emotional distress in the cancer and HC groups, respectively (Table 1).

Data Analysis

Differences in continuous (i.e., age and years of education) and categorical (i.e., gender and race) demographic variables were examined across groups using analysis of variance (ANOVA) and chi-squared test of independence, respectively. To describe the neurocognitive profiles, descriptive statistics (i.e., M, SD) were based on the standardized data across the 10 test scores. All standardized scores were transformed into z-scores via: $\frac{(X-M)}{SD}$. ANOVAs were used to examine neurocognitive test performances among the groups based on calibrated standardized scores. Eta squared (η2) was calculated for each ANOVA (small effect=.04, moderate effect=.25, and large effect=.64). For pairwise comparisons, Tukey's Honestly Significant Difference (HSD) post hoc analysis was performed only on ANOVA models that were significant at the omnibus level. Finally, we examined cumulative impairment of test scores for the participant groups, defined as scores falling at or below the 5th%ile (i.e., z-score ≤ -1.64).

We then examined the base-rate (i.e., prevalence) of cognitive impairment on 7 unique tasks, producing 10 total scores, looking at 0, ≥ 1, ≥ 2, and ≥ 3 impaired scores. Lastly, we examined proportional differences in rates of score impairment between the clinical groups using chi-squared tests of independence. The reference category was set to "0 impaired scores" for all the base rate and chi-squared

analyses. Effect sizes were measured with the phi (ϕ) coefficient. Statistical analyses were conducted using IBM SPSS version 25.

Results

Sample Characteristics

Clinical groups did not significantly differ in age, gender, ethnicity, depression, or anxiety (see Table 2). The HC group (M=14.6, SD=1.8) had more education than the BM group (BM: M=13.3, SD=2.6; on average, one more year of post-secondary education), but not the NBM group (M=13.8, SD=2.0). Since this difference in education was modest and not present between both clinical groups, this was not included as a covariate in our main findings since our primary interest was in the difference between BM and NBM groups. Further, analyses used normed scores, calibrated for demographic factors (depending on task). Nevertheless, we re-analyzed our data correcting for education and reported any discrepant results. Primary tumor locations and KPS data are in Table 3. In people with BM, 55.7% (34/61) had frontal lobe tumors, 21.3% (13/61) had temporal lobe tumors, and the remaining 23% had mixed tumor locations. All three groups measured in the normal range of emotional distress (Table 2 & 3).

Table 1: Description of Neurocognitive, Psychological, and Functional Measures.

Learning and Memory	The Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt and Benedict, 2001) was used as a measure of verbal learning and memory. Participants learn 12 words over three learning trials with delayed free recall and recognition trials after 20-25 minutes.
Attention and Working Memory	The Digit Span subtest from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997) is a measure of auditory attention and working memory, which requires participants to repeat digit strings aloud, forwards and backwards.
Processing Speed	The WAIS-III Digit Symbol subtest (Wechsler, 1997) is a measure of processing speed and divided attention. Participants correctly match pairs of numbers and symbols using a key at the top of the page (120").
Oral Expression	Verbal fluency measures required participants to name as many "C", "F", and "L" (letter-guided) as possible in 60 second, and as many animals (semantic) as possible in 60 seconds. Scores were calibrated for age and education based on published normative data (Ruff, Light, Parker and Levin, 1996).
Executive Functioning	The Trail Making Test (TMT) Parts A and B are measures of processing speed and executive functioning, respectively. For TMT-A, the numbers 1 through 25 are presented in an array across a page and participants were asked to quickly draw a line to connect the numbers in numerical order. For TMT-B, participants were required to switch between letters and numbers (i.e., 1 to A, A to 2, 2 to B). For both tasks, the raw score is equal to the completion time in seconds. Normative data was corrected for age, gender and education (Reitan and Wolfson, 1985).
Emotional Functioning	The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), was used to assess symptoms of depression and anxiety in both patient groups. The scale is comprised of 14-items (7 anxiety and 7 depression). Emotional distress was appraised in controls using the Beck Depression Inventory-II (BDI-II) (Beck, Steer and Brown, 1996), a 21-item self-report scale of broad depressive symptoms.
Functional Status	The Karnofsky Performance Status (KPS) scale was used to measure functional status (Karnofsky, 1949), with lower scores reflecting reduced independence. Scores of 80 and greater indicate minimal or no symptoms and intact functioning. Scores of 70 and below indicate obvious disease symptoms and functional impairments.

*Note: Raw scores for Digit Symbol, Digit Span, and HVLT were standardized using demographic calibrations for age according to the published test manuals, correcting for age.

Table 2: Participant Demographic Characteristics Stratified by Group.

Variable M(SD)	Controls(n=37)	NBM(n=40)	BM(n=61)	p
Age	56.8(12.1)	59.7(12.3)	59.8(11.6)	.436a
Education	14.6(1.8)	13.8(2.0)	13.3(2.6)	.031a
HADS-D	--	4.3(3.0)	5.4(4.0)	.17b
HADS-A	--	5.7(4.2)	6.7(4.2)	.25b
BDI-II	3.9(4.8)	--	--	--
Gender n(%)				
Male	17(45.9)	21(52.5)	32(52.5)	.794c
Female	20(54.1)	19(47.5)	29(47.5)	
Race n(%)				
Caucasian	31(83.9)	30(75.0)	47(77.0)	.702c
African American	6(16.2)	0(25.0)	13(21.3)	
Other	--	--	1(1.6)	

Abbreviations: NBM=non-brain metastatic cancer; BM=brain metastatic cancer; HADS-D and HADS-A=Hospital Anxiety. and Depression Scale-depression and anxiety subscale, respectively.

[a]p-values represent ANOVAs for age and education.

[b]p-values represent independent t-tests for HADS-D and HADS-A.

[c]p-values represent chi-square tests for gender and race.

Table 3: Functional Status and Primary Tumor Location.

Variable	NBM(n=40)	BM(n=61)
Karnofsky Score	*n*(%)	
100-80(Able to Work)	28(70)	46(75.4)
70-50(Unable to Work)	12(30)	14(23.0)
40-0(Functionally Disabled)	--	1(1.6)
Primary Tumor Location	*n*(%)	
Lung[1]	9(22.5)	32(52.5)
Breast	6(15.0)	10(16.4)
Melanoma	3(7.5)	4(6.6)
Gynecological[2]	3(7.5)	5(8.2)
Renal Cell	1(2.5)	2(3.3)
Gastrointestional[3]	10(25.0)	4(6.6)
Prostate	5(12.5)	1(1.6)
Testicular	--	1(1.6)
Other	3(7.5)	2(3.3)

Abbreviations: NBM=non-brain metastatic cancer; BM=brain metastatic cancer.

[1]NBM: 9 non-small cell; BM: 29 non-small cell, 3 small cell.

[2]NBM: 1 gynecological, 1 ovarian, 1 cervical; BM: 2 gynecological, 2 ovarian, 1 cervical.

[3]NBM: 2 pancreatic, 1 gallbladder, 1 liver, 1 rectum, 5 colon; BM: 2 pancreatic, 1 gastric, 1 colon.

Overall, 77.5% of NBM participants received chemotherapy in the past compared to 37.7% of BM participants. Additionally, 45.0% of NBM participants were receiving chemotherapy at the time of the study compared to 13.1% of BM participants. Among cancer participants, lifetime history of chemotherapy (past and/or present) was not significantly associated with cognitive performance while to our surprise, current chemotherapy treatment was weakly positively associated with higher) cognition across tasks (Pearson product moment correlation coefficients values ranging from .13 to .35). Surgical resection was more common among BM participants (11.5%) compared to NBM participants (5.0%). Comparable percentages of NBM (70.0%) and BM (65.6%) participants started radiation therapy within a week of the study. All BM participants had supratentorial lesions. Of the BM group, 41.0% had 1 metastasis, 32.8% had 2-3 metastases, and 26.2% had > 3 metastases. Functional ability was comparable between NBM and BM groups (median KPS score=80), and clinical participants were functionally intact on average. Eighteen HC (48.6%) were missing HVLT-R Delayed Recall and Retention data but all these participants had at least HVLT-R Recognition Discriminability Index scores. This was considered missing at random as there was no systematic statistical differences between controls with and without missing data. Further, this missing data did not interfere with our primary goal examining prevalence of score impairment and differences between the cancer groups. Nine BM participants (14.8%) had incomplete neuropsychological test data, though the majority (66.7%) were only missing 1 of 10 task scores. Missing data in the ANOVA models were handled via pairwise deletion.

Cognitive Performance

Examination of the neuropsychological profile for the clinical groups showed normatively low average-to-average performances across all tasks at a group level (see Table 4). However, BM participants performed below NBM participants across all tasks. Both BM and NBM participant groups showed preserved basic attention and working memory ability on the Digit Span task, and information processing speed on TMT-A, with comparable rates of impairment seen in a subgroup of individuals. Conversely, the clinical groups displayed lower mean performance on Digit Symbol Coding, a more complex task of rote visual learning and speed of mentation, with high rates of score impairment (NBM=22.5%; BM=33.3%). Though the BM and NBM groups had generally average mean performance and low rates of score impairment on Semantic Fluency (NBM=5.0%; BM=12.7%), performance on Letter-Guided Fluency was lower, with the BM group showing a markedly higher base rate of score impairment (NBM=12.5%; BM=34.9%). The clinical groups showed normatively lower performance on verbal learning (HVLT-R Total Recall: NBM=20.0%, BM=36.5%) and delayed memory (HVLT-R Delayed: NBM=15.0%, BM=36.5%), with BM participants having the highest prevalence of score impairment. Both clinical groups showed non-trivial base rates of score impairment on HVLT-R Retention (NBM=10.0%; BM=15.9%) and HVLT-R Recognition (NBM=12.5%; BM=15.9%). Regarding executive functioning, the participant groups displayed relatively worse normative performance on TMT-B with the BM group having a higher base rate of impaired score (NBM=12.5%; BM=23.8%) (Table 4).

Table 4: Neurocognitive Performance as a Function of Group and Domain.

Measures by Domain	Standard-score (*z*): *M*(*SD*)			%Impaired			*F*(*df*)[b]	*p*(η²)	Post-hoc[b,c]
	Controls	NBM	BM	Controls[a]	NBM	BM			
Attention									
Digit Span[d]	0.17(0.76)	-0.04(0.88)	-0.23(0.72)	0.0	5.0	4.8	3.1(2,134)	.048(.04)	C>BM
Processing Speed									
Digit Symbol Coding	0.49(1.03)	-0.55(1.09)	-0.84(1.03)	0.0	22.5	33.3	20.8(2,130)	<.001(.22)	C>NBM,BM
TMT-A(Time)	0.44(1.06)	0.31(1.01)	-0.18(1.18)	2.7	2.5	7.9	4.3(2,132)	.016(.06)	C<BM
Expressive Language									
Letter-Guided Fluency	-0.06(1.11)	-0.44(1.02)	-0.89(1.14)	13.5	12.5	34.9	6.6(2,133)	.002(.09)	C>NBM,BM
Semantic Fluency[e]	-0.04(0.87)	0.23(1.08)	-0.35(1.25)	0.0	5.0	12.7	3.3(2,133)	.038(.05)	NBM>BM
Memory									
HVLT-R Total Recall	-0.22(0.87)	-0.45(1.05)	-0.92(1.19)	2.7	20.0	36.5	5.4(2,135)	.005(.07)	C>BM
HVLT-R Delayed	-0.42(0.79)	-0.37(1.16)	-0.97(1.18)	0.0	15.0	36.5	6.5(2,117)	.002(.10)	C>BM
HVLT-R Retention(%)	0.07(0.89)	0.02(1.21)	-0.46(1.16)	2.7	10.0	15.9	2.8(2,117)	.063(.04)	--
HVLT-R Recognition	0.27(0.70)	-0.09(1.01)	-0.35(1.04)	2.7	12.5	15.9	4.9(2,135)	.009(.07)	C>BM
Executive Functioning									
TMT-B(Time)	0.22(1.19)	-0.40(1.14)	-0.78(1.16)	8.1	12.5	23.8	18.6(2,128)	<.001(.13)	C<BM,NBM

Abbreviations: NBM=non-brain metastatic cancer; BM=brain metastatic cancer; TMT=Trail Making Test; HVLT-R=Hopkins Verbal Learning Test-Revised.

[a]18 Controls missing full HVLT-R data; rates of impairment computed based on available data.

[b]Analyses based on standardized scores.

[c]Post-hoc analyses reflect pairwise comparisons using Tukey's HSD for statistically significant (α=.05) comparisons.

[d]Not significant after correcting for education (p=.123, η_p^2=.03).

[e]Not significant after correcting for education (p=.054, η_p^2=.04).

Next, test performances among the control and clinical groups were compared. Significant group differences in cognitive performance emerged for the Digit Span (p=.048, η2=.04), Digit Symbol Coding (p<.001, η2=.22), TMT-A (p=.016, η2=.06) and TMT-B (p<.001, η2=.13), Letter-Guided Fluency (p<.002, η2=.12), Semantic Fluency (p=.038, η2=.05), HVLT-R Total Recall (p=.005, η2=.07), HVLT-R Delayed Recall (p=.002, η2=.10), and HVLT-R Recognition (p=.009, η2=.07) tasks. No significant group differences in HVLT-R Retention was observed. Post-hoc analyses showed that the BM group performed significantly lower than controls on Digit Span, Digit Symbol Coding, TMT-A and TMT-B, Letter-Guided Fluency, as well as the HVLT-R Total and Delayed Recall. NBM participants performed lower than controls on Digit Symbol Coding, Letter-Guided Fluency, and TMT-B. NBM participants had greater Semantic Fluency performance than the BM group. All ANOVAs were re-run with education added as a covariate, and results were identical with exception of Digit Span (p=.123, ηp2=.03) and Semantic Fluency (p=.054, ηp2=.04) (Table 5).

Table 5: Frequency of Total Number of Impaired Cognitive Measures by Participant and Group

# of Impaired Tests[†a]	Controls[b]	NBM	BM[c]	$\chi^2(\phi)$[d]	*p*
	n(%)				
0	30(81.1)	21(52.5)	18(29.5)	--	--
≥ 1	7(18.9)	19(47.5)	43(70.5)	5.39(.23)	.020
≥ 2	3(8.1)	13(38.2)	34(65.4)	6.11(.29)	.013
≥ 3	2(5.4)	7(25.0)	24(57.1)	7.04(.32)	.008

Abbreviations: NBM=non-brain metastatic cancer; BM=brain metastatic cancer.

†Impaired at ≤ 5th percentile (z-score ≤ -1.64); based off a battery of 10 test scores unless otherwise specified.

[a]'0 impaired tests' was set as the comparison category for chi-square analyses.

[b]9 BM participants did not have full data; rates of impairment were based on available data.

[c]18 HC had partial HVLT-R data; rates of impairment were based on available data.

[d]Chi-square analyses based on NBM and BM groups

Within entire healthy control sample, 30 (81%) had no impaired scores, only four participants (10.8%) had one impaired score, and one person (2.7%) had two impaired scores. Lastly, base rate of cumulative score impairment was compared between clinical groups (Table 5). Relative to NBM participants, a greater proportion of BM participants had ≥ 1 impaired scores across tests (70.5% vs. 47.5%; ϕ=.23). Stated differently, a little over half of NBM (52.5%) and only around one quarter of BM (29.5%) participants had no impaired scores. A significantly greater proportion of BM vs. NBM participants had ≥ 2 (65.4% vs. 38.2%; ϕ=.27) as well as ≥ 3 (57.1% vs. 25.0%; ϕ=.32) impaired test scores. As expected, the HC group had lowest rates of impairment across virtually all test scores, and the majority (81.1%) had no impaired scores.

Discussion

This current study found evidence of cognitive impairment in participants with metastatic cancer. As expected, BM participants had higher rates of cognitive impairment across all domains. Rates of impairment among NBM participants were attenuated and generally limited to the domains of processing speed and executive functioning but were present in a quarter or more of individuals, depending on the number of impaired scores. While at a group level, the mean scores for BM and NBM groups were largely in the low average-to-average ranges, significant, non-trivial portions of both groups demonstrated varying rates of cognitive impairment. Fifty-seven percent of BM and 25% of NBM participants had impaired scores on three or more tests. This rate of cognitive impairment is consistent with prior findings of pre-treatment cancer affecting cognition in cancer participants with and without BM [12,13,14,15,19,25,26,30,32,44].

Broadly, this study investigated cognitive impairment in people with non-brain metastatic cancer. Cognitive impairment in cancer is likely multifactorial, related to factors of systemic illness and treatment effects [15,31,43,44], though we did not directly examine these factors. The majority of our NBM group had previously received chemotherapy, and 45% were receiving chemotherapy at the time of this study. While chemotherapy may possibly contribute to the CRCI in our NBM group, our study found the largest rates of cognitive impairment in the BM group, despite lower rates (13%) of chemotherapy. Furthermore, history of past and/or present chemotherapy was only modestly associated with cognitive data. In addition, all patients in our study were assessed within one week of starting radiation treatment. While radiation treatment can affect cognition [4,8,26], this is typically observed in 30% or more of patients after 4 months of radiation treatment (partial or whole brain), which is well beyond our one week time window. Moreover, for chemotherapy, the literature does not strongly indicate a significant decline in cognitive functioning within this short time interval [1]. In the BM group, the higher rate of cognitive impairment is not surprising due to the presence of metastasis in the brain. Rates of radiation treatment between our two groups did not differ and those receiving radiation treatment were only one week into treatment at the time of this study. This reduces the likelihood of radiation treatment being the primary factor of decline in our sample, but like chemotherapy, their effects on cognitive impairment could potentially be additive.

In both the BM and NBM groups, elevated rates of deficits in processing speed and executive functioning were observed, and the BM group also demonstrated deficits in attention and memory, consistent with prior studies [5,14,15,31,32]. Relative to our healthy control group, our two clinical groups had higher rates of impairment on all tests except for letter-guided verbal fluency, with no differences in impairment rates observed between the healthy control participants and NBM participants (13.5% and 12.5%, respectively). In contrast, 33.3% of the BM group met the previously established criteria for an impaired letter-guided verbal fluency score. When comparing our observed impairment rates to a study of colorectal cancer with metastasis conducted by Vardy and colleagues [41], our healthy control participants had notably lower rates of impairment across overlapping tests (e.g., Digit Span, Symbol Digit, TMT-A & B, and HVLT-R). While our HC sample impairment ranged from 0% - 8.1%, their HC sample impairment rates ranged from 14% - 19%. Their metastatic cancer group's impaired scores ranged from 15% - 47%, while our NBM group ranged from 5% - 22.5% and our BM group ranged 4.8% - 36.5%. This discrepancy is likely due their more liberal cutoff score (T-Score = 40 or 16th %ile), while we used a more conservative cutoff at the 5th %ile. A more liberal cutoff will inflate impairment rates. To demonstrate this point, in a study looking at how antiangiogenic treatment affects individuals with metastatic renal cancer, pre-treatment rates of cognitive impairment were highly similar with the rates observed in our sample when the same conservative cutoff is applied [17].

The impairments observed in both our clinical groups are possibly driven by frontostriatal dysfunction [12], with frontostriatal projections related to attention, processing speed, working memory, and executive functioning [9,21,39]. While cancer-related treatment does affect cognition, there is evidence to suggest that pre-chemotherapy, women who are diagnosed with breast cancer (stages I-III) have deficits in attention and working memory, along with an atypical pattern of increased hemodynamic response in anterior cingulate and inferior frontal gyrus as measured with functional MRI. Moreover, those who demonstrated greater task difficulty also had greater BOLD activation across more distributed brain regions [6] suggesting inefficient neural processing. Several other studies have shown that pre-chemotherapy, individuals with cancer have aberrant patterns of brain activity [24,35,36,46], reduced white matter integrity [24], and reduced cognitive functioning [16,24,32]. However, one study found the typically observed increased hemodynamic pattern in several brain regions (inferior frontal gyrus, insula, thalamus, midbrain), but no evidence of cognitive changes on a visuospatial n-back test designed to target working memory (Scherling, Collins, MacKenzie, Bielajew and Smith, 2012) [35]. Some, but not all, of these cognitive and

functional imaging changes appear to be partially related to depression, anxiety, and fatigue in early stage breast cancer (Zunini, Scherling, Wallis, Collins, MacKenzie, Bielajew and Smith, 2013) [46]. Thus, the presence of cancer appears to have an indirect effect on brain function that is not explained by these factors.

Depression is commonly experienced by individuals with cancer [7], and as described above, could be related to brain function in people with cancer [46]. To our surprise, our BM and NBM groups did not report different levels of depression on the HADS. Though we were not able to statistically test for group differences with HC participants because they were administered the BDI-II, all three groups measured in the normal range, on average. Therefore, mood symptoms affecting cognitive performance in our sample is unlikely.

While at the group level our cancer patients did not demonstrate frankly impaired scores (normatively), there are clinical implications stemming from the high base rate of cumulative score impairment observed. An important consideration for patients, caregivers, and treatment teams is that functional capacity and medical decision making is vulnerable to the combined effects of cancer and age-related cognitive impairments [11,38]. In a recently published study, 60% of individuals with BM, and 54% of NBM participants showed reduced capacity to consent to research [28]. Along these lines, people with BM and NBM who demonstrate cognitive deficits are at a higher risk for not comprehending medical treatments [11]. Hence, the assessment of cognition in cancer participants is crucial, especially in advanced metastatic cancer. Understanding the cognitive sequelae associated with brain and non-brain metastatic cancer has substantial implications for the individual, their treatment team, and their caregiver network. Our findings can help inform expectations as well as focus remediation and compensatory strategies. Education should be provided with the individual's cognitive capabilities in mind and caregivers, when possible, should be present since the observed cognitive impairments may interfere with their understanding and recall of medical information. Additionally, the treating team should regularly inquire about caregiver burden since this increases in the context of cognitive decline [10], which is present in a large percentage of both brain and non-brain metastatic cancer groups.

The current research is limited by several factors. Participants were recruited from a single academic medical center, and our sample was relatively small, both of which may have reduce the generalizability, although our clinical samples are well characterized. In addition, our sample is comprised of heterogeneous solid based primary tumors in a cross-sectional design, which precludes causal inference. It is unclear if metastatic cognitive profiles differ as a function of primary cancer types, although the prior literature is clear that cancer, brain metastases, and treatment, are all pathways to cognitive decline. Assessing cognition in relation to different primary tumor types may be informative, as well as how sociodemographic factors relate to cognition in BM and NBM participants. While our clinical groups did not report elevated rates of depression, other factors not measured, such as fatigue, could have possibly influenced cognition, functional decline, and disability, and should be further investigated. A sizable proportion of the HC group had incomplete HVLT-R data, although this did not detract from our primary research aim. Furthermore, this did not occur in a systemic manner and no significant differences in scores were observed between the three groups.

Conclusion

In summary, the presence of metastatic cancer, both with and without direct involvement of the central nervous system, is associated with higher prevalence of cognitive dysfunction. This study contributes to the relatively small number of investigations looking at cognition in non-brain metastatic cancer. In individuals with metastatic brain cancer, all cognitive domains showed diminishment, and these individuals had higher rates of cognitive impairment with deficits in processing speed and executive functioning observed in over a quarter of individuals. While the non-brain metastatic cancer group had lower rates of impairment than the brain metastatic group, 25% still demonstrated cognitive impairment on three or more tests, which has important clinical implications on treatment planning, consenting for treatment and research, quality of life, and caregiver burden. Our findings can help inform the individual with metastasis, their treatment team, and their caregivers.

Funding

This work was supported by the American Cancer Society [MRSG-14-204-01 to KT]; the National Institutes of Health/National Center for Advanced Translational Sciences [KL2 TR000166 to KT]; the National Cancer Institute [5R25CA076023]; and the University of Alabama at Birmingham Department of Neurology.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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