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Mild cognitive impairment in long-term brain tumor survivors following brain irradiation

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Abstract

Introduction—There is no accepted classification of cognitive impairment in cancer survivors. We assess the extent of mild cognitive impairment (MCI) syndrome in brain tumor survivors using criteria adapted from the National Institute on Aging and the Alzheimer's Association (NIA-AA).

Methods—We retrospectively reviewed the cognitive data of brain tumor survivors post-radiation therapy (RT) enrolled from 2008 to 2011 in a randomized trial of donepezil versus placebo for cognitive impairment. One hundred and ninety eight adult survivors with primary or metastatic brain tumors who were 6 months post RT were recruited at 24 sites in the United States. Cognitive function was assessed at baseline, 12 and 24 weeks post-randomization. For this analysis, we used baseline data to identify MCI and possible dementia using adapted NIA-AA criteria. Cases were subtyped into four groups: amnesic MCI-single domain (aMCI-sd), amnesic MCI-multiple domain (aMCI-md), non-amnesic MCI-single domain (naMCI-sd), and non-amnesic MCI-multiple domain (naMCI-md).

Results—One hundred and thirty one of 197 evaluable patients (66%) met criteria for MCI. Of these, 13% were classified as aMCI-sd, 58% as aMCI-md, 19% as naMCI-sd, and 10% as naMCI-

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

md. Patients with poorer performance status, less education, lower household income and those not working outside the home were more likely to be classified as MCI.

Conclusion—Two-thirds of post-RT brain tumor survivors met NIA-AA criteria for MCI. This taxonomy may be useful when applied to brain tumor survivors because it defines cognitive phenotypes that may be differentially associated with course, treatment response, and risk factor profiles.

Keywords

Mild cognitive impairment; Brain tumor; Radiation; Classification; Decline

Introduction

One of the most vexing problems for cancer survivors and health care providers alike are the cognitive sequelae of cancer and cancer treatments. While many studies have described acquired cognitive deficits, few have identified cognitive phenotypes. Advances made in the study of Alzheimer's dementia (AD) may provide a useful model for how to better characterize cancer-related cognitive dysfunction. Approximately 20 years ago Petersen et al. introduced the concept of mild cognitive impairment (MCI) as a syndrome prodromal to AD and related dementias [1]. Extensive research followed into the phenomenology and course of MCI and identified four phenotypes: amnesic MCI-single domain (aMCI-sd), amnesic MCI-multiple domain (aMCI-md), non-amnesic MCI-single domain (naMCI-sd), and non-amnesic MCI-multiple domain (naMCI-md) [2]. Standardized diagnostic criteria for MCI [3, 4] and AD [5–7] have helped to stimulate, organize and focus research efforts. We suggest that a similar effort be undertaken with cancer-related cognitive dysfunction.

Approximately 76,000 people are diagnosed annually with a brain tumor (benign or malignant) and many of them receive brain radiation therapy (RT) at some point in their treatment course [8]. Fifty percent or more of patients who survive 6 months or longer after RT report cognitive problems [9]. The cognitive effects from brain tumors and their treatment range from mild to severe and may be related to differences in risk factors, tumor type, tumor location, or treatment parameters (e.g., extent of surgical resection, total radiation dose, dose per fraction, treatment volume and exposure to chemotherapy) [10–13]. Various chemical compounds have demonstrated limited success in reversing these cognitive impairments [14–18]. One possible reason success has been limited may be a failure in the field to classify cognitive dysfunction in brain tumor patients using a multidimensional classification schema. The lack of a standard taxonomy for cancer-related cognitive syndromes may be limiting efforts to identify distinct risk factor profiles, etiologies, courses and treatment responses among cognitively impaired cancer survivors.

The National Institute on Aging (NIA) together with the Alzheimer's Association (AA) have specified criteria for MCI and AD. MCI is defined by the presence of a personal concern regarding a change in cognition and a measured deficit in at least one major cognitive domain with relative preservation of basic and instrumental functional abilities [4]. Additional criteria have been proposed for MCI subtypes that distinguish amnesic from non-amnesic cognitive deficits and single cognitive domain deficits from multi-domain

deficits [2]. These criteria have become standard in research and clinical care and have undergone recent updates [19]. These criteria may represent a reasonable starting point for characterizing different cognitive phenotypes seen in cancer populations, and thus may be helpful in diagnosing and treating cancer-related cognitive impairment.

The purpose of this study was to estimate the prevalence of MCI and the distribution of MCI subtypes among irradiated brain tumor survivors using the NIA-AA criteria and to characterize these patients by social, demographic, and clinical characteristics. Given the significant neurotoxic effects of brain cancer and its treatments, we expected there would be a higher rate of MCI in this sample compared to breast cancer survivors similarly characterized in a prior study [20] and compared to non-cancer populations.

Methods

Sample

Participants were 198 brain tumor survivors enrolled in the Wake Forest Clinical Community Oncology Program (WFC-COP) study #91105, which was a randomized, placebo-controlled, double-blind clinical trial of adults with primary or metastatic brain tumors. They were recruited at 24 sites affiliated with the WFCCOP, a National Cancer Institute Cancer Trials Support Unit site, and at M.D. Anderson Cancer Center, and were accrued from February 2008 until December 2011. To be eligible, a participant must have completed 30 Gray (Gy) of fractionated partial or whole brain RT 6 months prior to assessment. Patients treated with radiosurgery were not eligible. Survivors who received 30 Gy of whole brain irradiation for prophylactic cranial irradiation (PCI) were eligible if they met all other criteria. Individuals with radiographic progression within the prior 3 months and those already taking cognition-enhancing medications such as memantine, donepezil, or methylphenidate were excluded. Patients currently receiving active oncologic treatment (with the exception of hormonal agents or trastuzumab) or undergoing cognitive rehabilitation were also excluded. Participants were randomized to receive donepezil (n = 99) or placebo (n = 99) for a period of 24 weeks. Only pre-treatment baseline data were used for this analysis. Of the 198 patients enrolled, one was excluded from this analysis due to missing cognition data. The protocol was approved by the National Cancer Institute and the Wake Forest University Health Sciences Institutional Review Board (IRB) and each local IRB for all participating sites. All patients signed informed consent.

Definition of mild cognitive impairment

The criteria used for classifying MCI were those developed by the NIA-AA [4]. A classification of MCI required (1) a reported concern regarding a change in cognition, (2) a deficit in at least one major cognitive domain not attributable to major delirium or major psychiatric disorder, (3) preservation of independence of basic and instrumental functional abilities and (4) the absence of dementia. Participants meeting criteria for MCI were subsequently categorized into one of four subtypes: amnesic MCI-single domain (aMCI-sd), amnesic MCI-multiple domain (aMCI-md), non-amnesic MCI-single domain (naMCI-sd), and non-amnesic MCI-multiple domain (naMCI-md) [2].

Criterion 1: cognitive concern

Subjective cognitive concerns were assessed with four items from the Additional Concerns subscale of the validated Functional Assessment of Cancer Therapy-Brain scale (FACT-Br) [21]. For each item (“I can remember new things,” “I am able to put my thoughts into action,” “I am able to concentrate,” and “I am able to find the right words to say what I mean”) respondents rated its frequency over the past 7 days using a five-point Likert scale ranging from 0 (indicating “not at all”) to 4 (indicating “very much”). For this analysis, if the answer to any single item was 0, 1 or 2 (corresponding to “not at all,” “a little bit,” and “somewhat”), the patient was considered to have a subjective cognitive concern.

Criterion 2: cognitive deficit

Participants were administered a standardized battery of cognitive tests, which included assessment of key cognitive domains using validated instruments [18]. To determine the presence of a deficit for this analysis, their raw scores from their baseline (pre-treatment) assessment were compared to age- and education-adjusted normative data. The six cognitive measures used in the current analysis included: Immediate and Delayed Recall from the Hopkins Verbal Learning Test-Revised (HVLIT-IR, HVLIT-DR) [22], Trail Making Test Parts A (TMT-A) and B (TMT-B) [23], Digit Span (DS) [24] and Controlled Oral Word Association (COWA) [25]. If any single test score was ≥ 1.5 standard deviation (SD) below the normative mean, the participant was considered to have a cognitive deficit. For classification of MCI subtype, we used three domains: executive function (COWA and TMT-B), memory (HVLIT-IR and HVLIT-DR), and attention (DS and TMT-A). For comparison, we applied two additional more stringent definitions of a cognitive deficit: one requiring a participant to score ≥ 1.5 SD below the appropriate norm on two or more tests, and the other requiring the participant to score ≥ 2.0 SD below the norm on any single test.

Criterion 3: preservation of functional status

Enrollment in WFCCOP #91105 required adequate functional status (ECOG Performance Status score of 0–2). Participants were asked to rate two items from the FACT-Br [21] and functional assessment of chronic illness therapy-fatigue (FACIT-fatigue) [26]: “I need help caring for myself” and “I need help doing my usual activities.”

Participants were considered functionally independent if they rated these items 0 (“not at all”) or 1 (“a little bit”) or 2 (“somewhat”).

Criterion 4: no dementia

Patients with a diagnosis of dementia were excluded from enrollment on WFCCOP #91105.

Definition of (possible) dementia

Participants were classified as having possible dementia if there was a deficit (≥ 1.5 SD below the normative value) in one or more cognitive domains that interfered significantly with the ability to function at work or perform usual activities.

Statistical analysis

Chi square or Fisher exact tests were used to assess differences in categorical variables amongst the three cognitive groups (no cognitive impairment, MCI, and dementia) and to assess differences in categorical variables amongst the four subtypes (aMCI-sd, aMCI-md, naMCI-sd, and naMCI-md). Kruskal–Wallis tests were used to assess differences in continuous variables.

Results

Participant characteristics

Participant characteristics are summarized in Table 1. The participants were 91% white, 53% female, and the median age was 55 years. Sixty-five percent had primary tumors and 27% had brain metastases. The median time from diagnosis to study enrollment was 38 months. Ninety-five percent had ECOG performance status scores of 0 or 1.

Cognitive performance

Measures of executive function (COWA and TMT-B) were impaired in 35% and 61% of participants respectively (Table 2). Both measures of verbal memory (HVLIT-DR and HVLIT-IR) were impaired in 52% of participants. Measures of concentration (DS) and attention (TMT-A) were impaired in 7% and 41% of participants.

Prevalence of MCI

Of the participants, 131 (66%) met NIA-AA criteria for MCI, and 20 (10%) met criteria for possible dementia. Forty-six (23%) did not meet our criteria for cognitive impairment (Table 3). Using the more stringent definitions for a cognitive deficit (≥ 2.0 SD on one or more tests or ≥ 1.5 SD on two or more tests) slightly lowered the number of participants classified as MCI to 116 (59%) and 103 (52%). Of the participants meeting criteria for MCI, 17 (13%) were sub-classified as aMCI-sd, 76 (58%) as aMCI-md, 25 (19%) as naMCI-sd, and 13 (10%) as naMCI-md.

Participant characteristics by cognitive status

Cognitive classification, based on the criteria described above, is summarized in Table 4 by demographic and clinical characteristics. Classification differed by ECOG performance status ($p < 0.001$), education ($p = 0.009$), income ($p = 0.017$), and ability to work outside their home ($p = 0.001$). Those patients with worse performance status, less education, and lower incomes, and who did not work outside their home were more likely to be classified as MCI or possible dementia. There were no significant differences in classification by age, time from diagnosis, BMI, sex, marital status, tumor type (primary or metastatic), or RT treatment (WBI vs. PBI). MCI subtype by demographic and clinical characteristics are summarized in Table 5. Subtype distribution differed by BMI ($p = 0.031$), performance status ($p = 0.032$), sex ($p = 0.003$), and education ($p = 0.003$). Obese patients were more likely to be naMCI SD and less likely to be aMCI SD compared to those who were not obese. Patients with worse performance status and less education were more likely to have deficits in multiple cognitive domains. Women were less likely to have multiple deficits than

men. Subtype classification was not associated with age, time since diagnosis, race/ethnicity, marital status, income, work status, tumor type (primary, metastatic) or RT treatment (WBI vs. PBI).

Discussion

Two-thirds (66%) of our sample of long-term, primary and metastatic brain tumor survivors who had undergone a course of 30 Gy of whole brain or partial brain irradiation met NIA-AA criteria for MCI. When more stringent criteria were applied, the overall proportion of survivors with MCI changed only slightly—suggesting that this classification system is robust to changes in the definition of a cognitive deficit. An additional 10% of survivors met NIA-AA criteria for possible dementia, and 23% were classified as having no significant cognitive deficits. The high proportion of patients with cognitive impairment in this group is not surprising, given the neurotoxic effects of brain cancer and associated treatments including brain radiation. At the same time, the fact that one in five of our participants showed no apparent cognitive impairment indicates that some patients either maintain or recover full cognitive functioning following brain cancer diagnosis and therapy or have sufficient cognitive reserve that they still test within the normal range.

Of those participants meeting criteria for MCI, the most common subtype was amnesic MCI-multiple domain (58%). In a study of 60 breast cancer survivors (39–79 years of age) who were 1–5 years post 4 cycles of cytotoxic adjuvant chemotherapy for treatment of invasive disease, 58% were adjudicated MCI by expert clinicians using NIA-AA criteria [27]. Of them 26% were amnesic multi-domain while 49% were non-amnesic-single domain [20]. The greater overall prevalence of cognitive impairment and multi-domain impairment among brain tumor survivors compared to breast cancer survivors seems expected given the direct brain involvement in this population. Prevalence estimates for MCI among community samples of middle aged and older adults are between 16 and 22% [28–31], which is well below the 66% prevalence among brain tumor survivors indicating a substantial additional risk of cognitive impairment attributable to brain cancer and treatment.

As the number of long-term survivors of brain tumors increases, cognitive dysfunction is becoming more prevalent, raising the importance of developing efficacious treatments. Prior clinical trials aimed at improving cognition in cancer survivors have not tested specific cognitive phenotypes. For example, Brown et al. randomized 508 adult patients being treated with whole brain RT for brain metastases to memantine or placebo [15]. Memantine, a *N*-methyl-D-aspartate receptor antagonist used to improve memory in patients with AD, showed a non-significant protective effect on memory compared to placebo, raising the question whether treating only amnesic MCI patients might have produced stronger treatment effects. In WFCCOP #91105 (the parent study for this secondary analysis), participants were randomized to receive a daily dosage of donepezil (an acetylcholine esterase inhibitor used to treat mild to moderate symptoms of AD), or placebo for 24 weeks. There was not a significant beneficial effect of donepezil as measured by a cognitive composite score. However, among participants with poorer overall pre-treatment cognitive function, there were improvements in memory, motor speed, and dexterity [18]; indicating specific cognitive phenotypes (e.g., amnesic subtype) may have benefited more from this

treatment. In an ongoing randomized, placebo-controlled clinical trial of donepezil versus placebo (National Cancer Institute Community Oncology Research Program study #97116) for breast cancer survivors who have had prior chemotherapy, patients are only eligible if they have amnesic cognitive deficits (i.e., a memory deficit and reported memory difficulties). Identifying specific cognitive phenotypes and tailoring interventions to them may help to identify more effective treatments.

The validity of applying the NIA-AA MCI criteria to oncology patient populations requires further research. In the general population of older adults, MCI progresses to dementia in half or more of patients—at a rate of approximately 10–15% per year [32]. Use of standardized criteria for MCI and dementia has allowed clinicians and researchers to identify prognostic factors in the general population associated with progression of MCI to AD [3]. For example, the amnesic form of MCI confers a higher risk of progression to AD than the other MCI subtypes, and individuals with a family history of dementia have a higher risk of transitioning from MCI to dementia. Similarly, apolipoprotein $\epsilon 4$ genotype carriers are at higher risk for progression of MCI to AD [4]. Ahles et al. reported that among long-term breast cancer and lymphoma survivors, those who were $\epsilon 4$ carriers had poorer cognitive function compared to non-carriers, suggesting this genotype may be a potent risk factor for cancer-related cognitive impairment [33]. Advanced imaging techniques and biomarkers found in cerebrospinal fluid are being used to predict risk of AD and might be predictive of cancer related cognitive dysfunction. At present, the rate of progression from MCI to dementia in irradiated brain tumor survivors is not known. Prospective studies are needed to identify risk and protective factors of cognitive dysfunction. Identifying cognitive phenotypes could facilitate such research and could help identify which patients are likely to have substantial cognitive decline after treatment or are likely to benefit from prevention and treatment interventions.

Our analysis has several limitations. First, it is a secondary analysis at single time point and provides only a cross-sectional perspective. Study participants were classified using an algorithm rather than by expert adjudication which can inflate estimates somewhat [34]. Secondly, survivors with greater cognitive concerns may have been more likely to enroll in a treatment study, so the proportion of patients classified as MCI may be inflated compared to the general population of brain tumor survivors. Notably, however, our more stringent MCI criteria reduced the proportion of patients meeting MCI criteria only slightly. Along similar lines, by allowing participants to have some functional impairment and still be classified MCI, we may have underestimated the number of patients with possible dementia.

Generalization of our data is limited by the sociodemographic characteristics of our sample. Additionally, determining a decline in cognitive function specifically attributable to brain RT requires pre-treatment assessment of cognitive function, which we did not have since the clinical trial design of WFCCOP #91105 required patients to be at least 6 months post-RT. Similarly, WFCCOP #91105 did not collect tumor histology, date of last RT treatment, or complete dosimetric data which precluded us from incorporating these variables in to our analysis. We have previously published a detailed analysis in a subset of these patients where full dosimetric data was available looking at the relationship between RT dose to multiple anatomic substructures in the brain (for example the hippocampus) and cognition

[11, 35] but could not perform this analysis on the full cohort of patients used for this analysis. Lastly, although we excluded patients with recent radiographic progression, we cannot exclude the possibility that some patients may have had subclinical progressive disease that was undetectable on MRI but could have impacted their cognitive performance.

In conclusion, a substantial number of irradiated brain tumor patients meet the NIA-AA criteria for Mild Cognitive Impairment syndrome. The potential advantage of applying a phenotypic taxonomy is that doing so may help to identify important risk and protective factors, clinical characteristics, and responses to treatment among survivors. This in turn could lead to more specific matching of patient to treatment and ultimately improve quality of life for the growing number of survivors experiencing neurocognitive dysfunction.

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Table 1

Participant characteristics

Characteristic	# (%)
N	197 (100)
Age	
Median, years (range)	55 (19–84)
Age 50	118 (60)
Months since diagnosis	
Median, mos. (range)	37.9 (7.3–423.2)
36 months	106 (54)
BMI	
Median (range)	27.4 (17.3–49.4)
Underweight-normal (< 25)	64 (32)
Overweight (25–30)	67 (34)
Obese (30+)	66 (34)
ECOG performance status	
0	94 (48)
1	93 (47)
2	10 (5)
Sex	
Female	105 (53)
Male	92 (47)
Race	
Hispanic	1 (1)
Asian	1 (1)
Black	16 (8)
White	179 (91)
Marital status ^a	
Single	22 (11)
Married/married-like	138 (70)
Sep/divorced/widowed	36 (18)
Education ^a	
HS	61 (31)
Vocational/some college	79 (41)
College graduate	54 (28)
Income ^a (K)	
< 20	64 (39)
20–50	58 (35)
50+	44 (27)
Work outside home ^a	59 (30)
Diagnosis	

Characteristic	# (%)
Primary brain tumor	129 (65)
Brain metastasis	53 (27)
PCI	15 (8)
Radiotherapy type	
Whole brain	80 (41)
Partial brain	117 (59)

Median time from diagnosis refers to the time between brain tumor diagnosis and study enrollment

^aSome missing data

Table 2

Cognitive performance (N = 197)

Test	Frequency (%) with cognitive deficit ^a
Controlled Oral Word Association (executive function)	68 (35)
Trail Making Test part B (executive function)	121 (61)
Hopkins Verbal Learning Test revised—delayed recall (verbal memory)	102 (52)
Hopkins Verbal Learning Test revised—immediate recall (verbal memory)	102 (52)
Digit span (attention)	13 (7)
Trail making test part A (attention)	81 (41)

^a 1.5 SD poorer than normative comparison group

Table 3

Frequency (%) of participants classified with possible dementia and MCI by cognitive deficit criterion

	1.5 SD on one or more test	2.0 SD on one or more test	1.5 SD on two or more tests
No impairment	46 (23%)	62 (31%)	75 (38%)
MCI	131 (66%)	116 (59%)	103 (52%)
A, SD	17 (13%)	19 (16%)	10 (10%)
A, MD	76 (58%)	55 (47%)	76 (74%)
NA, SD	25 (19%)	28 (24%)	4 (4%)
NA, MD	13 (10%)	14 (12%)	13 (13%)
Possible dementia	20 (10%)	19 (10%)	19 (10%)

Subtype percentages are conditional on having MCI

A Amnesic, *NA* non-amnesic, *MD* multiple domains, *SD* single domain

Table 4

Cognitive status by demographic and clinical variables

Characteristic	N	No impairment [# (%)]	MCI [# (%)]	Possible dementia [# (%)]	p-value
Overall	197	46 (23)	131 (66)	20 (10)	
Age					
Age > 50	79	23 (29)	51 (65)	5 (6)	0.146
Age ≤ 50	118	23 (19)	80 (68)	15 (13)	
Months since diagnosis					
< 36 months	91	20 (22)	60 (66)	11 (12)	0.681
≥ 36 months	106	26 (25)	71 (67)	9 (8)	
BMI					
Underweight-normal (< 25)	64	16 (25)	44 (69)	4 (6)	0.303
Overweight (25–30)	67	18 (27)	39 (58)	10 (15)	
Obese (30+)	66	12 (18)	48 (73)	6 (9)	
ECOG performance status					
0	94	29 (31)	59 (63)	6 (6)	< 0.001
1	93	17 (18)	68 (73)	8 (9)	
2	10	0 (0)	4 (40)	6 (60)	
Sex					
Female	105	24 (23)	69 (66)	12 (11)	0.817
Male	92	22 (24)	62 (67)	8 (9)	
Race					
Hispanic	1	0 (0)	1 (100)	0 (0)	0.050
Asian	1	1 (100)	0 (0)	0 (0)	
Black	16	0 (0)	14 (88)	2 (13)	
White	179	45 (25)	116 (65)	18 (10)	
Marital status ^a					
Single	22	3 (14)	17 (77)	2 (9)	0.819
Married/married-like	138	35 (25)	89 (64)	14 (10)	
Sep/divorced/widowed	36	8 (22)	24 (67)	4 (11)	
Education ^a					

Characteristic	N	No impairment [# (%)]	MCI [# (%)]	Possible dementia [# (%)]	p-value
HS	61	8 (13)	48 (79)	5 (8)	0.009
Vocational/some college	79	18 (23)	48 (61)	13 (16)	
College graduate	54	19 (35)	33 (61)	2 (4)	
Income ^a (K)					
< 20	64	11 (17)	44 (69)	9 (14)	0.017
20–50	58	10 (17)	41 (71)	7 (12)	
50+	44	19 (43)	21 (48)	4 (9)	
Work outside home ^a					
No	137	22 (16)	98 (72)	17 (12)	0.001
Yes	59	24 (41)	32 (54)	3 (5)	
Diagnosis					
Primary brain tumor	129	36 (28)	82 (64)	11 (9)	0.142
Brain metastasis	53	7 (13)	40 (75)	6 (11)	
PCI	15	3 (20)	9 (60)	3 (20)	
RT					
Whole brain	80	12 (15)	59 (74)	9 (11)	0.073
Partial brain	117	34 (29)	72 (62)	11 (9)	

^aSome missing data

Table 5

MCI Subtype by demographic and clinical variables

Characteristic	N	Amnestic single domain [# (%)]	Amnestic multiple domain [# (%)]	Non-amnestic single domain [# (%)]	Non-amnestic multiple domain [# (%)]	p-value
Overall	131	17 (13)	76 (58)	25 (19)	13 (10)	
Age						
< 50	51	7 (14)	26 (51)	11 (22)	7 (14)	0.525
50	80	10 (13)	50 (63)	14 (18)	6 (8)	
Months since diagnosis						
< 36	60	9 (15)	32 (53)	10 (17)	9 (15)	0.264
36	71	8 (11)	44 (62)	15 (21)	4 (6)	
BMI						
< 25	44	8 (18)	25 (57)	6 (14)	5 (11)	0.031
25–30	39	7 (18)	25 (64)	3 (8)	4 (10)	
30	48	2 (4)	26 (54)	16 (33)	4 (8)	
ECOG performance status						
0	59	11 (19)	25 (42)	17 (29)	6 (10)	0.032
1	68	6 (9)	47 (69)	8 (12)	7 (10)	
2	4	0 (0)	4 (100)	0 (0)	0 (0)	
Sex						
Female	69	5 (7)	35 (51)	20 (29)	9 (13)	0.003
Male	62	12 (19)	41 (66)	5 (8)	4 (6)	
Race						
Hispanic	1	0 (0)	1 (100)	0 (0)	0 (0)	0.666
Black	14	0 (0)	9 (64)	3 (21)	2 (14)	
White	116	17 (15)	66 (57)	22 (19)	11 (9)	
Marital status ^a						
Single	17	5 (29)	8 (47)	1 (6)	3 (18)	0.227
Married/married-like	89	9 (10)	53 (60)	18 (20)	9 (10)	
Sep/divorced/widowed	24	3 (13)	14 (58)	6 (25)	1 (4)	
Education ^a						
HS	48	5 (10)	38 (79)	4 (8)	1 (2)	0.003
Vocational/some college	48	5 (10)	22 (46)	13 (27)	8 (17)	
College graduate	33	7 (21)	14 (42)	8 (24)	4 (12)	
Income ^a (K)						
< 20	44	7 (16)	25 (57)	8 (18)	4 (9)	0.294
20–50	41	3 (7)	27 (66)	9 (22)	2 (5)	
50+	21	6 (29)	8 (38)	5 (24)	2 (10)	
Work outside home ^a						
No	98	12 (12)	58 (59)	18 (18)	10 (10)	0.880
Yes	32	5 (16)	17 (53)	7 (22)	3 (9)	

Characteristic	N	Amnesic single domain [# (%)]	Amnesic multiple domain [# (%)]	Non-amnesic single domain [# (%)]	Non-amnesic multiple domain [# (%)]	p-value
Diagnosis						
Primary brain tumor	82	13 (16)	45 (55)	16 (20)	8 (10)	0.670
Brain metastasis	40	3 (8)	26 (65)	6 (15)	5 (13)	
PCI	9	1 (11)	5 (56)	3 (33)	0 (0)	
RT						
Whole brain	59	4 (7)	39 (66)	10 (17)	6 (10)	0.199
Partial brain	72	13 (18)	37 (51)	15 (21)	7 (10)	

^aSome missing data