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Scientific Article

Association of Pretreatment Hippocampal Volume With Neurocognitive Function in Patients Treated With Hippocampal Avoidance Whole Brain Radiation Therapy for Brain Metastases: Secondary Analysis of NRG Oncology/RTOG 0933

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Abstract

Purpose: Hippocampal volume (HV) is an established predicting factor for neurocognitive function (NCF) in neurodegenerative disease. Whether the same phenomenon exists with hippocampal-avoidant whole brain radiation therapy is not known; therefore, we assessed the association of baseline HV with NCF among patients enrolled on RTOG 0933.

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Methods and Materials: Hippocampal volume and total brain volume were calculated from the radiation therapy plan. Hippocampal volume was correlated with baseline and 4-month NCF scores (Hopkins Verbal Learning Test–Revised [HVLT-R] Total Recall [TR], Immediate Recognition, and Delayed Recall [DR]) using Pearson correlation. Deterioration in NCF was defined per the primary endpoint of RTOG 0933(mean 4-month relative decline in HVLT-R DR). Comparisons between patients with deteriorated and nondeteriorated NCF were made using the Wilcoxon test.

Results: Forty-two patients were evaluable. The median age was 56.5 years (range, 28-83 years), and 81% had a class II recursive partitioning analysis. The median total, right, and left HVs were 5.4 cm^3 (range, 1.9-7.4 cm^3), 2.8 cm^3 (range, 0.9-4.0 cm^3), and 2.7 cm^3 (range, 1.0-3.7 cm^3), respectively. The median total brain volume was 1343 cm^3 (range, 1120.5-1738.8 cm^3). For all measures of corrected HV, increasing HV was associated with higher baseline HVLT-R TR and DR scores (ρ: range, 0.35-0.40; *P*-value range, .009-.024) and 4-month TR and DR scores (ρ: range, 0.29-0.40; *P*-value range, .009-.04), with the exception of right HV and 4-month DR scores (ρ: 0.29; $P = .059$). There was no significant association between HV and NCF change between baseline and 4 months. Fourteen patients (33.3%) developed NCF deterioration per the primary endpoint of RTOG 0933. There was no significant difference in HV between patients with deteriorated and nondeteriorated NCF, although in all instances, patients with deteriorated NCF had numerically lower HV.

Conclusions: Larger HV was positively associated with improved performance on baseline and 4-month HVLT-R TR and DR scores in patients with brain metastases undergoing hippocampal-avoidant whole brain radiation therapy but was not associated with a change in NCF.

Introduction

Metastatic disease is the most common central nervous system malignancy.[1] Radiation therapy remains the cornerstone for a majority of these patients. Although the use of stereotactic radiation surgery is increasing,[2] there remains a cohort of patients in which radiation surgery is not feasible or appropriate. In this cohort, whole brain radiation therapy (WBRT) remains the preferred treatment option. However, all forms of brain radiation therapy, including WBRT, have well-known deleterious effects on neurocognitive function (NCF).[3,4] As overall survival in metastatic disease continues to improve, there has been considerable interest in reducing iatrogenic neurocognitive toxic effects associated with this form of therapy.

The subgranular zone of the hippocampus houses a major stem-cell niche, and continuous neuroregeneration from this radiosensitive structure has been theorized to be responsible for the formation of cells that participate in the formation and imprinting of new memory.[5] To mitigate the negative effects of WBRT, NCTN GROUP conducted a single-arm phase 2 trial, RTOG 0933, to determine the feasibility and safety of hippocampal-avoidant WBRT (HA-WBRT) and its effect on NCF. Hypothesis-generating preliminary data from this study noted that HA-WBRT reduces the risk of neurocognitive decline at 4 months relative to historical controls treated with standard WBRT.[6] Given these positive results, a randomized trial of WBRT versus HA-WBRT (NRG CC001) has been completed, and positive results have been presented in abstract form.[7]

Although HA-WBRT was noted to reduce the risk of neurocognitive decline, patient-specific variables were also found to be correlated with NCF, such as age and the presence of pre-existing neurologic symptoms.[6] However, the role of patient-specific variables and their effect on NCF has not been well investigated in patients receiving HA-WBRT.

A robust body of data exploring patient-specific imaging biomarkers of neurocognitive decline extracted from magnetic resonance imaging (MRI) exists in neurodegenerative diseases such as Alzheimer's. Hippocampal volume (HV) has emerged as a strong predictor, with smaller HV closely associated with decreased NCF.[8,9] However, HV has not been well explored as an imaging biomarker in patients with brain metastases, a population with multiple competing reasons for NCF decline including the metastases themselves.

We hypothesized that HV may be predictive of NCF in patients undergoing HA-WBRT for brain metastases. To explore this, we performed a secondary analysis of patients enrolled on RTOG 0933, extracting HV from protocol-compliant contours.

Methods

Study design and patients

The methods for RTOG 0933 are described in the published primary analysis.[6] In brief, RTOG 0933 was a single-arm, phase 2 study examining NCF in patients undergoing HA-WBRT compared with historical controls treated with standard WBRT. Eligibility criteria for enrollment were a brain metastasis outside a 5-mm margin around the hippocampus, a pathologically proven diagnosis of nonhematopoetic malignancy other than small cell carcinoma, and recursive partitioning analysis class I or II. Patients younger than 18 years of age and those with leptomeningeal metastases, prior brain-directed radiation therapy, or an inability to undergo MRI were excluded.

Segmentation and radiation therapy planning

All patients underwent 3-dimensional spoiled gradient echo, magnetization prepared rapid gradient echo, or turbo field axial MRI of the brain with axial slice thickness of ≤1.5 mm, which was then fused to computed tomography simulation brain imaging with axial slice thickness ≤2.5 mm. Hippocampal volumes were manually delineated on the fused image set and expanded by 5 mm to generate the hippocampal avoidance regions. The clinical target volume was defined as the whole-brain parenchyma, and the planning target volume was defined as the clinical target volume minus the hippocampal avoidance regions. Intensity modulated radiation therapy was delivered to a dose of 30 Gy in 10 fractions to cover the planning target volume while avoiding the hippocampus. All treating physicians were required to complete dry-run quality assurance testing in image fusion, contouring, and treatment planning for a 5-patient test group before trial participation. Additionally, before individual patient enrollment, central rapid review of HV contours and HA-WBRT planning was conducted in real time before treatment initiation. After completion of 3 protocol-compliant cases, investigators were permitted to enroll subsequent patients without prior central review.

Cognitive assessment

All patients underwent neurocognitive assessment using the Hopkins Verbal Learning Test–Revised (HVLT-R). The HVLT-R has been used as a validated standard for neurocognitive assessment in prior phase 3 cooperative group brain metastasis trials. The HVLT-R consists of a list of 12 nouns with 4 words drawn from 3 semantic categories. To mitigate the effect of repeated administration, a total of 6 different forms were used. Testing consists of memorization of 12 nouns for 3 trials (total recall [HVLT-R TR]), recognition of 12 nouns from a list of related or unrelated items (immediate recall [HVLT-R IR]), and recalling 12 nouns after a 20-minute delay (delayed recall [HVLT-R DR]). Raw scores are derived for these 3 separate domains and then were standardized against normative data to correct for age effects.[10] Patients underwent testing at baseline as well as at 2-, 4-, and 6-month follow-up intervals from the start of HA-WBRT and then quarterly until death.

At the completion of RTOG 0933, a total of 113 patients were accrued, of whom 100 were included in the initial analysis. For the purpose of this study, a total of 42 patients were evaluable for the primary endpoint of HVLT-R DR decline at 4 months after exclusions secondary to death, failure to follow up, or inability to obtain imaging. Pretreatment and 4-month NCF scores were obtained. Change scores between baseline and the 4-month time point were calculated by subtracting the follow-up score from the baseline score, such that a positive change score indicated a decline in function. Patients were categorized as deteriorated if they were determined to have a significant decline in NCF at 4 months using a version of the reliable change index[11,12] as described in the primary publication of RTOG 0933.

Hippocampal volumes

Centrally submitted radiation therapy plans were obtained for all 42 evaluable patients. Left, right, and total hippocampal volumes were obtained and reported in cubic centimeters. Total brain volume (TBV), inclusive of the hippocampus, was also obtained from radiation therapy plans and reported in cubic centimeters. Using an established method[13] to correct for differences in age and sex in hippocampal volumes, a ratio of the hippocampal volume to the total brain volume (corrected hippocampal volume [C-HV] ratio = HV/TBV) was calculated.

Statistical analysis

The C-HV was correlated with baseline and 4-month NCF scores as well as NCF change scores using Pearson correlation coefficients because the data for all patients were approximately normally distributed. The C-HV was also compared between patients with deteriorated and nondeteriorated NCF, as determined by the relative change index, at 4 months, conducted separately for each NCF score (ie, determination of deterioration status for each NCF score and comparison of the C-HV between deteriorated and nondeteriorated NCF) using the Wilcoxon test owing to the small sample size within each deterioration group.

Results

Baseline patient characteristics are presented in Table 1. The median age was 56.5, with 81% of patients having recursive partitioning analysis class II disease. Hippocampal volume data were available for all 42 patients from RTOG 0933. The median baseline total, right, and left HV values were 5.4 cm^3 (range, 1.9-7.4 cm^3), 2.8 cm^3 (range, 0.9-4.0 cm^3), and 2.7 cm^3 (range, 1.0-3.7 cm^3), respectively, and the median baseline total, right and left C-HV values were 0.0041 cm^3 (range, 0.0016-0.0052 cm^3), 0.0021 cm^3 (range, 0.0008-0.0027 cm^3), and 0.0019 cm^3 (range, 0.0008-0.0019 cm^3), respectively (Table 1). The median TBV was 1343 cm^3 (range, 1120.5-1738.8 cm^3). There was no statistically significant difference in total, right, or left C-HV between deteriorated and nondeteriorated patients (Fig. 1). However, in all instances, patients with deteriorated NCF had a numerically smaller baseline

Table 1 Pretreatment characteristics

Characteristic	Patients, No. (%) (N = 42)*
Age, y	
Median	56.5
Range	28-81
Q1-Q3	52-63
<60	27 (64.3)
≥60	15 (35.7)
Sex	
Male	17 (40.5)
Female	25 (59.5)
Race	
American Indian or Alaskan Native	2 (4.8)
Asian	3 (7.1)
Black or African American	4 (9.5)
White	30 (71.4)
More than 1 race	1 (2.4)
Unknown	2 (4.8)
Ethnicity	
Hispanic or Latino	2 (4.8)
Not Hispanic or Latino	38 (90.5)
Unknown	2 (4.8)
Karnofsky Performance Status score	
70	6 (14.3)
80	4 (9.5)
90	19 (45.2)
100	13 (31.0)
RPA class	
I	8 (19.0)
II	34 (81.0)
Neurologic function status	
No symptoms	29 (69.0)
Symptoms	13 (31.0)
Total HV, cm^3	
Mean	5.4
SD	1.2
Median	5.5
Range	1.9-7.4
Q1-Q3	4.8-6.1
Right HV, cm^3	
Mean	2.7
SD	0.6
Median	2.8
Range	0.9-4.0
Q1-Q3	2.4-3.1
Left HV, cm^3	
Mean	2.6
SD	0.6
Median	2.7
Range	1.0-3.7
Q1-Q3	2.3-3.0
Total intracranial volume, cm^3	
Mean	1373.4
SD	157.5
Median	1343.0
Range	1120.5-1738.8
Q1-Q3	1273.4-1476.8
Total C-HV, cm^3	
Mean	0.0039
SD	0.0008
Median	0.0041
Range	0.0016-0.0052
Q1-Q3	0.0036-0.0045
Right C-HV, cm^3	
Mean	0.0020
SD	0.0004
Median	0.0021
Range	0.0008-0.0027
Q1-Q3	0.0018-0.0023
Left C-HV, cm^3	
Mean	0.0019
SD	0.0004
Median	0.0019
Range	0.0008-0.0025
Q1-Q3	0.0017-0.0023

Abbreviations: C-HV = corrected hippocampal volume; Q1 = first quartile; Q3 = third quartile; RPA = recursive partitioning analysis; SD = standard deviation.

* Data are presented as the number and percentage of patients unless otherwise indicated.

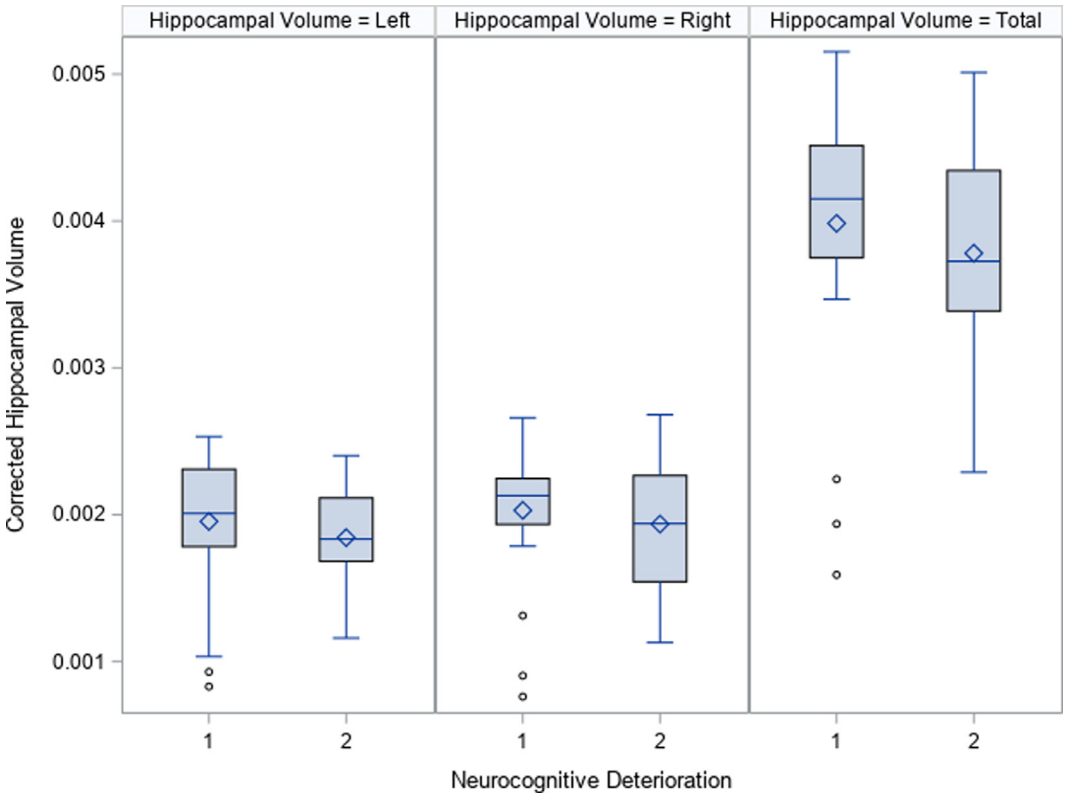

Figure 1 Box plot of corrected hippocampal volume by neurocognitive deterioration. There were no significant differences between deterioration status for left, right, and total hippocampal volume.

total HV. The total, right, and left C-HVs were significantly correlated with HVLT-R recall and delayed recall but not with recognition at baseline (Table 2). The total, right, and left C-HVs correlated with HVLT-R recall and delayed recall but not with recognition at 4 months (Table 3). There was no significant correlation between C-HVs and change scores from baseline to 4 months for any measure of HVLT.

Table 2 Correlations of C-HV with HVLT-R scores at baseline among 42 participants

C-HV		HVLT-R score		
		Recall	Delayed recall	Recognition
Total	ρ	0.38	0.37	0.045
	P value*	.013	.0090	.78
Right	ρ	0.34	0.35	−0.0046
	P value*	.029	.014	.98
Left	P	0.39	0.35	0.092
	P value*	.012	.024	.56

Abbreviations: C-HV = corrected hippocampal volume; HVLT-R = Hopkins Verbal Learning Test–Revised.
* *P* value from Pearson correlation coefficient.

Discussion

Neurocognitive toxic effects associated with WBRT are a well-recognized issue.[14] With improvements in systemic therapies leading to increased overall survival, prophylactic mitigation of the deleterious effects of WBRT remain of great interest. Memantine[3] and HA-WBRT[6] have both demonstrated protective effects for NCF relative to standard WBRT. Although these interventions are feasible, important considerations must be given to survival, cost, time, and the pathogenesis and incidence of neurocognitive toxic effects. An improved ability to predict neurocognitive toxic effects would allow clinicians to more appropriately select radiotherapeutic options. Patient-specific variables have predictive value for NCF in patients with neurodegenerative disease. One such marker is HV. In this secondary analysis of RTOG 0933, we found that all measures of HV correlated with HVLT-R recall and delayed recall at baseline and 4 months. This result was consistent with those of prior studies in neurodegenerative disease. Multiple studies have noted a strong correlation between hippocampal volume[15–17] and Alzheimer disease. More recently, Petersen et al[18] and others have reported a correlation with HV not just for Alzheimer disease but across a spectrum of cognitive dysfunction, from normal aging to mild cognitive impairment.

Table 3 Correlations with C-HV and HVLT-R standardized score and raw change score at 4 months among 42 patients

C-HV		Recall		Delayed recall		Recognition	
		Score	Change score	Score	Change score	Score	Change score
Total	ρ	0.39	−0.08	0.31	−0.05	−0.0086	0.06
	P value*	.01	.61	.045	.74	.96	.71
Right	ρ	0.37	−0.11	0.28	−0.03	−0.045	0.03
	P value*	.015	.50	.071	.85	.78	.83
Left	ρ	0.37	−0.05	0.31	−0.07	0.029	0.08
	P value*	.015	.76	.043	.66	.85	.62

Abbreviations: C-HV = corrected hippocampal volume; HVLT-R = Hopkins Verbal Learning Test–Revised.
* *P* value from Pearson correlation coefficient.

Hippocampal volume did not significantly correlate with change scores in any measure of HVLT. This is likely secondary to the fact that all patients received HA-WBRT, and therefore, the lack of correlation may be seen as additional evidence supporting the role of HA-WBRT in sparing NCF decline. There were also a limited number of patients; more patients may be needed to detect any correlation between baseline HV and decline in NCF.

The HVLT-R scores at baseline and 4 months and the change score were not correlated with HV. The lack of correlation between recognition testing and HV is not surprising. The prefrontal, parietal, and medial temporal cortices have been shown to be responsible for recognition memory.[19] Functional magnetic resonance and lesion studies have demonstrated that changes in these neuroanatomic regions result in significant change in recognition testing.[20] Although the hippocampus has been demonstrated to be responsible for portions of recognition, it is evident that hippocampal volume alone is unlikely to result in significant change in recognition testing.

Despite these hypothesis-generating results, this study has a number of limitations. First, in the primary analysis, 113 patients were enrolled, but only 42 were analyzable secondary to exclusions for ineligibility, death, and noncompliance with follow-up at 4 months. As a result, the total number of patients was limited and may not be representative of a larger cohort. Second, the ability to control for additional confounding variables is narrow, partly owing to the limited number of patients. Tumor- and treatment-related factors such as white matter change (unpublished data), as well as other neuropsychiatric diseases,[21] are known to affect cognition independently of HV. Additionally, HV and its correlation with NCF in this study were limited to a single time interval. Analysis including pretreatment brain MRI, such as that for newly diagnosed stage III non small cell lung cancer, or follow-up brain MRI would be more robust. Lastly, the ability to assess the effect of hippocampal volume on neurocognitive function was incomplete. Although the HVLT is a validated assessment and has been used in multiple studies in the treatment of brain metastasis, our ability to discern effects on other measures of neurocognition was limited. However, despite these limitations, the available data represent a product of a robust quality assurance protocol. Investigators were required to complete preenrollment hippocampal contouring training, and each case was centrally reviewed in a prospective fashion. Additionally, neurocognitive testing was performed by centrally certified research assistants. NRG CC003, a phase II/III trial of prophylactic cranial irradiation with or without HA for small cell lung cancer, has addressed a number of these limitations with increased patient enrollment and a more robust battery of neurocognitive assessments such as controlled oral word association and the trail making test.

Conclusion

Hippocampal volume is predictive of neurocognitive function in patients with brain metastasis undergoing hippocampal-avoidant whole brain radiation therapy at baseline and 4 months. Given this, hippocampal volume may potentially serve as a metric to better characterize NCF to tailor therapy; however, continued investigation is needed. NRG CC001 and CC003 are currently under way and have the potential to answer these clinically relevant questions.

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