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Hippocampal volume and NCF after HA-WBRT

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Hippocampal volume and NCF after HA-WBRT

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Summary

XXXX reported that hippocampal avoidant WBRT reduced neurocognitive decline compared to historical controls. However, clinical determinants of cognitive decline are not well described. Larger hippocampal volume is positively associated with improved performance on cognitive testing at baseline and 4 months. Additional confirmatory studies are warranted.

Hippocampal volume and NCF after HA-WBRT

Abstract

Background: Hippocampal volume (HV) is an established predictor of NCF in neurodegenerative disease; whether the same phenomenon exists with hippocampal-avoidant whole brain radiotherapy (HA-WBRT) is not known, and therefore, we assessed the association of baseline HV with NCF of patients enrolled on XXXX.

Methods: HV and total brain volume (TBV) were calculated from the radiotherapy plan. HV was correlated with baseline and 4 month NCF scores (Hopkins Verbal Learning Test-Revised (HVLT-R) Total Recall (TR), Immediate Recognition (IR), and Delayed Recall (DR)) using Pearson correlation. NCF deterioration was defined per the primary endpoint of XXXX (mean 4 month relative decline in HVLT-R DR). Comparisons between NCF deteriorated and non-deteriorated patients were made using Wilcoxon.

Results: Forty-two patients were evaluable. Median age was 56.5 years (range, 28-83), and 81% had a Class II RPA. Median HV-Total, HV-Right, and HV-Left was 5.4 cc (range, 1.9-7.4), 2.8 cc (range, 0.9-4.0), and 2.7 cc (range, 1.0-3.7), respectively. Median TBV was 1343 cc (range, 1120.5-1738.8). For all measures of corrected HV, increasing HV was associated with higher baseline HVLT-R TR and DR (ρ range=0.35-0.40, p-value range=0.009-0.024) and 4 mo TR and DR (ρ range=0.29-0.40, p-value range=0.009-0.04), with the exception of HV-Right and 4 mo DR (ρ=0.29, p-value=0.059). There was no significant association between HV and NCF change between baseline and 4 months. Fourteen (33.3%) patients developed NCF deterioration per the primary endpoint of XXXX. There was no significant difference in

HV between NCF deteriorated and non-deteriorated patients, though in all instances deteriorated patients had numerically lower HV.

Conclusions: Larger HV is positively associated with improved performance on baseline and 4 month HVLT-R TR and DR in patients with brain metastases undergoing HA-WBRT, but is not correlated with change in NCF.

Introduction

Metastatic disease is the most common central nervous system malignancy (1). Radiotherapy remains the cornerstone for a majority of these patients. While the utilization of stereotactic radiosurgery is increasing (2), there remains a cohort of patients in which radiosurgery is not feasible or appropriate. In this cohort, whole brain radiotherapy (WBRT) remains the preferred treatment option. However, all forms of brain radiotherapy, 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 toxicity associated with this form of therapy.

The subgranular zone of the hippocampus houses a major stem cell niche, and continuous neuro-regeneration from this radiosensitive structure has been theorized to be responsible for formation of cells that participate in the formation and imprinting of new memory (5). To mitigate the negative impact of WBRT, NCTN GROUP conducted a single arm Phase II trial, XXXX, to determine the feasibility and safety of hippocampal avoidant WBRT (HA-WBRT) and its impact 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 vs. HA-WBRT (AAAA) has been completed and positive results have been presented in abstract form (7)(8).

However, while 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). Yet, the role of patient specific variables and their impact 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 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 (11)(12). 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 XXXX, extracting HV from protocol compliant contours.

Methods

Study design and patients

The methodology for XXXX is described in the published primary analysis (6). In brief, XXXX was a single arm phase 2 study examining NCF in patients undergoing HA-WBRT against historical controls treated with standard WBRT. Patients with brain metastasis outside a 5 mm margin around either hippocampus, pathologically proven diagnosis of non-hematopoetic malignancy other than small cell carcinoma, and recursive partitioning analysis (RPA) class I or II were eligible for enrollment. Patients under 18 years of age, with leptomeningeal metastases, prior brain directed radiotherapy, or inability to undergo magnetic resonance imaging were excluded.

Segmentation and Radiotherapy Planning

All patients underwent a three-dimensional spoiled gradient echo, magnetization prepared rapid gradient echo, or turbo field axial MRI of the brain with axial slice thickness </= 1.5 mm which was then fused to CT simulation brain imaging with axial slice thickness </= to 2.5 mm. HVs were manually delineated on the fused image set and expanded by 5 mm to generate the hippocampal avoidance regions. Clinical target volume (CTV) was defined as the whole-brain parenchyma, and the planning target volume (PTV) was defined as CTV minus hippocampal avoidance regions. IMRT was delivered to a dose of 30 Gy in 10 fractions to cover the PTV 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 five patient test group prior to trial participation. Additionally, prior to individual patient enrollment central rapid review of HV contours and HA-WBRT planning was conducted in real time before treatment initiation. After completion of three protocol compliant cases, investigators were permitted to enroll subsequent patients without prior central review.

Cognitive Assessment

All patients underwent neurocognitive assessment using Hopkins Verbal Learning Test-Revised (HVLT-R). HVLT-R has been used as a validated standard for neurocognitive assessment in prior phase III cooperative group brain metastasis trials. HVLT-R consists of a list of 12 nouns with four words drawn from three semantic categories. In order to mitigate the effect of repeated administration, a total of six different forms were utilized. Testing consists of memorization of 12 nouns for three 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 three separate domains and then were standardized against normative data to correct for age effects (13). 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 XXXX, a total of 113 patients were accrued of which 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 secondary to death, failure to follow up, or inability to obtain imaging. Pre-treatment and 4-month NCF scores were obtained. Change scores between baseline and the 4-month timepoint were calculated by subtracting follow-up from baseline score (baseline – follow-up), such that a *positive* change score indicates 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 (14)(15) as described in the primary publication of XXXX.

Hippocampal Volumes

Centrally submitted radiotherapy plans were obtained for all 42 evaluable patients. Left, right, and total hippocampal volumes were obtained and reported in cubic centimeters (cc). Total brain volume (TBV), inclusive of the hippocampus, was also obtained from radiotherapy plans and reported in cc. Using an established method (16) to correct for differences in age and sex in hippocampal volumes, a ratio of hippocampal volume to

total brain volume (Corrected hippocampal volume ratio, C-HV=HV/TBV) was calculated.

Statistical Analysis

C-HV was correlated with baseline and 4-month NCF scores as well as NCF change scores using Pearson correlation coefficient since the data for all patients are approximately normally distributed. C-HV was also compared between deteriorated and not deteriorated patients, as determined by the RCI, at 4 months, conducted separately for each NCF score (i.e. determine deterioration status for each NCF score and compare C-HV between deteriorated and not deteriorated) using the Wilcoxon test due to the small sample size within each deterioration group.

Results

Baseline patient characteristics are presented in Table 1. Median age was 56.5, with 81% of patients having RPA class II disease. HV data was available for all 42 patients from XXXX. Baseline total, right, and left HV values were 5.4 cc (range, 1.9-7.4), 2.8 cc (range, 0.9-4.0), and 2.7 cc (range, 1.0-3.7), respectively, and baseline total, right and left C-HV values were 0.0041 (range, 0.0016-0.0052), 0.0021 (range, 0.0008-0.0027), and 0.0019 (range, 0.0008-0.0019), respectively (Table 1). Median TBV was 1343 cc (range, 1120.5-1738.8). There was no statistically significant difference in total, right, or left C-HV between deteriorated and non-deteriorated patients (Figure 1). However, in all instances deteriorated patients had numerically smaller baseline total HV. Total, right, and left C-HV significantly correlated with HVLT-R recall and delayed recall but not recognition at baseline (Table 2). Total, right, and left C-HV correlated with HVLT-R

recall and delayed recall but not recognition at 4 months (Table 3). There was no significant correlation between C-HV and change score from baseline to 4 months for any measure of HVLT.

Discussion

Neurocognitive toxicity associated with WBRT is a well-recognized issue (17). With improvements in systemic therapies leading to increased overall survival, prophylactic mitigation of the deleterious effects of WBRT remains of great interest. Memantine (3) and HA-WBRT (6) have both demonstrated protective effects on NCF relative to standard WBRT. While these interventions are feasible, important considerations must be given to survival, cost, time, as well as the pathogenesis and incidence of neurocognitive toxicity. An improved ability to predict neurocognitive toxicity 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 XXXX, we found that all measures of HV correlated with HVLT-R recall and delayed recall at baseline and 4 months. This result is consistent with prior studies in neurodegenerative disease. Multiple studies have noted a strong correlation between hippocampal volume (18)(19)(20) and Alzheimer's disease. More recently, (21) and others, have reported correlation between HV for not just Alzheimer's, but across a spectrum of cognitive dysfunction from normal aging to mild cognitive impairment.

Hippocampal volume did not significantly correlate with change score 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, and therefore more patients may be needed to detect any correlation between baseline HV and decline in NCF.

HVLT-R recognition at baseline, 4 months, or change score was not correlated with HV. Lack of correlation between recognition testing and HV is not surprising. The prefrontal, parietal, and medial temporal cortices have been demonstrated to be responsible for recognition memory (23). Functional MR and lesion studies have demonstrated that changes in these neuroanatomic regions result in significant change in recognition testing (24). While 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, however only 42 were analyzable secondary to ineligibility, death, and non-compliance at 4 months. As a result, the total number of patients is limited and may not be representative of a larger cohort. Second, the ability to control for additional confounding variables is narrow, partly due to the limited number of patients. Tumor and treatment related factors, such as white matter change (unpublished data), as well as other neuropsychiatric diseases (25) are known to impact cognition independent of HV. Additionally, HV and its correlation with NCF in this study is limited to a single time interval. Analysis including pre-treatment brain MR imaging, such as that for newly diagnosed stage III NSCLC or follow up brain MR imaging would be more robust. Lastly, the ability to determine the

impact of hippocampal volume on neurocognitive function is incomplete. While HVLT is a validated assessment and has been utilized in multiple studies in the treatment of brain metastasis, our ability to discern impact on other measures of neurocognition is limited. However, despite these limitations the available data represent a product of a robust quality assurance protocol. Investigators were required to complete pre-enrollment hippocampal contouring training and each case was centrally reviewed in a prospective fashion. Additionally, neurocognitive testing was performed by centrally certified research assistants. AAAA BBBB, a phase II/III trial of prophylactic cranial irradiation with or without HA for small cell lung cancer, have 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 radiotherapy 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. AAAA and BBBB are currently underway and have the potential to answer these clinically relevant questions.

Figures

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

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Table 1

Pretreatment Characteristics

(n=42)

Age (years)	
Median	56.5
Min - Max	28 - 81
Q1 - Q3	52 - 63
Age	
< 60 years	27 (64.3%)
>= 60 years	15 (35.7%)
Gender	
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 one race	1 (2.4%)
Unknown	2 (4.8%)

Table 1

Pretreatment Characteristics

(n=42)

Ethnicity	
Hispanic or Latino	2 (4.8%)
Not Hispanic or Latino	38 (90.5%)
Unknown	2 (4.8%)
Karnofsky Performance Status	
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	
Mean	5.4
Std. Dev.	1.2
Median	5.5

Table 1

Pretreatment Characteristics

(n=42)

Min - Max	1.9 - 7.4
Q1 - Q3	4.8 - 6.1
Right HV	
Mean	2.7
Std. Dev.	0.6
Median	2.8
Min - Max	0.9 - 4.0
Q1 - Q3	2.4 - 3.1
Left HV	
Mean	2.6
Std. Dev.	0.6
Median	2.7
Min - Max	1.0 - 3.7
Q1 - Q3	2.3 - 3.0
Total intracranial volume	(n=42)
Mean	1373.4
Std. Dev.	157.5
Median	1343.0
Min - Max	1120.5 - 1738.8
Q1 - Q3	1273.4 - 1476.8

Table 1

Pretreatment Characteristics

(n=42)

Total C-HV	
Mean	0.0039
Std. Dev.	0.0008
Median	0.0041
Min - Max	0.0016 - 0.0052
Q1 - Q3	0.0036 - 0.0045
Right C-HV	
Mean	0.0020
Std. Dev.	0.0004
Median	0.0021
Min - Max	0.0008 - 0.0027
Q1 - Q3	0.0018 - 0.0023
Left C-HV	
Mean	0.0019
Std. Dev.	0.0004
Median	0.0019
Min - Max	0.0008 - 0.0025
Q1 - Q3	0.0017 - 0.0023

Table 1

Pretreatment Characteristics

(n=42)

RPA=Recursive partitioning analysis; C-HV=Corrected-Hippocampal Volume; Q1= first quartile; Q3 = third quartile.

Table 2

Correlations of C-HV with HVLT-R scores at Baseline

(n=42)

		Recall	Delayed Recall	Recognition
Total C-HV	ρ	0.38	0.37	0.045
	p-value	0.013	0.0090	0.78
Right C-HV	ρ	0.34	0.35	-0.0046
	p-value	0.029	0.014	0.98
Left C-HV	ρ	0.39	0.35	0.092
	p-value	0.012	0.024	0.56

C-HV=Corrected-Hippocampal Volume; HVLT-R=Hopkins Verbal Learning Test-Revised.

P-value from Pearson correlation coefficient.

Table 3

Correlations with C-HV and HVLT-R Standardized Score and Raw Change Score at 4 months

(n=42)

		Recall		Delayed Recall		Recognition	
		Score	Change Score	Score	Change Score	Score	Change Score
Total C-HV	ρ	0.39	-0.08	0.31	-0.05	-0.0086	0.06
	p-value	0.01	0.61	0.045	0.74	0.96	0.71
Right C-HV	ρ	0.37	-0.11	0.28	-0.03	-0.045	0.03
	p-value	0.015	0.5	0.071	0.85	0.78	0.83
Left C-HV	ρ	0.37	-0.05	0.31	-0.07	0.029	0.08
	p-value	0.015	0.76	0.043	0.66	0.85	0.62

C-HV=Corrected-Hippocampal Volume; HVLT-R=Hopkins Verbal Learning Test-Revised.

P-value from Pearson correlation coefficient.

Hippocampal volume and NCF after HA-WBRT