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Radiation dose-dependent hippocampal atrophy detected with longitudinal volumetric MRI

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Abstract

Purpose/Objectives—Following brain radiation therapy (RT), patients often experience memory impairment, which may be partially mediated by damage to the hippocampus. Hippocampal sparing in RT planning is the subject of recent and ongoing clinical trials. Calculating appropriate hippocampal dose constraints would be improved by efficient *in vivo* measurements of hippocampal damage. In this study we sought to determine whether brain RT was associated with dose-dependent hippocampal atrophy.

Materials/Methods—Hippocampal volume was measured with MRI in 52 patients who underwent fractionated, partial brain RT for primary brain tumors. Study patients had high-resolution, 3D volumetric MRI prior to and one year post-RT. Images were processed using software with FDA clearance and CE (Conformité Européene) marking for automated measurement of hippocampal volume. Automated results were inspected visually for accuracy. Tumor and surgical changes were censored. Mean hippocampal dose was tested for correlation with hippocampal atrophy one year post-RT. Average hippocampal volume change was also calculated for hippocampi receiving high (>40 Gy) or low (<10 Gy) mean RT dose. A multivariate analysis was conducted with linear mixed-effects modeling to evaluate other potential predictors

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Conflict of interest notification

The other authors have no conflicts of interest.

of hippocampal volume change, including patient (random effect), age, hemisphere, sex, seizure history, and baseline volume. Statistical significance was evaluated at $\alpha=0.05$.

Results—Mean hippocampal dose was significantly correlated with hippocampal volume loss ($r=-0.24$, $p=0.03$). Mean hippocampal volume was significantly reduced one year after high-dose RT (mean −6%, $p=0.009$), but not after low-dose RT. In multivariate analysis, both RT dose and patient age were significant predictors of hippocampal atrophy ($p<0.01$).

Conclusions—The hippocampus demonstrates radiation dose-dependent atrophy following treatment for brain tumors. Quantitative MRI is a non-invasive imaging technique capable of measuring radiation effects on intracranial structures. This technique could be investigated as a potential biomarker for development of reliable dose constraints for improved cognitive outcomes.

Summary

Damage to the hippocampus is thought to contribute to memory impairment after brain radiation therapy. Hippocampal volumes were measured prior to and one year after brain radiotherapy, using quantitative, volumetric MRI. Hippocampal atrophy at one year after treatment was significantly associated with mean hippocampus radiation dose.

Introduction

Following brain radiation therapy (RT), patients often experience memory impairment, which may be partially mediated by damage to the hippocampus or depletion of the neurogenic stem cell population residing in the hippocampal dentate gyrus (1–4). As a result, there have been increased efforts to spare the hippocampus during RT planning. In the whole-brain RT setting, hippocampal avoidance has shown promise for reducing early cognitive decline (5) and this is currently being investigated in a randomized clinical trial (NRG-CC001, https://www.nrgoncology.org/Clinical-Trials/NRG-CC001). In the setting of partial-brain irradiation, there is also evidence that higher RT dose to the hippocampus may be associated with worse memory impairment (6–8).

Designing appropriate hippocampus dose-reduction strategies would be improved by efficient means of detecting *in vivo* hippocampal damage in patients with brain tumors after a range of radiation dose exposures. Hippocampal volume as measured on structural MRI has proven clinical utility in a variety of diseases, including Alzheimer's disease (9, 10), temporal lobe epilepsy (11), and traumatic brain injury (12). Additionally, children treated with radiation for medulloblastoma may have altered hippocampal volume compared to healthy controls with a normal pattern of development (13, 14). However, this technique has not yet been successfully implemented as a biomarker for radiation-related hippocampal volume loss in adults.

In the present study, we used quantitative, volumetric MRI to measure hippocampal volumes prior to and approximately one year after patients received brain radiotherapy. We sought to determine whether brain RT was associated with dose-dependent hippocampal atrophy.

Methods and Materials

Patient cohort

This retrospective study was approved by the institutional review board. Study patients underwent fractionated (1.8–2.0 Gy per fraction) partial brain radiation for primary brain tumors at our institution between 2010 and 2014. Inclusion criteria required a standardized MRI protocol prior to RT (or within the first week of RT start) and approximately one year after RT start (9–15 months). A cohort of 58 primary brain tumor patients was identified meeting these criteria. Five of these were excluded for poor image quality, and one was excluded for large surgical resection, leaving a final cohort of 52 patients for analysis.

Forty-two of the 52 patients were treated with a total of 30 fractions. Radiation dose for the other 10 patients was converted at each voxel location in the volume to a 30-fraction equivalent for direct comparison. Dose conversion was achieved using principles of biologically equivalent dose and an alpha/beta ratio of 2 Gy (15, 16).

Image acquisition

All images were acquired using a 3T Signa Excite HDx system (GE Healthcare, Milwaukee, WI) with an 8-channel dedicated head coil. Images were acquired before start of RT and at approximately one year (9–15 months) after start of RT. The standardized protocol included a 3-dimensional (3D) volumetric T_1-weighted inversion recovery spoiled gradient-echo sequence (TE, 2.8 ms; TR, 6.5 ms; TI, 450 ms) obtained both pre- and post-infusion of IV gadolinium contrast, as well as a 3D T_2-weighted FLAIR sequence (TE, 126 ms; TR, 6000 ms; TI, 1863 ms).

Image processing and hippocampal volume measurement

All images, including FLAIR and post-contrast T_1-weighted images were inspected visually to ensure there was no overlap of tumor or post-surgical effects with the hippocampus. Two physician reviewers independently performed slice-by-slice evaluation of each MRI study. Reviewers were blinded to hippocampal dose and hippocampal volume measurements. If either tumor or resection cavity came within 5 mm of a hippocampus, it was excluded from analysis to mitigate the possibility that volume changes resulted from tumor involvement or post-surgical effects. Tumor and/or resection cavity were defined by the individual patient's radiation oncologist at time of treatment planning. The 5 mm margin accounts for uncertainty in contouring (17). Hippocampi were also excluded if there was any distortion of hippocampal anatomy due to post-surgical effects.

Pre-contrast T_1-weighted images were processed using software with FDA clearance and CE (Conformité Européene) marking for automated measurement of hippocampal volume in clinical practice (NeuroQuant, CorTechs Labs, Inc., La Jolla, CA). Methodological details are described elsewhere (18). Briefly, the images are corrected for distortion from gradient nonlinearity and static field inhomogeneity; the brain is segmented from skull structures; and individual brain structures (including the hippocampus in each hemisphere) are segmented with reference to a probabilistic atlas. The software output includes volume measurements of the hippocampus (in mL), as well as annotated images with color overlay for segmented

structure (Figure 1). Color images were inspected slice-by-slice by two physicians for confirmation of accurate segmentation. Volume measurements from this software have previously been shown to have high correlation with expert segmentation (18) and clinical utility in a wide array of conditions, including neurodegenerative disease (9, 10), traumatic brain injury (12), and temporal lobe epilepsy (11).

The pre-contrast T_1-weighted images were then co-registered to the CT simulation images that were used in the patient's original radiation treatment plan using custom software (19). After visual confirmation of accurate registration, the transformation matrix from this registration was used to resample the delivered radiation dose distribution from the treatment plan to the MRI volume space.

Statistical analysis - univariate

Mean radiation dose was calculated for each hippocampus using the co-registered RT dose and segmented MRI data. The change in hippocampal volume was calculated by subtracting the volume at approximately one year post-RT from the pre-RT baseline. Percent change in hippocampal volume was determined by taking the above difference and dividing by the pre-RT baseline for each hippocampus.

The relationship of mean radiation dose and hippocampal volume change was assessed by Pearson's correlation coefficient, using all hippocampi that were not censored during the quality assurance steps described above.

The effect of RT dose on hippocampal atrophy was further explored by comparing the mean pre-post volume loss after high (>40 Gy) or low (<10 Gy) mean RT dose using *t*-tests. Another *t*-test was performed to determine whether the high-dose group had greater pre-post change in hippocampal volume than the low-dose group.

All statistical tests were two-sided, with a threshold of $\alpha = 0.05$.

Statistical analysis - multivariate

A multivariate analysis was conducted to evaluate other potential predictors of hippocampal volume change. A linear mixed-effects (LME) model was constructed using the R environment for statistical computing ("lme4" version 1.1–7) (20). Percent hippocampal volume change, calculated as described above, was chosen as the dependent variable. The primary predictor of interest remained the mean radiation dose to each hippocampus, as in the first analysis. In this model, patient was included as a random intercept. Additional potential fixed-effect predictors were assessed in step-wise fashion by likelihood ratio test for statistically significant contribution to the model. These were: age, hemisphere (left or right), sex, seizure history, history of bevacizumab treatment during study period, and baseline volume. For seizure history, specifically patients were identified who experienced one or more major seizures (generalized tonic-clonic or status epilepticus) during the period between their imaging time points. Factors with $p < 0.05$ were included in the final model. Interaction terms for fixed effects were also tested for contribution to the model with the same threshold for inclusion. Fixed effects parameters in the final model were estimated

using restricted maximum likelihood, and the corresponding (two-sided) p-values were taken as significant at $\alpha = 0.05$.

Results

Cohort characteristics

Table 1 reports characteristics of the included patient cohort, including histology, sex, age, tumor location, seizure history, bevacizumab history, and radiation fractionation schemes.

Hippocampal volume measurement

After the quality assurance steps described above, 12 left hippocampi and 13 right hippocampi were excluded from further analysis due to tumor, surgery, or segmentation effects. Censoring was performed separately for each hemisphere; only one patient had both hippocampi excluded from analysis by these criteria. After censoring, there were 79 hippocampi available for full analysis.

Statistical analysis - univariate

Mean RT dose to the hippocampus was significantly correlated with hippocampal volume loss ($r = -0.24$, $p = 0.03$; Figure 2).

Mean hippocampal volume was significantly reduced one year after high-dose (>40 Gy) RT, but not after low-dose (<10 Gy) RT (Table 2). Atrophy in the high-dose hippocampi was also significantly greater than in the low-dose hippocampi.

Statistical analysis - multivariate

Mean hippocampus radiation dose (fixed effect) and patient (random effect) were included as predictors of hippocampal volume change at one year post-RT in a linear mixed-effects model. Addition of patient age as a fixed effect significantly contributed to the model ($p = 0.01$). Hippocampus hemisphere, patient sex, seizure history, bevacizumab history, and baseline volume were also tested via likelihood ratio test, but none significantly contributed to the model ($p > 0.05$). Estimated parameters for radiation dose and patient age are reported in Table 3.

Discussion

This is the first study to detect dose-dependent hippocampal volume loss in adults after irradiation of primary brain tumors. Using quantitative, volumetric MRI, we observed hippocampal atrophy approximately one year after brain RT that was correlated with mean hippocampus dose (Figure 2). This effect remained significant (Table 3) after accounting for patient age and a range of other clinical variables.

For hippocampi receiving greater than 40 Gy (mean dose), hippocampal volume decreased by nearly 6% at one year. This represents significant atrophy in the high-dose group ($p < 0.01$; Table 2). For context, normal aging typically results in annual hippocampal volume changes of less than 1% even in the elderly (23, 24). The changes observed here after high-

dose RT exceed those reported in Alzheimer's disease, where hippocampal atrophy is a hallmark feature and is correlated with cognitive decline (21–23).

No significant hippocampal atrophy was detected after low-dose RT (mean <10 Gy) exposure. These findings are consistent with a previous study of 15 patients with head and neck malignancy, where low-dose incidental RT dose to the hippocampus did not result in hippocampal volume loss (25). Similarly, a study of 14 glioblastoma patients found no volume change 6 months after start of chemoradiation in hippocampi contralateral to the tumor (26). Interestingly, a phase II trial investigating hippocampal avoidance in the whole-brain radiation therapy setting (30 Gy in 10 fractions, RTOG 0933) also found less short term memory impairment compared to historical controls when constraining the mean dose to the hippocampus to less than 10 Gy (5).

These findings have potential application in clinical trials and practice. The current NRG-CC001 study randomizes WBRT patients to hippocampal sparing RT, and hippocampal volume could be incorporated in such efforts as a quantitative imaging measure to monitor treatment effects. Future work could also correlate hippocampal volume with cognitive outcomes, potentially affording a biomarker of radiation damage for the development of robust hippocampus dose constraints. Possible risk factors for accelerated hippocampal atrophy (e.g., systemic therapy, patient age, seizure history) could be rigorously studied to guide treatment-planning decisions.

The automated method used for measuring hippocampal volume in this study has practical advantages over the manual tracings used in prior studies (13, 14, 25), which requires greater user expertise and is more time intensive. While visual confirmation of accuracy (as was done in this study) is recommended, especially where there may be surgical or tumor effects near the hippocampus, automated volumes have been shown to rival expert segmentation (18). We chose to use a commercial product with FDA clearance and CE marking in this study to maximize clinical applicability, but we note that freely available research tools have excellent agreement with the measurements from the commercial software (27).

Previous studies have established an association between hippocampal irradiation and the development of cognitive impairment, particularly deficits in verbal learning and memory (5, 6, 8). The radiobiological mechanisms of the hippocampal damage implied in those studies (and measured in the present work) is not well known. In fact, a small study of irradiated rats showed no significant histopathologic difference in neuron number, neuronal volume, or neuropil volume one year after whole-brain RT (28). Other reports, on the other hand, have described decreased neural precursor cell proliferation (1) and damage to vascular structures within the hippocampus (29) after brain RT. Additionally, one study in living humans used dynamic contrast enhanced MRI to show a transient increase in vascular leakiness one month after RT in women whose hippocampal dose was greater than 19 Gy (7).

Limitations of this work include those common to retrospective studies from a single institution. Moreover, the small cohort here does not afford sufficient power to thoroughly evaluate the potential contributions of non-radiation factors to hippocampal atrophy. Brain tumor patients are often exposed to surgical procedures, various systemic therapies, and

tumor effects, in addition to seizures and unidentified environmental and genetic features that may affect the hippocampus. Future work may permit investigation of these possibilities as independent etiologies and/or synergistic effects. Finally, the relationship of hippocampal atrophy and cognitive impairment after radiotherapy is not understood, though it is being studied prospectively at our institution. Increased hippocampal dose has been associated with memory loss in brain RT patients (5, 6, 8), and hippocampal volume change is correlated with memory impairment in other brain conditions (9, 10, 12).

Conclusions

The human hippocampus demonstrates radiation dose-dependent atrophy following treatment for primary brain tumors. Consistent with clinical observations of memory impairment in long-term survivors of brain tumors, this finding suggests quantitative MRI could be studied as a potential non-invasive imaging biomarker of radiation effects on intracranial structures. Such a biomarker could possibly lead to reliable dose constraints and, ultimately, improved cognitive outcomes in brain tumor patients.

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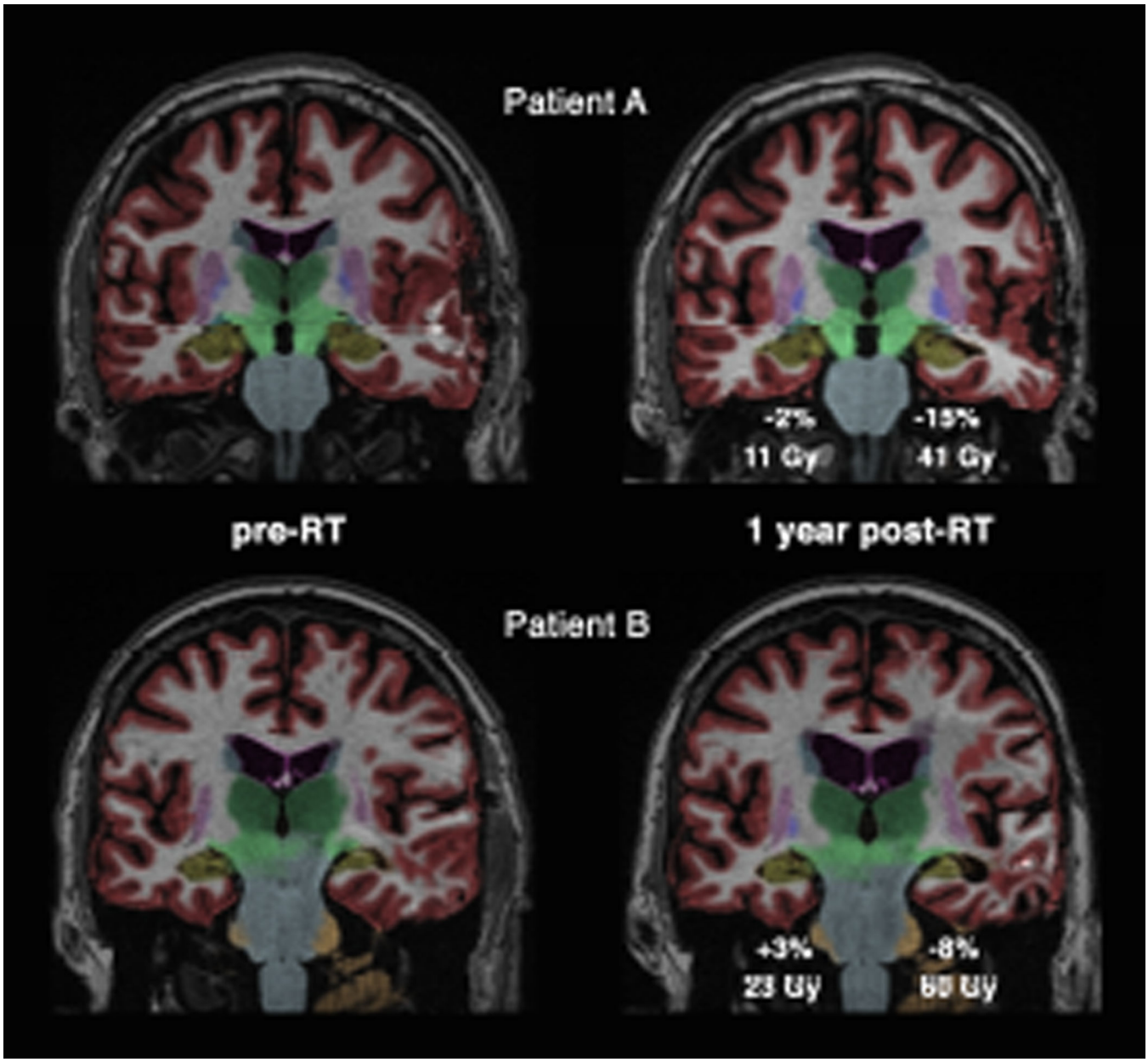

Figure 1. Two illustrative cases

Pre-radiotherapy (pre-RT) MRI on left, with color overlay showing automated segmentation of hippocampus in yellow. The text under each hippocampus on the segmented post-RT MRI (right) gives the corresponding percent change in hippocampal volume compared to pre-RT baseline and the mean hippocampus RT dose.

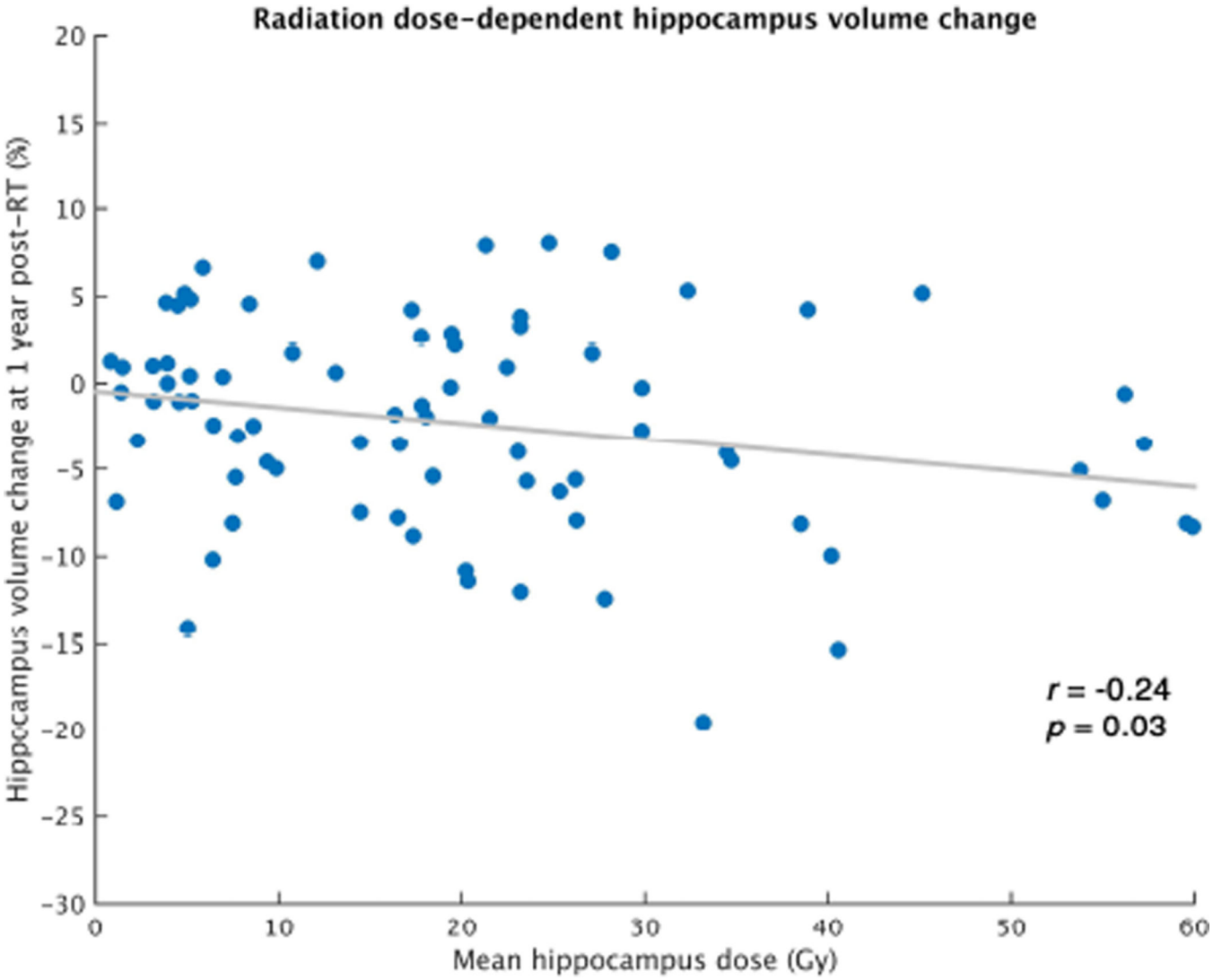

Figure 2.

Hippocampal volume change at one year after radiation therapy (RT) compared with mean RT dose to the hippocampus. Each data point represents one hippocampus (left or right). Volume change is reported as percent change relative to pre-RT baseline.

TABLE 1

Patient/Tumor Characteristics

Characteristic	Number of patients (Total = 52)	%
Sex:		
Male	35	67
Female	17	33
Median age (years): (range)	54 (19–77)	
Tumor histology:		
Grade IV glioma	30	58
Grade III glioma	12	23
Grade II glioma	7	13
Other low grade glioma	1	2
Low grade glioneural tumor	1	2
Meningioma	1	2
Tumor location:		
Frontal	18	35
Temporal	16	31
Parietal	2	4
Occipital	3	6
Temporoparietal	4	8
Frontoparietal	2	4
Frontotemporal	1	2
Parietooccipital	1	2
Thalamus	2	4
Cavernous Sinus	1	2
Cerebellum	1	2
Surgery:		
Gross total resection	22	42
Subtotal resection	24	46
Biopsy	5	10
None[a]	1	2
Radiation therapy dose, Gy (fraction size):		
60(2)	39	75
59.4 (1.8)	6	12
55.8 (1.8)	1	2
54 (1.8)	3	6
50.4 (1.8)	3	6
Radiation therapy technique:		

Characteristic	Number of patients (Total = 52)	%
Static intensity modulated RT (IMRT)	36	69
Volumetric modulated arc therapy (VMAT) Non-coplanar Co-planar	 14 2	 27 4
Seizure history		
Generalized tonic-clonic seizures during study period	15	29
Systemic therapy		
Temozolomide[b] alone	18	35
Temozolomide[b] + bevacizumab	4	8
Temozolomide[b] + bevacizumab + other chemotherapy[c]	5	10
Temozolomide[b] + bevacizumab + other clinical trial[d]	1	2
Temozolomide[b] + other clinical trial[e]	9	17
Temozolomide[f] + other chemotherapy[g]	14	27
None	1	2
Additional local therapy		
Tumor treating fields	2	4

[a]Tumor was diagnosed as meningioma without histopathology.

[b]Temozolomide given concurrently with radiotherapy for all of these patients.

[c]Carboplatin (n = 3), CCNU (n = 2), irinotecan (n = 1), veliparib (n = 1), buparsilib (n = 1).

[d]Oncolytic retrovirus clinical trial.

[e]Oncolytic retrovirus clinical trial (n = 5), tumor antigen vaccine clinical trial (n = 3), dendritic cell vaccine (n = 2). Patients in this category also received: CCNU (n = 4), carboplatin (n = 3), nilotinib (n = 2), capecitabine (n = 1), everolimus (n = 1), palbociclib (n = 1), galunisertib (n = 1), irinotecan (n = 1).

[f]Temozolomide given concurrently with radiotherapy in 13 of these 14 patients.

[g]Carboplatin (n = 9), CCNU (n = 9), irinotecan (n = 4), erlotinib (n = 2), nilotinib (n = 2), galunisertib (n = 2), thalidomide (n = 1), etoposide (n = 1), pemetrexed (n = 1), lapatinib (n = 1), rapamycin (n = 1), vemurafenib (n = 1), trametinib (n = 1), debrafinib (n = 1), mipsagargin (n = 1), palbociclib (n = 1).

TABLE 2

Radiation dose effect on hippocampal volume

	Change in hippocampal volume at 1 year[a]		
	(%)	(mL)	*p*-value[b]
High dose (> 40 Gy)	−5.8	−0.3	0.02[c]
Low dose (< 10 Gy)	−1.2	−0.1	0.20

[a] Change from pre-radiation baseline to approximately 1 year after start of radiation therapy.

[b] Student's *t*-test for significant hippocampal atrophy (two-sided test).

[c] Also significantly greater atrophy versus low-dose hippocampi ($p = 0.02$).

TABLE 3

Linear mixed-effects model of hippocampal volume change

Predictor	Volume change[a]	Standard error	*p*-value [b]
Radiation dose	−0.13 %/Gy	0.04	0.002
Age	−0.13 %/year	0.05	0.008

[a] Hippocampal volume change one year after start of radiation therapy, given as percent change from pre-radiotherapy baseline per unit of predictor (Gy of dose or year of age, respectively).

[b] Univariate *p*-value from linear mixed-effects model (two-sided test).