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Clinical Investigation

Dose-Dependent Cortical Thinning After Partial Brain Irradiation in High-Grade Glioma



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Summary

Dose-dependent thinning of cerebral cortex was observed after fractionated partial brain radiation therapy in high-grade glioma patients. The magnitude of thinning parallels 1-year atrophy rates seen in neurodegenerative diseases like Alzheimer and may contribute in part to cognitive decline following brain radiation therapy.

Purpose: Radiation-induced cognitive deficits may be mediated by tissue damage to cortical regions. Volumetric changes in cortex can be reliably measured using high-resolution magnetic resonance imaging (MRI). We used these methods to study the association between radiation therapy (RT) dose and change in cortical thickness in high-grade glioma (HGG) patients.

Methods and Materials: We performed a voxel-wise analysis of MRI from 15 HGG patients who underwent fractionated partial brain RT. Three-dimensional MRI was acquired pre- and 1 year post RT. Cortex was parceled with well-validated segmentation software. Surgical cavities were censored. Each cortical voxel was assigned a change in cortical thickness between time points, RT dose value, and neuroanatomic label by lobe. Effects of dose, neuroanatomic location, age, and chemotherapy on cortical thickness were tested using linear mixed effects (LME) modeling.

Results: Cortical atrophy was seen after 1 year post RT with greater effects at higher doses. Estimates from LME modeling showed that cortical thickness decreased by -0.0033 mm ($P < .001$) for every 1-Gy increase in RT dose. Temporal and limbic cortex exhibited the largest changes in cortical thickness per Gy compared to that

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in other regions ($P < .001$). Age and chemotherapy were not significantly associated with change in cortical thickness.

Conclusions: We found dose-dependent thinning of the cerebral cortex, with varying neuroanatomical regional sensitivity, 1 year after fractionated partial brain RT. The magnitude of thinning parallels 1-year atrophy rates seen in neurodegenerative diseases and may contribute to cognitive decline following high-dose RT. © 2016 Elsevier Inc. All rights reserved.

Introduction

Radiation therapy (RT) is considered standard of care in the treatment of primary brain tumors but can cause devastating late deficits in neurocognitive function (1, 2). Despite substantial advancements in high-precision radiation treatment planning and delivery, large amounts of normal-appearing cerebral tissue will be incidentally irradiated (3). Identifying critical neuroanatomic structures that undergo radiation-induced damage may shed light on the complicated pathogenesis of radiation-induced neurocognitive decline and may offer the possibility of cognitive sparing via selective sparing of these structures.

Quantitative magnetic resonance imaging (MRI) can be used to probe anatomic brain microstructure with high spatial resolution (4). Radiation-induced imaging changes, as detected with quantitative MRI, have been correlated with structural changes in cerebral tissue in animal models (5). Most imaging studies have focused on quantifying radiation-induced damage within the cerebral white matter or the hippocampus (6, 7). Associations between cortical regions and neurocognitive functions such as memory and semantic processing (8) are clear, but data are sparse on the effects of radiation on cerebral cortex (9, 10).

Recent advances in quantitative MRI and automatic segmentation have streamlined the complete parcelling of the cerebral cortex (11). These methods can be used to generate accurate, automated measurements of cortical thickness at each point on the cortical surface, rivaling measurements by postmortem histopathology (12–14). Such tools have been used extensively in the study of cortical atrophy in neurodegenerative diseases (15, 16) including Alzheimer disease (AD) and mild cognitive impairment (17). Similar analyses of cortical degeneration in patients undergoing partial brain RT may improve our understanding of radiation-induced tissue injury and cognitive decline.

In this study, we investigated the relationship between radiation dose and changes in cerebral cortical thickness in patients treated for high-grade glioma (HGG) with partial brain RT, accounting for potential confounders such as neuroanatomical location, age, and chemotherapy. For the purposes of this study, cerebral cortex was confined to neocortical regions in the brain that consist of 6 cell layers. The analysis did not consider phylogenetically older regions consisting of 3 or 4 cell layers such as the olfactory cortex and hippocampus (18).

Methods and Materials

Patients

The retrospectively studied cohort consisted of 15 consecutively treated HGG patients who underwent fractionated partial brain radiation therapy at University of California San Diego/Moores Cancer Center between 2011 and 2013. From January 2011 to December 2013, 32 patients with primary HGG tumors treated with fractionated brain RT underwent a standardized MRI imaging protocol prior to RT on the same 3-Tesla MR system in our institution's cancer center. From this group, 22 patients were selected who had been imaged 1 year post RT with no intervening additional radiation. Seven of these patients were excluded from analysis due to significant anatomical changes (large surgical resection [$n=3$], tumor growth [$n=4$]) over the course of the year, which prevented accurate imaging correspondence between the 2 time points. This study was approved by the institutional review board.

MR imaging

MR imaging was performed using a 3-T Signa Excite HDx scanner (GE Healthcare, Milwaukee, WI) equipped with an 8-channel head coil. The imaging protocol included pre- and post contrast 3-dimensional (3D) volumetric T1-weighted inversion recovery spoiled gradient-echo sequence (TE, 2.8 ms; TR, 6.5 ms; TI, 450 ms) and a 3D T2-weighted FLAIR sequence (TE, 126 ms; TR, 6000 ms; TI, 1863 ms). Before analysis, all MR images were processed to correct for geometric distortions (19). The T1-weighted precontrast images were rigidly coregistered to the treatment planning CT images using custom-made software (20) developed in Matlab (MathWorks, Natick, MA). The registered images were visually inspected for accuracy after which, the transformation matrix was used to resample the radiation dose maps, calculated on the treatment planning CT, to the MR imaging space.

Cortical thickness

Cortical thickness was estimated using Freesurfer version 5.3 software (<http://surfer.nmr.harvard.edu>) and the T1-weighted precontrast images, weighted by T2-weighted

FLAIR to correct for regions of edema or hypointensity (21, 22). Cortical thickness is calculated at each vertex of the reconstructed cortical mantle as the distance between white matter and pial surfaces (23). The Freesurfer processing pipeline was run independently for each time point (pre RT and 1 year post RT). The 1-year post-RT cortical surface was resampled onto the baseline surface using the “mri_surf2surf” function (Freesurfer).

After temporal correspondence was established, 1-year change in cortical thickness was calculated as the difference in thickness between the pre- and 1-year post RT time points for each vertex of the baseline cortical surface. Because a voxel includes many vertices, all vertices were then grouped by voxel location. Thus, the 1-year change in cortical thickness for each cortical voxel represented the average change in cortical thickness of all the vertices located within that voxel. The radiation dose at each voxel was determined by sampling the coregistered dose map at that location. Each voxel was also assigned an anatomic location (frontal, temporal, occipital, parietal, or limbic). An example of the cerebral cortex segmented on MR images is shown in Figure 1A with the neuroanatomical locations used in this study illustrated in Figure 1B. Surgical scars, tumors, tumor beds, and resection cavities were censored from analyses, to mitigate mislabeling of cortex, and all images were

inspected for errors in segmentation. For patients with intervening surgeries between the 2 time points, the new tumor cavity was also censored from analyses.

Statistical analysis

Data consisted of a large number of voxels (>100,000) per patient, which provided substantial power to evaluate the primary dependent variable. As an initial step, voxels were grouped by patient and anatomic location. A segmented linear regression analysis, using maximum likelihood, was conducted to test whether the relationship between dose and patient-averaged cortical atrophy could be separated into 2 intervals with different slopes by a breakpoint dose. Confidence intervals were estimated using profile likelihood. We next performed linear mixed effects (LME) modeling on the effect of radiation dose on 1-year change in cortical thickness at each voxel, considering cortical location (categorical variable), age (continuous variable), and chemotherapy (temozolomide vs temolozolomide + other) as potential covariates (24). All possible interaction terms were tested. To control for correlated observations within subjects, we tested a subject-specific random slope and intercept for dose. With the

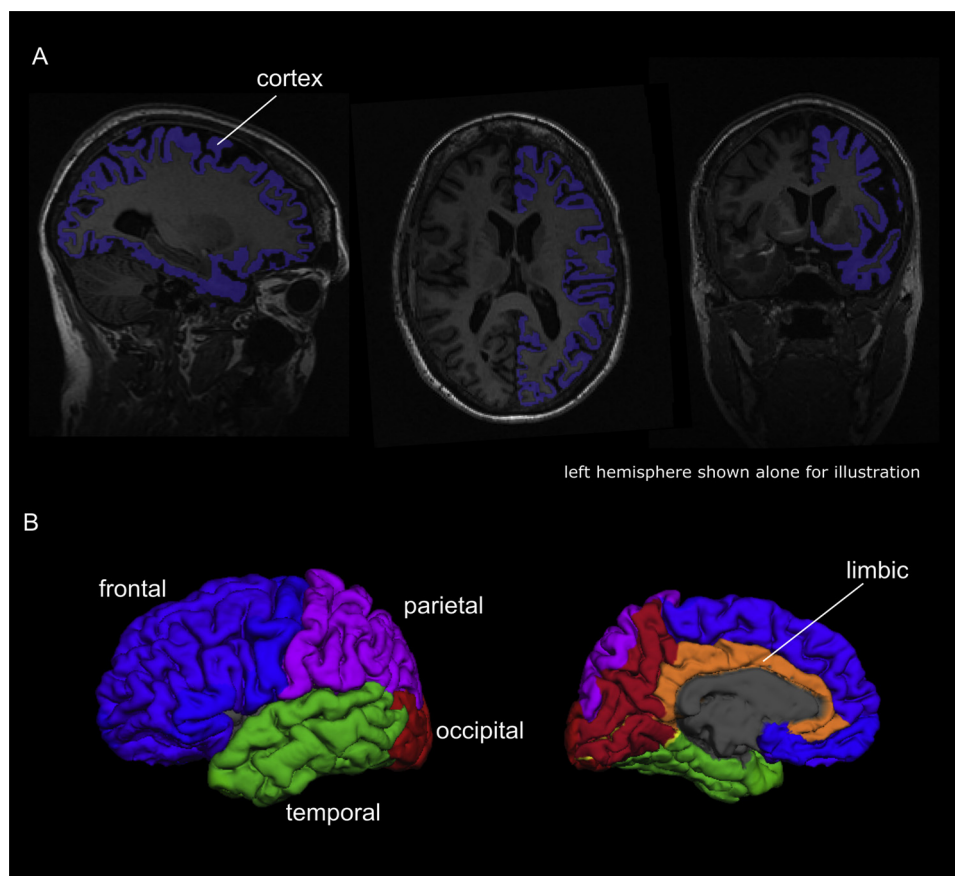


Fig. 1. (A) Cortical segmentation of left hemisphere overlaid on T1-weighted precontrast MR sagittal, axial, and coronal images. (B) Neuroanatomical labels by lobe are shown in color on the left pial surface. A color version of this figure is available at www.redjournal.org.

addition of each random effects term, the model was tested using a likelihood ratio test. Estimation of fixed effects parameters was based on restricted maximum likelihood. Main effects and interaction terms were significant at $P < .05$. Statistical analyses were performed using R environment for statistical computing (“lme4” version 1.1-7 software) (25).

Results

Patient characteristics

Patient, tumor, and treatment characteristics are shown in Table 1. The cohort consisted of 10 males and 5 females with a median age of 60 years. Most patients had glioblastoma, and median preoperative tumor size was 3.3 cm. Most of the patients were treated with concurrent and adjuvant temozolomide with or without additional standard or investigational therapies as described in Table 1. Five patients had intervening surgeries between the 2 time points, of which four were due to tumor recurrence.

Whole-brain dose response

Voxel-wise 1-year change in cortical thickness (by patient and averaged) is shown in Figure 2. The average change in thickness increased in magnitude with increasing dose, from a value of -0.02 mm at 1 Gy to -0.30 mm at 60 Gy. Using segmented linear regression analysis, a breakpoint of 34.6 Gy [95% CI: 31.9-39.9] separated the cortical atrophy-dose relationship into 2 linear segments with slopes of -0.0013 mm/Gy [95% confidence interval [CI]: -0.00089 to 0.0017] and -0.0078 mm/Gy [95% CI: -0.0072 to -0.0084] before and after the breakpoint, respectively. The adjusted R-squared of the model was 0.96, compared to 0.92 when a continuous linear regression model using a single slope was used to fit the data.

Variation in dose-response with anatomic location

The dose-associated cortical thinning for each neuroanatomic location (frontal, temporal, parietal, occipital, and limbic lobe) is shown in Figure 3A-E. The solid line in each panel represents a linear univariate regression of the location-specific change in thickness as a function of radiation dose. All locations showed similar trends of increased cortical thinning with increasing radiation dose. The slopes of the univariate linear regression, in mm/Gy, were calculated for the five locations as: frontal (-0.0024 ; 95% CI: -0.0022 to -0.0027), temporal (-0.0046 ; 95% CI: -0.0043 to -0.0049), occipital (-0.0025 ; 95% CI: -0.0021 to -0.0028), parietal (-0.0029 ; 95% CI: -0.0024 to -0.0033), and limbic (-0.0034 ; 95% CI: -0.0025 to -0.0043). The effect of the neuroanatomic location of the applied dose on cortical thinning was further analyzed using linear mixed effects modeling on the full dataset.

Table 1 Patient, tumor, and treatment characteristics (n = 15)

Characteristic	Number of patients (%)
Sex	
Male	10 (66.7)
Female	5 (33.3)
Median age (y) (range)	60 (40-77)
Tumor histology	
Glioblastoma	14 (93.3)
Anaplastic ganglioglioma	1 (6.7)
Median largest dimension of preoperative tumor (cm) (range)	3.3 (1.0-7.7)
Median planning target volume (cc) (range)	162.7 (59.8-571.3)
Tumor location:	
Temporal	8 (66.7)
Frontal	2 (13.3)
Frontotemporal	1 (6.7)
Parietal	1 (6.7)
Parietotemporal	2 (13.3)
Parietooccipital	1 (6.7)
Surgery	
Gross total resection	11 (73.3)
Subtotal resection	4 (26.7)
RT dose, Gy (fraction size)	
60 (2)	13 (86.7)
60 (3)	1 (6.7)
59.4 (1.8)	1 (6.7)
Concurrent chemotherapy	
Temozolomide only	9 (60.0)
Temozolomide + vaccine trial*	4 (26.7)
Temozolomide + other clinical trial†	2 (13.3)
Adjuvant chemotherapy	
Temozolomide only	5 (33.3)
Temozolomide + other chemotherapy‡	4 (26.7)
Temozolomide + bevacizumab	2 (13.3)
Temozolomide + other clinical trial§	2 (13.3)
Temozolomide + vaccine trial	1 (6.7)
No adjuvant chemotherapy	1 (6.7)

Abbreviation: RT = radiation therapy.

* Vaccine trial targeting tumor antigens (n = 2); vaccine trial of activated dendritic cells (n = 2).

† α_v integrin inhibitor trial (n = 1); poly(ADP-ribose) polymerase (PARP) inhibitor trial (n = 1).

‡ Lapatinib, rapamycin, lomustine, irinotecan, and carboplatin.

§ Poly(ADP-ribose) polymerase (PARP) inhibitor trial (n = 2).

|| Vaccine trial of activated dendritic cells (n = 1).

Linear mixed modeling of cortical atrophy

Results of LME modeling, with dose as the main predictor variable and location as covariate, are presented in Table 2. Age and chemotherapy were not significantly associated with the degree of cortical thinning ($P > .05$) and were, thus, excluded from the final model. Occipital cortex was the reference location. Estimates and P values are shown for each of the main effects and interaction terms. The intercept of the model, 0.0043 mm,

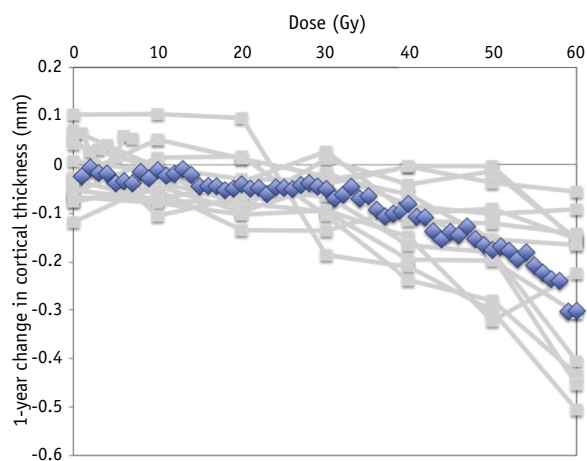


Fig. 2. Patient-specific (gray lines) and patient-averaged (blue diamond data points) 1-year changes in cortical thickness for radiation doses from 0 to 60 Gy. A color version of this figure is available at www.redjournal.org.

corresponds to the atrophy observed in the occipital lobe, controlling for dose. Main effects for other locations (frontal, limbic, temporal, and parietal) are listed and

Table 2 Linear mixed-effects model estimates for changes in cortical thickness with dose as the main predictor variable and location as a covariate

Characteristic	Estimate	P
Dose	−0.0026	<.001
Location		
Occipital (reference)	0.0043	.81
Frontal	−0.023	<.001
Limbic	0.037	<.001
Temporal	−0.0038	.13
Parietal	0.000041	.94
Interaction		
Frontal dose	0.0015	<.001
Limbic dose	−0.00095	<.001
Temporal dose	−0.0027	<.001
Parietal dose	0.00045	<.001

represent the difference in 1-year cortical thinning compared to the occipital lobe.

The dose estimate for the model, −0.0026 mm, corresponds to the rate of cortical thinning observed for every 1-Gy increase in dose within the occipital lobe ($P < .001$). The interaction terms between dose and location represented how the rate of thinning with dose among the various locations differed from that of the occipital lobe. All interaction terms were found to be statistically significant. Temporal and limbic lobes had negative interaction estimates, indicating that the cortical thinning per unit dose was greater in these locations than in the occipital lobe, whereas the inverse was true for the frontal and parietal lobes. Increase in atrophy for every 1-Gy increase in dose for each location independent of a reference lobe was calculated as (in mm): frontal (−0.0010, 95% CI: −0.005 to −0.0021), temporal (−0.0053; 95% CI: −0.0041 to −0.0063), occipital (−0.0026; 95% CI: −0.0014 to −0.0037), parietal (−0.0021; 95% CI: −0.0010 to −0.0032), and limbic (−0.0035; 95% CI: −0.0023 to −0.0046).

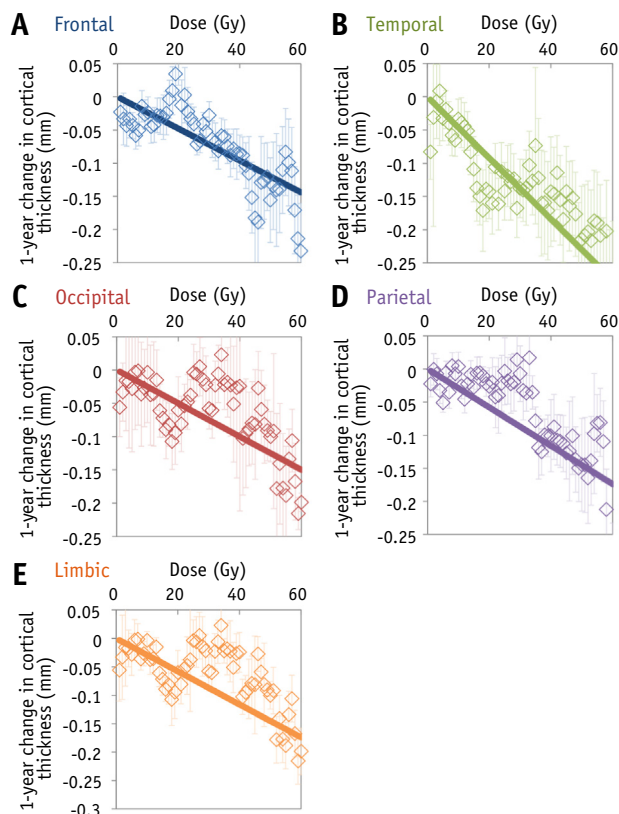


Fig. 3. Relationship between 1-year change in cortical thickness and radiation dose for (A) frontal, (B) temporal, (C) occipital, (D) parietal, and (E) limbic lobes. Error bars are standard errors. The solid line represents results of univariate regression. The limbic, temporal, and parietal lobes exhibited the steepest rate of change of cortical thickness with dose.

Discussion

Quantification of microstructural changes to normal brain tissue after radiation therapy may help us understand the physiologic processes that underlie radiation-induced neurocognitive decline. Our results show that both radiation dose and neuroanatomic location are significantly associated with cortical thinning at 1 year post RT in HGG patients. This relationship is illustrated graphically in Figure 4 for an example patient. The cortical surface is overlaid with color maps representing radiation dose (Fig. 4A) and cortical thinning (Fig. 4B) values at 1 year post RT. Regions of cortex that received higher radiation dose (Fig. 4, yellow) coincide with those showing greater degree of cortical thinning (Fig. 4, light blue).

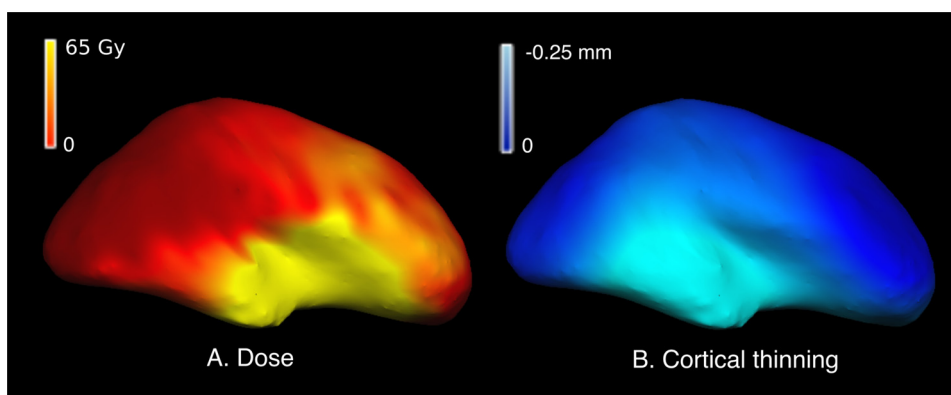


Fig. 4. Cortical surface representation of (A) radiation dose in Gy and (B) cortical thinning at 1 year observed in an example patient. Regions receiving a higher dose show a greater degree of cortical thinning at 1 year post radiation therapy. A color version of this figure is available at www.redjournal.org.

A segmented linear regression analysis tested for the presence of a breakpoint dose, which separated the patient-averaged cortical atrophy-dose relationship at 34.6 Gy into 2 intervals with different regression coefficients (slope). However, the very modest increase in adjusted R^2 value of the segmented model compared to a continuous linear regression model (0.96 vs 0.92) suggested the latter might be sufficient in explaining the relationship. Dose-associated cortical thinning also varied by neuroanatomic location. In particular, the temporal and limbic lobes exhibited the greatest rate of cortical loss with radiation dose. To our knowledge, this is the first study that establishes a quantitative association between regional cortical atrophy and radiation dose in adult patients treated for brain tumors.

Volumetric cortical analysis has been previously investigated in pediatric patients treated for medulloblastoma (26) with chemotherapy and radiation. Cortical thickness of these patients was found to be between 0.23 and 0.39 mm thinner than age- and sex-matched controls. These values are similar to the cortical thinning observed in the present study at the higher dose ranges (-0.3 mm). However, cortical thinning reported in the pediatric study represents a difference between 2 groups whereas the values reported in the present study represent longitudinal change within the same patient cohort. Cortical thinning in the pediatric population (26) was predominantly found in the posterior portion of the brain, such as the parieto-occipital and lateral temporal lobes. The authors hypothesize that these areas of cortex overlap with those undergoing active development in children and are therefore most sensitive to the effects of radiation. In the present study, the temporal lobe was also determined to be the most radiosensitive neuroanatomic location in adults, although one would expect the underlying radiobiological process responsible to be different from that hypothesized for the pediatric population.

The cellular basis for radiation-associated cortical thinning in the brain is not well understood. The cerebral cortex consists primarily of neuronal cells (pyramidal and granular), neuroglial cells (astrocytes, oligodendroglial), and capillaries (27). A recent study (28) suggested that vascular

endothelial cells are the primary target for radiation necrosis of the cortex. However, that study was performed using animals at a single irradiation of 25 Gy, which likely elicits a different radiobiological response than the fractionated radiation therapy used in our study. Although there has been no study to demonstrate the dose-response of vascular endothelial cells in the cortex, irradiation of rat spinal cord tissue has shown dose-dependent loss in the number of endothelial cells (27). Radiation-associated decrease in vascular density may therefore result or be involved in neuronal degeneration, which could subsequently manifest macroscopically as a decrease in cortical thickness. There are studies showing comparable decreases in vascular density in AD (29). Although the mechanism by which neurodegenerative disease and RT affect cortical vasculature may differ, the downstream influence on cortical thickness may be similar. For example, a recent study demonstrated that exposure of cultured primary neurons to radiation increased tau phosphorylation at several sites, similar to changes observed in AD (30).

The magnitude of radiation-associated cortical thinning can be better appreciated by comparison with values reported in the studies of other conditions. The thinning observed in the highest dose regions (0.3 mm) at 1 year post RT in our analysis was greater than the annual rate observed in AD patients, of 0.07 to 0.1 mm (31, 32). In the spectrum of neurodegenerative diseases (including mild cognitive impairment and other dementia subtypes), AD is typically associated with a high degree of cortical degeneration (15). By comparison, the annual rate of cortical loss observed in a control population, due to normal aging, has been reported to be on average 0.01 to 0.02 mm (33). Therefore, the magnitude of cortical thinning observed in our cohort, using well-validated cortical volumetric methods, may represent a pathologic degree of atrophy.

We found that the sensitivity of cerebral cortex to radiation-induced atrophy varies by anatomic location. One possible explanation for this phenomenon is the difference in the cellular composition of different portions of the

brain. Regional patterns of degeneration are also widely reported in neurodegenerative diseases (22). In AD, for example, cortical atrophy and neuronal cell loss were found to be most severe in the medial temporal lobe and limbic areas (34). This commonality in location of greatest cortical atrophy in AD and RT suggests that, while the underlying biological pathogenesis may differ, there may exist an inherent cellular property that makes some regions of cortex more vulnerable to injury than others. It is important to note that although the patterns of cortical atrophy post RT are comparable to those seen in AD, the prognosis for these 2 sets of patients is quite different, and this work is not intended to suggest that patients receiving high-dose RT will develop AD.

Due to the small sample size and relatively homogenous population of the cohort, the effects of chemotherapy could not be well controlled for in this study. When we grouped the cohort by standard temozolomide versus temozolomide and other adjuvant therapy, we did not observe a difference in 1-year cortical thinning. Chemotherapy has been previously associated with structural changes in cerebral white matter and cognitive function (35), suggesting that similar trends may be found with cortical thickness. It is possible that concurrent and adjuvant chemotherapy may potentiate the effects of radiation dose on cortical atrophy.

This study has other limitations. The patient sample size is small; however, the quantitative, voxel-wise analysis affords considerable power to detect changes in cortical thickness by voxel. Also, cortical thickness changes in this cohort were not tested against a control population of patients with HGG who did not receive radiation therapy. Thus, thinning of the cortex cannot be definitively attributed to brain RT as the biologic effect of HGG itself on the cellular makeup of cortical tissue is unclear. The effect of intervening surgeries or tumor recurrence also remains unclear. However, cortical changes were observed in areas of normal-appearing brain, suggesting direct tumor or surgery effect would be less likely than other explanations.

The effect of edema on cortical thickness measurements is unknown and is a limitation of imaging analysis in high-grade glioma patients. In addition, the preponderance of temporal lobe tumors will have likely resulted in a larger sample of high-dose temporal lobe voxels. This may have consequently given us greater power to detect high-dose related changes in the area. Finally, the segmentation tool used in this study (Freesurfer) was developed and validated in nontumor patients and is currently being validated for use in brain tumor populations. To help mitigate these effects, a single radiation oncologist manually checked all cortical segmentations from each of the subjects. Also, cortical scars, tumor beds and resection cavities that could potentially be mislabeled were censored.

While the present study showed dose-dependent cortical thinning with brain radiation therapy, it remains to be seen whether these changes at the voxel level have implications for neurocognitive function. Future studies of radiation-associated cortical thickness changes should incorporate

neurocognitive outcomes, and prospective studies of this kind are currently underway at our institution. This may help establish correspondence between domain-specific neurocognitive decline and radiation-associated atrophy in corresponding cortical regions.

Conclusions

Dose-dependent thinning of the cerebral cortex was observed in patients treated for HGG with fractionated partial brain radiation therapy. Cortical thinning was also found to vary by neuroanatomical location. The magnitude and regional specificity of cortical degeneration observed at 1 year post therapy parallels neurodegenerative diseases such as AD. Future studies will attempt to further characterize this effect, as well as to correlate RT-associated changes in cortical thickness with changes in neurocognitive function. This information may prove vital to developing new dose-safety guidelines for minimizing the detrimental effects of brain radiation therapy and improving patient quality of life.

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