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CNS imaging

Radiation sparing of cerebral cortex in brain tumor patients using quantitative neuroimaging

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ABSTRACT

Background and purpose: Neurocognitive decline in brain tumor patients treated with radiotherapy (RT) may be linked to cortical atrophy. We developed models to determine radiation treatment-planning objectives for cortex, which were tested on a sample population to identify the dosimetric cost of cortical sparing.

Material and methods: The relationship between the probability of cortical atrophy in fifteen high-grade glioma patients at 1-year post-RT and radiation dose was fit using logistic mixed effects modeling. Cortical sparing was implemented using two strategies: region-specific sparing using model parameters, and non-specific sparing of all normal brain tissue.

Results: A dose threshold of 28.6 Gy was found to result in a 20% probability of severe atrophy. Average cortical sparing at 30 Gy was greater for region-specific dose avoidance (4.6%) compared to non-specific (3.6%). Cortical sparing resulted in an increase in heterogeneity index of the planning target volume (PTV) with an average increase of 1.9% (region-specific) and 0.9% (non-specific).

Conclusions: We found RT doses above 28.6 Gy resulted in a greater than 20% probability of cortical atrophy. Cortical sparing can be achieved using region-specific or non-specific dose avoidance strategies at the cost of an increase in the dose heterogeneity of the PTV.

Long-term neurocognitive dysfunction is an unfortunate consequence of brain radiotherapy (RT) [1–3]. The quantitative analysis of normal tissue effects in the clinical (QUANTEC) review of RT-induced brain injury supports the need for conclusive evidence relating radiotherapy and neurocognitive decline, citing imaging changes as a potential early identifier of clinically relevant endpoints [4]. Imaging provides robust estimates of treatment-induced toxicity before detection by routine clinical methods [5]. Continued study into the effects of RT on normal brain can provide dosimetric objectives for organs-at-risk (OAR) that were not previously considered to be important.

We recently published our findings on dose-dependent cortical thinning in high-grade glioma (HGG) patients one year after fractionated partial-brain RT [6]. The magnitude of atrophy parallels one-year atrophy rates in neurodegenerative diseases, with greater effects seen in regions of the cortex treated with higher doses. In addition, recent studies suggest that radiation results in a decreased density of vascular endothelial cells [7] and an increased rate of tau protein misfolding within cultured primary neurons [8]. Vascular degeneration and abnormal protein accumulation have been reported in several forms of clinical dementia [9,10], suggesting that the neurocognitive sequelae observed in RT patients may be linked to radiation effects in cortical tissue.

Dose guidelines and planning constraints for OAR in the brain are widely available in the literature [11–13], and are built on the work by Emami et al. [14]. These parameters serve as guidelines for physicians to predict the relative safety of proposed treatment plans. However, the division of the brain into OAR remains crude with no region-specific objectives for subcortical white matter, cortical gray matter, and deep lying gray matter – all of which may have varying sensitivity to radiation dose. The brain is a highly complex organ, and tissue that is not currently considered critical may be involved in the regulation of several cognitive processes [15]. Compared with neurosurgery [16,17], radiation-planning pays little attention to the functional importance of different areas of the brain.

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In this study, we explore the feasibility of employing RT dose avoidance of cortex in patients treated for HGG using inverse-optimized planning. Dose objectives were formulated using complication probability modeling of the effect of radiation dose on changes in cortical thickness. Cortical thinning, detected using volumetric magnetic resonance imaging (MRI), was selected as an imaging biomarker of cortical damage due to its extensive application in the neuroimaging literature [18–20], including studies on Alzheimer's disease [21] and vascular dementia[22]. Cortical dose avoidance strategies were tested on the sample population to identify any dosimetric cost to imposing cortical dose constraints.

Materials and methods

Patients

The cohort consists of fifteen consecutively treated HGG patients who underwent fractionated partial brain RT at the University of California San Diego between 2011 and 2013 [6]. To meet inclusion criteria, patients must have undergone high-resolution brain MRI prior to RT and at 1-year post-RT. Among 72 HGG patients treated with partial brain RT from 2011 to 2013, 22 patients had the necessary imaging scan dates. Of these 22 patients, seven were removed due to image misregistration and severe mass-effect. The remaining 15 cases were used for this analysis. This study was approved by the institutional review board.

MR imaging

MR imaging was performed on a 3T Signa Excite HDx scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with an 8-channel head coil. The imaging protocol included pre- and post-contrast 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). All MR images were corrected for geometric distortions due to susceptibility, gradient nonlinearities, and eddy currents [23]. Patient motion between sequences was corrected using rigid-body registration algorithms developed in MATLAB (Mathworks, Natick, Massachusetts). The treatment planning CT images were rigidly co-registered to the pre-RT T1-weighted pre-contrast images [24] and the transformation matrix was used to project the radiation dose maps, to the MR images [6].

Cortical thinning

Cortical thickness was measured using Freesurfer (version 5.3; available at http://surfer.ndm.harvard.edu), as previously described [6]. Vertices corresponding to the cortical surface were grouped into 1 Gy dose bins. Surgical scar, tumor, tumor beds and resection cavities were manually censored from analyses. The 1-year percent cortical thinning for each dose bin was calculated as the vertex-averaged ratio of change in thickness (pre RT – post-RT) to the baseline value (pre-RT).

NTCP modeling of cortical atrophy

Three grades of complication were used to classify the 1-year percent cortical thinning in this study: >2% (grade 1), >3% (grade 2), and >5% (grade 3). These cutoffs were chosen to reflect the average percent thinning reported in the literature for mild cognitive impairment (MCI), Alzheimer's disease (AD), and severe Alzheimer's disease, respectively [25]. The effect of dose on the incidence of each grade of complication in the study sample was fit using a logistic mixed effects model. A patient-specific intercept and slope were tested to control for correlated data points within patients. Main effects were significant at $p < 0.05$. Estimates of main fixed effects were used to calculate R_X, the radiation dose corresponding to a X% incidence of complication, and γ, the normalized slope of the dose–response curve, using:

$$R_X = \left[-\ln\left(\frac{1}{\left(\frac{X}{100}\right)} - 1\right) - \beta_0\right] \Big/ \beta_1$$

$$\gamma = -\beta_0/4, \quad (1)$$

β_0 is the log odds at a dose of 0 Gy, β_1 is the change in the log odds per unit increase in dose. We used bootstrap resampling with 1000 samples and replacement to obtain 95% confidence intervals for the model parameters. Statistical analyses were conducted in *R* ("lme4" package, version 1.1–7).

Importing cortical segmentation into treatment planning software

Radiation structure files containing the original structure set and cortical segmentations from Freesurfer were generated. Radiation treatment files were imported into a research Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto, CA) for re-planning. Contours were visually inspected in the treatment planning software to ensure that the cortex was properly segmented. Subcortical white matter and hippocampus segmentation volumes were also imported from Freesurfer into the treatment planning system. Cortical, hippocampal, and white matter segmentations were processed to remove regions that overlapped with the planning target volume (PTV). An example of the updated structure set is shown in Supplementary Fig. 1. Doses were calculated on a $2.5 \times 2.5 \times 1.25$ mm grid using the analytic anisotropic algorithm (AAA) that includes tissue heterogeneity corrections.

Re-planning using cortical NTCP constraint

Patients were planned with and without cortical NTCP dose constraints to determine whether cortical radiation sparing is possible. Dose constraints to the target, planning treatment volume (PTV), and standardized OAR, such as brain stem and optic nerve, matched those used clinically and conform to the guidelines set by RTOG 0825 [26]. The primary objective was to maintain at least 95% volume coverage to the PTV at 100% prescription dose. All plans were matched on this objective. Cortical dose sparing was achieved by minimizing cortical volume above R_{20}, dose corresponding to 20% probability of complication, for grade 3 thinning. R_{20} for grade 3 was chosen as it represented a tradeoff between imposing too stringent an optimization requirement (such as R_{50} for grade 3), versus a lenient approach (R_{50} for grade 1), which would allow for too high a probability of cortical thinning. Cortical sparing was quantified by calculating V_Y, defined as the volumetric percentage receiving doses greater than Y Gy. Dosimetric indices such as mean dose, D_Z (defined as the minimum dose to the hottest Z% of the volume), heterogeneity index (HI, defined as $(D_2 - D_{98})/60$ Gy * 100%) were used to quantify the effect of imposing cortical dose constraints on the PTV. An alternate dose avoidance strategy of minimizing R_{20} of all normal brain was tested to determine whether cortical sparing could be achieved by non-specific avoidance of normal brain tissue.

Results

The cohort consisted of 10 males and 5 females with a median age of 60 years (range 40–77). Most patients had glioblastoma with a median pre-operative tumor size and planning target volume of 3.3 cm (range: 1.0–7.7 cm) and 162.7 cc (range: 59.8–571.3 cc),