Assessing Radiation Toxicity to the Normal Brain by Echo-Planar Spectroscopic Imaging and Diffusion Tensor Imaging

Sanjeev Chawla[1], Sumei Wang[1], Sungheon Kim[2], Sulaiman Sheriff[3], Ramesh Rengan[4], Alexander Lin[4], Elias R Melhem[1], Andrew Maudsley[3], and Harish Poptani[1]
[1]Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Radiology, New York University, New York, NY, United States, [3]Radiology, University of Miami, Miami, FL, United States, [4]Radiation Oncology, University of Pennsylvania, Philadelphia, PA, United States

Introduction: Whole brain radiation therapy (WBRT) is a common treatment strategy for patients with brain metastases. However, WBRT leads to damage of the normal brain areas as well, resulting in deterioration of cognitive functions including memory, intelligence, and attention.[1] Dentate subgranular zone of the hippocampus is considered as a site of active neurogenesis in the mammalian brain.[2] Multipotent progenitor cells located in this region are sensitive to radiation induced injury.[3] It has also been demonstrated that damage to the supratentorial white matter regions such as centrum semiovale and corpus callosum is also associated with impaired neurocognition.[4] Therefore, it is imperative to assess treatment-induced neurotoxicity in these areas such that the radiation beam can be specifically tailored to limit damage. Some early proton magnetic resonance spectroscopy (^{1}H MRS) studies have evaluated the normal brain toxicity secondary to irradiation.[5-7] However; these studies used single voxel or 2D chemical shift imaging techniques, which provides restricted spatial coverage in evaluating the brain damage. Reduced NAA due to radiation damage has also been reported after whole brain ^{1}H MRS[8]. However, this technique does not provide spatial information and hence may not be suitable for planning radiation dosage. On the other hand, echo planar spectroscopic imaging (EPSI) has recently been developed to map metabolite distribution throughout the brain with excellent spectral resolution and quality.[9,10] Using diffusion tensor imaging (DTI), several pre-clinical and clinical studies have shown damage to different regions of the normal brain parenchyma following radiation therapy.[11,12] In the present study, we sought to determine the potential of EPSI and DTI in detecting the extent of damage to normal brain parenchyma in patients irradiated with WBRT.

Methods: Four patients with brain metastases were irradiated with fractionated WBRT (total dose=35Gy) and three patients with small lung cancer underwent prophylactic cranial irradiation (PCI, total dose=25Gy). These patients were subjected to conventional magnetic resonance imaging, whole brain EPSI and DTI on a 3 Tesla MR system at two time points (pre-radiation, and one month post-irradiation). The spin-echo EPSI data were acquired with CHESS water suppression pulses and lipid inversion nulling using an inversion time of 198 ms. Typical acquisition parameters were: TR/TE=1710/70ms, 50x50x18 phase encoding steps, excitation angle=73°, voxel size=5.6x5.6x10mm^3, FOV=280x280x180mm^3. The sequence also included an interleaved water reference acquisition scan. DTI was acquired using a single-shot, spin-echo EPI sequence using 30 non-collinear/non-coplanar directions (b = 1000s/mm^2). Additional parameters were: TR/TE=5000ms/86ms, NEX = 3, FOV = 220x220 mm^2, slice thickness= 3.0 mm, voxel dimension 1.7x1.7x3.0 mm^3. Automated MIDAS tool was used to generate maps of NAA, Cr and Cho. Post processing of the DTI data included application of algorithms to reduce eddy-current and/or motion-induced artifacts and generation of mean diffusivity (MD) and fractional anisotropy (FA) maps. Parametric maps of NAA, Cr, Cho, MD and FA were co-registered to post-contrast T1 weighted and FLAIR images using in house developed algorithms. Regions of interest (20 pixels) were drawn on different normal appearing gray-matter (hippocampus, thalamus, motor cortex, cingulate gyrus, and basal ganglia) and white-matter (periventricular frontal and occipital white matter, centrum semiovale, and corpus callosum,) regions as these locations are sensitive to radiation induced injury and associated with cognitive, behavior and motor activities. The parameters from each region were compared between baseline and one-month post-irradiation periods to assess acute effects of radiation (n=7).

Results and Discussion: Co-registered parametric maps and images from a patient are shown in Fig 1. Variations in the MD, FA, NAA/Cr and Cho/Cr values from the right hippocampus and centrum semiovale region are presented in Fig 2. Significantly increased MD (p=0.013), Cho/Cr (p=0.022) and a trend towards decreased NAA/Cr (p=0.081) and FA (p=0.69) were observed in the right hippocampus post-irradiation. Significant decrease in FA (p=0.042) was also observed from the right centrum semiovale after radiation therapy. Additionally, significant increase in MD (p=0.047) and Cho/Cr (p=0.020) were observed from genu of corpus callosum. Similar but non-significant (p>0.05) findings were observed from splenium of corpus callosum and thalamus. Other regions of the brain did not demonstrate any consistent findings. Increased Cho/Cr after radiation may be due to demyelination and axonal degeneration secondary to radiation induced injury.[5-7] Variations in MD and FA values might result from complex pathological events characterized by apoptosis of myelin producing oligodendrocytes, neurodegeneration, astrogliosis fibrosis and vascular damage that occur in normal gray and white matter regions following radiation therapy. Histopathological studies from the irradiated rat brains confirm these diffuse changes .[11] Recent evidences suggests that sparing the hippocampus, via helical tomotherapy and linear accelerator based intensity modulated radiotherapy techniques[13] may prevent neurocognitive decline. Our preliminary findings suggest that EPSI and DTI may be used to assess radiation toxicity in normal brain. Future studies comparing the imaging findings with neuro-cognitive function may aid in establishing these imaging parameters as markers for neuro-toxicity and may aid in planning radiation therapy.

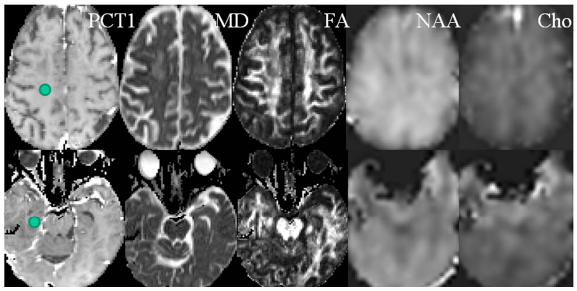

Fig 1. Co-registered post-contrast T1 and parametric DTI and EPSI maps through the centrum semiovale (upper-panel) and hippocampal regions (lower-panel) of a patient. ROIs from hippocampus and centrum semiovale are shown in green color.

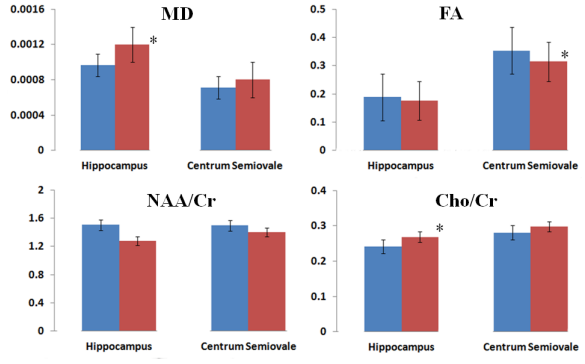

Fig2. Bar diagrams showing variations in mean ± standard error values of different parameters from hippocampus and centrum semiovale between baseline (blue) and post-radiation (red). * indicates significant difference.

References: 1. Davey P, et al. CNS Drugs. 16:325-38, 2002, 2. Gage FH. Science. 287:1433-8, 2000, 3. Hellstrom NA, et al. Stem Cells. 27:634-41, 2009, 4. Khong PL, et al. Am J Neuroradiol. 24:734-40, 2003, 5. Kaminaga T, et al. J Comput Assist Tomogr. 29:293-7, 2005, 6. Estève F, et al. Int J Radiat Oncol Biol Phys. 40:279-86, 1998. 7. Chernov MF, et al. Brain Tumor Pathol. 21:63-7,2004. 8. Movsas B, et al. Radiology.;22:327-31, 2001 9. Ebel A, et al. Magn Reson Med 46:1072-78; 2001, 10. Maudsley AA, et al. Magn Reson Med. 61:548-59;2009, 11. Wang S, et al. Cancer Res. 69:1190-8, 2009, 12. Kitahara S, et al. Am J Neuroradiol.26:2200-6, 2005. 13. Gondi V, et al. Int J Radiat Oncol Biol Phys. 78:1244-52, 2010.