Evaluation of Radiation Lung Injury from Tomotherapy Using Hyperpolarized Helium-3 Diffusion MRI

J. Mata[1], J. Cai[2], K. Sheng[2], K. Ruppert[3,4], P. Read[2], K. Hagspiel[1], T. Altes[3,5], J. Brookeman[1], and J. Mugler III[1]

[1]Radiology, University of Virginia, Charlottesville, Virginia, United States, [2]Radiation Oncology, University of Virginia, Charlottesville, Virginia, United States, [3]University of Pennsylvania, Philadelphia, Pennsylvania, United States, [4]Radiology, Children's Hospital of Philadelphia, Philadelphia, Virginia, United States, [5]Radiology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States

Introduction: Hyperpolarized He-3 diffusion MRI can detect changes in the pulmonary microstructure that occur in emphysema (1-5). He-3 diffusion MRI may also be valuable for other applications such as longitudinal assessment of changes in the pulmonary microstructure that occur in patients undergoing radiation therapy for lung cancer. In this study, a rabbit model was used to evaluate the effects of the new Tomotherapy radiation delivery technique on the pulmonary microstructure. He-3 diffusion MRI and CT were performed in-vivo at 4 week intervals following stereotactic image-guided irradiation of the lung and compared with histology obtained at week 16 post-radiation.

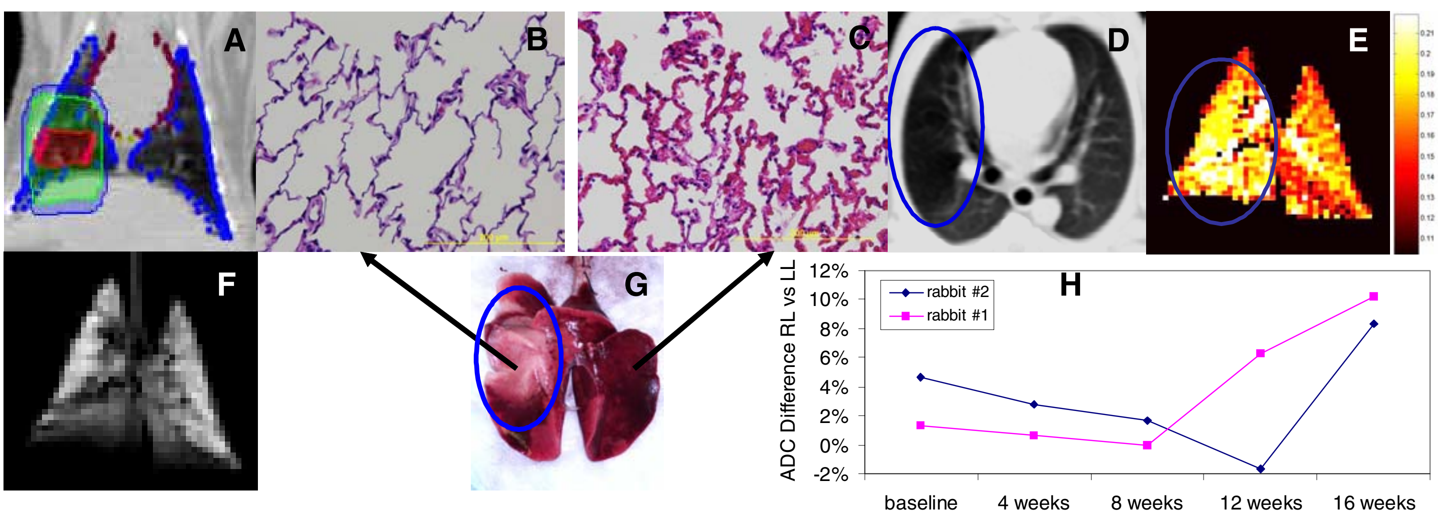
Methods and Materials: A 1.6 cc target volume in the mid-section of the right lung was irradiated with three fractions of 20 Gy each, for a total local dose of 60 Gy (Figure A, red area). Irradiation was performed in two New-Zealand rabbits using a Hi-Art Helical Tomotherapy unit (Helical TomoTherapy, Madison, WI); the three fractions were administrated within one week. He-3 diffusion MRI (1.5T Sonata; Siemens, Malvern, PA) of each rabbit was performed at baseline and at 4, 8, 12 and 16 weeks post-radiation (Figures E and H). A FLASH-based sequence with bipolar diffusion-sensitization gradients was used with a b-value pair of 0 and 4 s/cm^2 for measurement of the apparent diffusion coefficient (ADC). Three contiguous coronal slices with a voxel size of 2.2 x 2.2 x 20 mm covered the entire lung. CT images (PQ5000; Philips, Bothell, WA) were obtained at baseline and at 6, 10 and 14 weeks post radiation (Figure D). The CT images had a voxel size of 0.49 x 0.49 x 2.0 mm. Perfusion MRI with a gadolinium based contrast agent was performed at the same time points as the He-3 ADC measurements. Immediately after the MRI scan at week 16, the rabbits were euthanized, their lungs harvested in block (Figure G) and fixed in a 10% formalin solution. Six tissue samples were obtained from each lung (1 upper lobe, 2 middle posterior, 2 middle anterior and 1 lower lobe) for a total of 12 samples per animal. Each tissue sample was processed, cut in 5µm thick slices, stained with H&E and photographed with a high-resolution digital camera (Figures B & C). Mean chord lengths of the alveolar spaces were calculated using the method described by Lum et al (6).

Results: Nearly identical changes were observed in the lungs of both rabbits at corresponding time points (Figure H). He-3 ventilation (b = 0) images of the lungs showed no marked changes over the 16-week period (Figure F). After 12 weeks, a regional increase of the ADC values became evident in the irradiated region of the right lung of rabbit #1 (Figure H). At week 16, the difference between the mean ADC of the mid-coronal slice of the right lung and the corresponding region of the left lung was 10.2% for rabbit #1 (Figure E & H) and 8.3% for rabbit #2 (Figure H). At week 14, a noticeable decrease in the CT signal intensity developed in the irradiated region of the right lung compared to the corresponding region in the left lung (Figure D). At this time point, the attenuation difference was 15.6% and 9.7% for rabbits #1 and 2, respectively. The irradiated volume could be easily identified at necropsy since it exhibited a different texture and white color (Figure G, blue oval). Histological slides from the irradiated region showed a reduction in the number of red blood cells, and thinning and destruction of the parenchymal walls (Figures B & C). The mean chord lengths for the irradiated region of the right lung and the corresponding non-irradiated region of the left lung were 90µm and 65µm, respectively, for rabbit #1 (Figures B & C) and 81µm and 65µm for rabbit #2. A decrease in regional perfusion, which corresponded to the irradiated area, was observed after week 8 (results not shown).

Discussion: He-3 diffusion MRI detected regional microstructural changes in the lung parenchyma due to radiation injury that corresponded well with the changes observed on CT images and with histology (blue ovals on Figures D, E and G). The percentage changes observed at the final time point were greater with CT than with He-3 ADC, which was not surprising since changes in the CT attenuation can be caused by structural changes, as well as by the decrease in blood volume observed in the irradiated region, while He-3 ADC is believed to be specific to the microstructural changes only. These results suggest that He-3 diffusion MRI can provide information on early changes that occur in the lung microstructure with radiation treatment, and thus He-3 diffusion MRI may be a valuable tool for the longitudinal follow-up of patients that undergo radiation lung therapy. Additional rabbits are undergoing radiation therapy and serial MRI and CT imaging as part of this project.

References: 1. Saam B et al. Magn. Reson. Med. 2000; 44:174-179.
2. Salerno M et al. Radiology 2002; 222:252-260.
3. Yablonskiy D et al. PNAS 2002, 99(5); 3111-3116.
4. Chen XJ et al. Magn. Reson. Med. 2000; 42:721-728.
5. Peces-Barba G et al. European Resp. J. 2003; 22: 14-29.
6. Lum H, Huang I, Mitzner W. J Appl Physiol 1990;68(6):2280-2286.

Acknowledgements: This work was supported by NIH grant R01 EB003202, CTRF grant IN2002-01 and Siemens Medical Solutions.



A: CT scan at baseline showing the Tomotherapy treatment plan. The red area was irradiated with 3 fractions of 20 Gy each (full dose); the green area corresponds to 50% of the full dose. **B:** Histological image of a tissue sample from the irradiated region of the right lung. **C:** Histological image of a tissue sample from the non-irradiated left lung. **D:** CT scan at 14 weeks. Note the region of reduced attenuation in the blue oval. **E:** ADC map from a mid-coronal slice at 16 weeks. Note the area of higher ADC values in the blue oval. **F:** He-3 ventilation (b=0) image at 16 weeks. **G:** Necropsy photo of the fixed lungs. Note the white region of tissue in the blue oval, which matched the location of the irradiated area. **H:** ADC difference between right lung vs. left lung for each animal at different time points. All images are from the same rabbit (#1).