Time-resolved MRA Assessment of Pulmonary Toxicity in a Rabbit Model of Stereotactic Lung Radiation Therapy: Preliminary Results on the Efficacy of a Radioprotector

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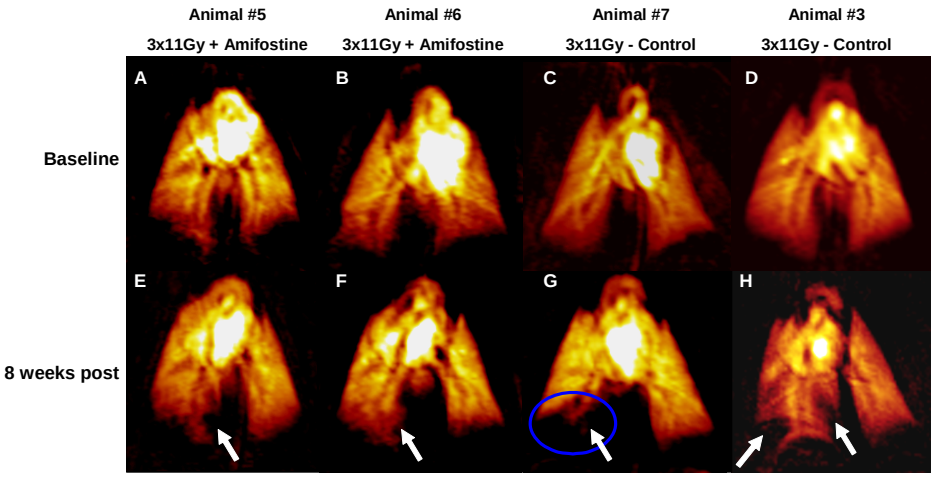
Introduction: Radiation-induced pulmonary symptoms occur in approximately 20% of patients who receive radiation treatment for cancer of the lung or breast. Presently, there is no standard clinical test available to predict the likelihood of symptomatic toxicity or to assess the extent of radiation-induced lung injury early after treatment. However, early detection might allow for preventative therapy to reduce toxicity and, if early lung damage could be detected during radiotherapy, this would allow the radiation oncologist to adapt the plan prior to extensive damage. We have shown that time-resolved MRA can detect early changes in lung physiology due to radiation-induced injury two months ahead of high-resolution computed tomography (1,2).

Stereotactic radiation therapy with high doses of conformal radiation is being used clinically to treat early lung cancer with high rates of local control. However, this can lead to high rates of local radiation injury. In this work we report the use of time-resolved MRA to assess the efficacy of a radioprotector in limiting radiation toxicity in a rabbit model of stereotactic-radiation pulmonary injury.

Methods & Materials: Seven New Zealand white rabbits were used. Of these, four received different radiation doses in three equal fractions of 7 Gy, 9 Gy, 11Gy or 13 Gy within a week, and were intended to determine the minimum radiation dose capable of producing detectable injury using our time-resolved MRA technique. Effects were measurable by MRA at the dose of 3 x 9 Gy fractions. We irradiated the remaining three rabbits with 3 x 11Gy, which was 6 Gy above the minimum dose. Two of these three animals received 50 mg/Kg of the radioprotector (Amifostine, MedImmune, Gaithersburg, MD), through an I.V., 20 minutes before each stereotactic radiation dose to the lower lobe of the right lung, delivered on a TomoTherapy Hi-Art scanner (TomoTherapy Inc, Madison, WI). Time-resolved MRA was performed using a 1.5-Tesla clinical scanner (Sonata, Siemens Medical Solutions, Malvern, PA) at baseline, 4 and 8 weeks post-radiation treatment. A 3D FLASH pulse sequence was used with 6 slices per slab; in-plane resolution, 1.4 x 1.1mm^2; slice thickness, 12 mm; flip angle = 25°; matrix, 192 x 80; TR/TE, 3.3/1.2 ms; and bandwidth, 400 Hz/pixel. Fifty consecutive measurements of the volume were acquired, requiring a total time of 32 seconds. Two seconds after the beginning of the pulse sequence, a 3cc I.V. injection of a gadolinium chelate was delivered through an ear vein. Each image was subtracted automatically from the corresponding image acquired during the first measurement. Maximum Intensity Projection (MIP) images of the acquisition time were generated for perfusion visualization and evaluation. Perfusion changes were assessed by calculating the area of perfused tissue in the MIP images.

Results: The mean baseline areas of perfused tissue were 11.3±1.4 cm^2 (mean±STD) for the right lung (RL) and 8.6±1.3 cm^2 for the left lung (LL). At 4 weeks post treatment, the two control rabbits (3 x 11Gy and no radioprotector) had mean perfused areas of 8.8±3.0 cm^2 for the RL and 9.7±0.2 cm^2 for the LL. At the same time point, the two animals that received the same radiation dose plus the radioprotector had mean perfused areas of 11.9±1.8 cm^2 for RL and 10.2±0.3 cm^2 for the LL. At 8 weeks post treatment, the control rabbits had obvious perfusion defects in the irradiated zone, with mean perfused areas of 7.5±2.3 cm^2 (RL) and 8.7±0.1 cm^2 (LL). At this time point the animals that received the radioprotector had mean values of 10.4±0.8 cm^2 (RL) and 9.4±0.6 cm^2 (LL).

Discussion: In our rabbit model, time-resolved MRA detected radiation-induced pulmonary injury 4 weeks post treatment, and was able to detect reduced early treatment toxicity as a result of a clinically used radioprotector. To our knowledge, this is the first report of reduced pulmonary toxicity by a radioprotector for stereotactic radiation therapy. Longer follow-up of the treated animals and a higher number of subjects are required to confirm these initial promising results.



References: **1)** Cai J, Mata J, Sheng K, Read P, Ruppert K, Altes T, et al. Proc. 48th ASTRO conference, Philadelphia Nov. 2006, S20-S21. **2)** Mata J**,** Cai J, Sheng K, Ruppert K, Read P, Hagspiel K, et al. Proc.15th I.S.M.R.M., Berlin, Germany, May 2007.

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Figure 1 – Images A, B, E and F are from the two rabbits that received 3 x 11 Gy of radiation plus the radioprotector Amifostine. Images C, D, G and H are from the two rabbits that received 3 x 11 Gy of radiation but no radioprotector. The blue oval shows the perfusion deficit that corresponds to the irradiated area in control animal #7. White arrows indicate the most significant perfusion deficits seen in each animal.