Early detection of radiation response in non-Hodgkin's lymphoma xenografts

S. C. Lee[1], T. Jenkins[2], S. Pickup[1], H. Poptani[1], E. J. Delikatny[1], and J. D. Glickson[1]

[1]Dept of Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Dept of Radiation Oncology, University of Pennsylvania, Philadelphia, PA, United States

INTRODUCTION

Non-invasive detection of early treatment response is very important as it can provide information of response to specific drugs/treatment and tailor-fit treatment for individual patients. Methods that are currently available have limited sensitivity in detecting early response. While ^{31}P MRS has shown promise as a pre-treatment prognostic index for the non-responding non-Hodgkin's lymphoma (NHL) patients[1], its use is limited to large superficial tumors. ^{1}H NMR has 15 fold higher sensitivity than ^{31}P NMR and thus is applicable to much smaller tumors. Previously we have shown in a human NHL xenograft model[2] that lactate detected by in vivo MRS can be used as a very early marker of response to CHOP chemotherapy. As radiation therapy is also commonly used as a therapeutic regimen in NHL, we tested in vivo MRS and MRI methods to determine if the MR indices can be used as early markers of response to radiation therapy in an NHL xenograft.

METHODS

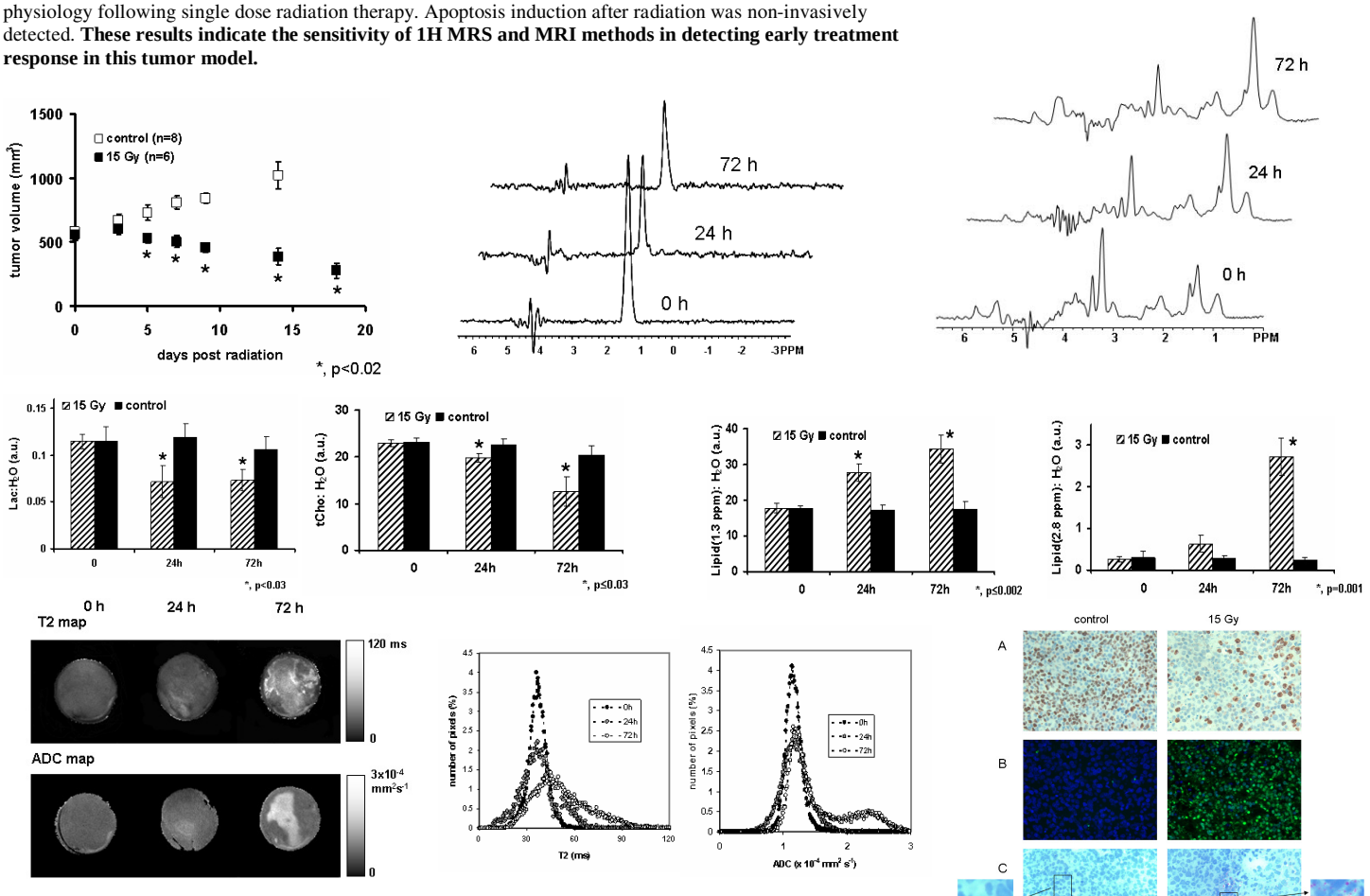
Xenografts were prepared as previously described[2]. WSU-DLCL2 cells were implanted in nude mice. *In vivo* MRS and MRI measurements were performed on a 9.4 T/8.9 cm Varian vertical bore instrument and a home-built loop-gap resonator before and 24 hr and 72 hr after radiation treatment. Lactate was detected with a newly developed Hadamard slice selected SelMQC sequence[3] utilizing 2 slices. For signal normalization, we employed a Hadamard slice spin echo sequence to detect water from the same slice used for lactate detection. ^{1}H NMR spectra of choline and lipid were achieved using the STEAM sequence. T2-maps were generated using a spin echo sequence and TE values from 20 to 80 ms, while diffusion maps were acquired using diffusion weighting by the trace of the diffusion tensor[4] and b-values ranging from 0 to 6400 s/mm^2. For radiation, Phillips RT250 x-ray irradiator was used. Mice were shielded with lead except for the tumor region and irradiated at 3.4 Gy/min up to 15 Gy.

RESULTS

A single bolus of 15 Gy radiation caused tumor volume regression. Lac:H_2O decreased just 24 h post-radiation as did tCho:H_2O. The 1.3 ppm peak (lipid/Lac) of the STEAM spectrum increased after radiation. To see if this increase was associated with apoptosis, we analyzed the 2.8 ppm peak of unsaturated lipid, which also showed significant increase after radiation. Ki67 staining and oil red-O staining confirmed changes in proliferation and apoptosis in radiation-treated tumors. T2 and ADC maps showed heterogeneous response in the tumor, however the changes in ADC (p=0.02) were much greater than T2 changes.

DISCUSSION

The WSU-DLCL2 NHL xenograft model was very responsive to radiation treatment. In vivo MRS and MRI detected early changes in tumor metabolism and physiology following single dose radiation therapy. Apoptosis induction after radiation was non-invasively detected. **These results indicate the sensitivity of 1H MRS and MRI methods in detecting early treatment response in this tumor model.**



Figures Left to right: Tumor volume, HDMD-SelMQC spectra, STEAM spectra, Lac:H_2O, tCho:H_2O, Lipid(1.3, 2.8ppm):H_2O, T_2 and ADC maps, histograms of T2 and ADC, histology (Ki67, TUNEL, oil red-O).

References [1]Arias-Mendoza et al., *Acad Radiol* 11:368, 2004. [2]Lee et al., *NMR Biomed* 21:723, 2008. [3]Pickup et al., *MRM* 60:299, 2008. [4]Mori and van Zijl. *MRM* 33:41, 1995.