

Hyperpolarized ^{13}C Biomarkers of Response to Prostate Cancer Radiation Therapy

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Introduction: Prior ^{13}C MR imaging studies of hyperpolarized (HP) $[1-^{13}\text{C}]$ pyruvate and ^{13}C urea in the TRAMP model of prostate cancer have demonstrated the ability to monitor changes in metabolism and perfusion that are predictive of therapeutic response after androgen deprivation therapy (ADT) (1, 2). Like ADT, radiation therapy represents another very common treatment of prostate cancer that could clinically benefit from an early assessment of therapeutic efficacy. After radiation therapy, serum prostate specific antigen (PSA) levels take years to nadir and often never are reduced to undetectable levels, as after radical prostatectomy. The goal of this work was to investigate serial changes in perfusion (HP urea) and HP pyruvate metabolism in TRAMP tumors following exposure to increasing doses of radiation therapy in order to better understand the potential clinical value of HP ^{13}C MR for monitoring prostate cancer radiation therapy.

Methods: Three TRAMP tumors (mean tumor size = 4.3 ± 1 cc) were exposed to varying doses of radiation by placing a single radioactive seed source using a Nucletron microSelectron-HDR applicator on the surface of the tumor for 2-5 min. dwell periods. This resulted in doses of 14 Gy (close to the seed) to 5 Gy (deeper within the tumor) (3), and a representative dose distribution diagram overlaid on the CT axial image of a TRAMP mouse is shown in Fig. 1. Imaging studies were performed on a 14T,

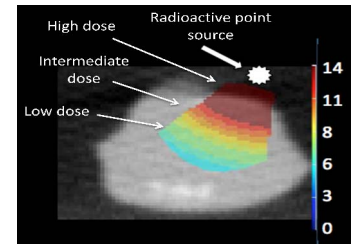


Fig 1: Radiation dose distribution (from 14Gy to 0 Gy) overlaying axial CT image of a TRAMP mouse.

600WB micro-imaging spectrometer equipped with 55mm, 100G/cm gradients (Varian Inc). A 10mm broadband (H-X) probe was used for signal detection. An echo planar imaging (EPI) based pulse sequence was constructed using frequency specific pulses to generate a 3D image for each metabolite with an acquisition time of approximately 180ms (4). $[1-^{13}\text{C}]$ pyruvic acid (14.2M) and ^{13}C Urea (6.4M) were prepared using the trityl radical OX063 and co-polarized using a HyperSense DNP polarizer (Oxford Instruments (1,2). MR and CT

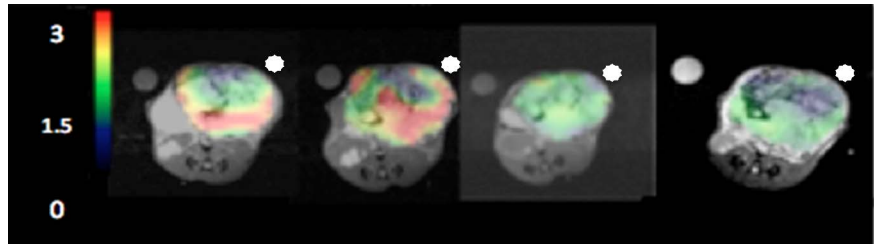


Fig 2: Corresponding overlaid lac/pyr images on corresponding axial T2 weighted MR images, from baseline, and 1, 4, and 8 days after.

image co-registration was done using an external fiducial landmark as well as internal anatomic landmarks using custom in-house software. For spectroscopic voxels within the high (14-12 Gy), intermediate (12-7 Gy) and low (5-7 Gy) dose regions of interest the absolute signal intensities of lactate, HP pyruvate and alanine were normalized to the maximum total HP carbon (lac+pyr+ala) signal from the kidney, and HP urea was normalized to maximum HP urea in the kidney. Additionally, tumor HP lactate-to-pyruvate (pyr/lac) ratios were calculated and images generated and overlaid on the corresponding T_2 weighted images. Changes in HP biomarkers from baseline were analyzed using a student t-test.

Results: Fig. 2 shows representative lac/pyr ratio images overlaid on T_2 weighted images of a late stage TRAMP tumor at baseline, 1, 4, and 8 days after radiation therapy. There are visually clear dose dependent changes in the lac/pyr ratio over time. Fig. 3 provides a quantitative summary of the changes from baseline in HP urea and HP lac/pyr ratios from high, intermediate and low dose regions of tumor at 1 to 8 days after treatment. HP urea and total HP carbon significantly decreased in tumor regions receiving both high ($p < 0.01$; and 0.05, respectively) and intermediate doses ($p < 0.01$, for both) by 1 day after treatment. Whereas HP urea and total HP carbon initially increased in the low dose regions and then decreased. For all three doses, the lac/pyr ratios significantly decreased ($p < 0.01$ for all doses) by 8 days following treatment.

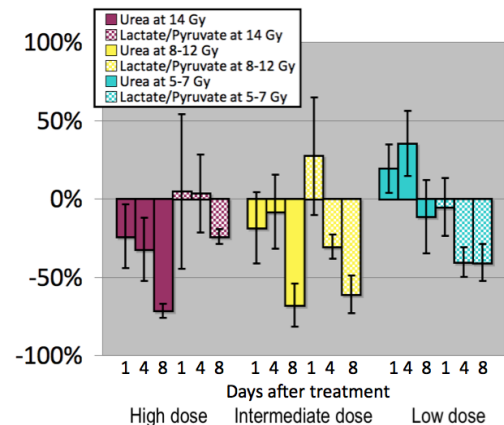


Fig 3: Mean percentage changes from baseline values of urea (solid) and lac/pyr (checker board pattern) for 1, 4 and 8 days after radiation therapy in ROIs within the tumor receiving high (plum), intermediate (yellow) and low doses (turquoise) of radiation.

Discussion: Significant, dose-dependent decreases in perfusion and pyruvate-to-lactate flux were observed after radiation therapy. Ongoing serial radiation studies of TRAMP tumors are investigating the relationship between perfusion and metabolic changes and therapeutic efficacy.

Reference:

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