Imaging of tumor metabolism: a longitudinal study of tumor response to therapies using hyperpolarized [1-^{13}C]pyruvate.

Heeseung Lim[1], Kundan Thind[1], Timothy Pok Chi Yeung[1,2], Francisco M Martinez-Santiesteban[1], Eugene Wong[2,3], Paula J Foster[1,4], and Timothy J Scholl[1,4]
[1]Medical Biophysics, Western University, London, Ontario, Canada, [2]London Regional Cancer Program, London Health Sciences Centre, London, Ontario, Canada, [3]Physics and Astronomy, Western University, London, Ontario, Canada, [4]Robarts Research Institute, Western University, London, Ontario, Canada

Target audience Hyperpolarized ^{13}C MRSI, MRI, Brain cancer, Therapies for cancer, Metabolic imaging and Molecular imaging.

Purpose: To image and quantify longitudinal metabolic changes of brain cancer in response to therapies, using hyperpolarized [1-^{13}C]pyruvate with ^{13}C magnetic resonance spectroscopy imaging.

Methods: The brains of 18 Wistar rats were implanted with C6 Glioma cells. Ten days after surgery, rats were divided into four groups; no therapy, radiotherapy, chemotherapy, combined radio- and chemotherapy. All animals were imaged with ^{1}H MRI and hyperpolarized ^{13}C MRSI on days 7, 12, 15, 18, 21, 24 (experimental end point) after the surgery. During ^{1}H MRI, pre & post-Gd T_1-weighted, T_2-weighted and DSC images of the brain were acquired. For hyperpolarized ^{13}C MRSI, [1-^{13}C]pyruvic acid was hyperpolized by a Hypersense DNP (1) (Oxford instruments) and injected through a tail vein catheter. 2D ^{13}C spectra of the rat brains were acquired using FID-CSI. All images and spectroscopy were acquired using a custom-built switch-tuned ^{13}C-^{1}H RF coil to achieve high SNR and facilitate image registration (2).

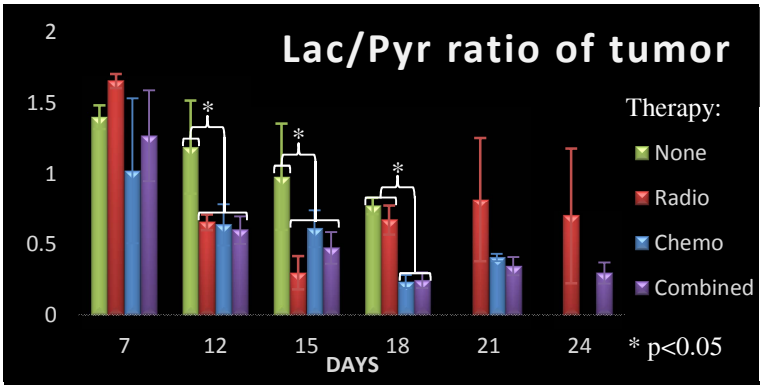

Figure 1. Longitudinal Lac/Pyr ratio of tumors for 4 different groups. Animals receiving only chemotherapy or no therapy did not survive to day 24.

Results: For all animals receiving therapy, their tumors showed significant ($p<0.05$) early response measured as a decrease of the lactate to pyruvate ratio (lac/pyr). Some animals in the radiotherapy group showed a subsequent increase in lac/pyr at later time points. The chemotherapy group didn't survive as long as the radiotherapy group despite that the lac/pyr was significantly ($p<0.05$) suppressed. The combined therapy group showed the best survivability and a low lac/pyr was maintained post therapy.

Discussion: Hyperpolarized ^{13}C pyruvate imaging has the capability of detecting changes in the tumor metabolism related to glycolysis in the cell's cytoplasm. As shown in Figure 1, tumors showed significant metabolic changes as early as two days after therapy. Commensurate changes in tumour volume were not readily noticeable with proton imaging (Figure 2). As shown in Figure 2, lactate and pyruvate can measure longitudinal changes in the tumor's metabolism in response to therapy. ^{13}C MRSI indicated the likelihood of tumor reoccurrence for the radiotherapy-only cohort based on an increase in lac/pyr later in the longitudinal study, which was not detectable by measurements of tumor volume from ^{1}H MRI.

Conclusion: This work demonstrated that the use of hyperpolarized [1-^{13}C] pyruvate to probe real time tumor metabolism can provide *longitudinal non-invasive biomarkers* for therapeutic response to therapy. Also, it has provided strong evidence of detection of early metabolic changes as a result of tumor response to radiotherapy and chemotherapy. In the future, we will compare these methods with clinical applications such as DSC, DWI and histology.

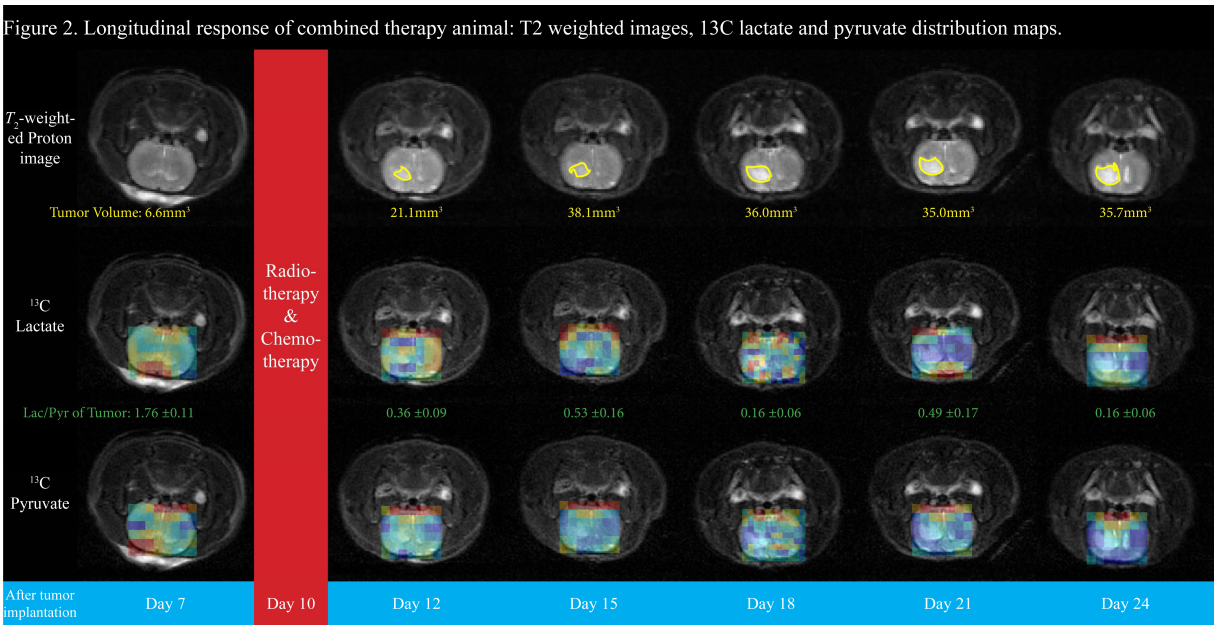

Figure 2. Longitudinal response of combined therapy animal: T2 weighted images, 13C lactate and pyruvate distribution maps.

References

1. Chattergoon N, Martinez-Santiesteban F, Handler WB, Ardenkjaer-Larsen JH, Scholl TJ. Field dependence of T1 for hyperpolarized [1-^{13}C]pyruvate. Contrast media & molecular imaging 2013;8(1):57-62.

2. Lim H, Thind K, Martinez-Santiesteban F, Scholl TJ. Construction and Evaluation of a Switch-Tuned ^{13}C - ^{1}H Birdcage Radiofrequency Coil for Imaging the Metabolism of Hyperpolarized ^{13}C-Enriched Compounds J Magn Reson Imaging. Accepted, ready for publication .