Imaging biomarkers: a comparison of hyperpolarized 13C MRS and diffusion-weighted MRI

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Introduction Development of novel targeted anti-cancer therapies is highly dependent on qualified in-vivo biomarkers for the therapeutic response. Small molecule drug FX11 that inhibits the lactate dehydrogenase A (LDHA) alters cellular energy metabolism, and reduces the tumor progression[1]. This procedure could be captured in-vivo by monitoring the metabolic conversion rate of ^{13}C-labled substrates using dynamic nuclear polarization (DNP)[2]. This measurement could be compared with the most common imaging response biomarker: diffusion-weighted MRI (DW-MRI), a measure of tumor cellularity. The apparent diffusion coefficient (ADC) of tumors calculated from DW-MRI has been shown to be valuable for predicting early response to therapies in a variety of cancers[3]. The purpose of this study is to demonstrate the dynamics of metabolic conversion from ^{13}C pyruvate to ^{13}C lactate with FX11 treatment and compare the ability of two response biomarkers: hyperpolarized (HP) ^{13}C-labeled magnetic resonance spectroscopy (MRS) and DW-MRI in the drug sensitive tumor Panc253.

Methods Sixteen animals propagated as subcutaneous tumors separated into two groups that are sensitive (Panc253) and control to FX11. The tumors were treated with FX11 four days with doses of 42 µg daily through i.p. injection, whereas the control group received DMSO. ^{13}C pyruvic acid mixed with 15mM trityl radical (OX63) was hyperpolarized by an Oxford DNP Polarizer, HyperSense®. The polarized substrate was quickly dissolved in Tris/EDTA, NACl and NaOH at 37°C, yielding 80 mM pyruvate at neutral pH. A jugular catheter was surgically implanted into the animal's vessel. Each animal was placed inside a dual band 1H-^{13}C volume coil in a Agilent ASR 310 7T small animal imaging system. After administration of 0.35 ml of hyperpolarized solution, ^{13}C spectra were acquired with a TR of 1000 ms and flip angle 9° for 5 minutes. DW-MRI was performed before the injection with 10 slices covering the whole tumor. Four b-values (50, 500, 800, 1000 s/mm^2) were used to generate the ADC maps. Both ^{13}C spectra and DW-MRI were measured pre- and post- (4 days) treatment for both drug and control groups for comparison.

Results ^{13}C spectra for pyruvate, lactate and alanine were observed following the administration of hyperpolarized solution. The lactate vs. pyruvate ratio (Lac/Py) was calculated to represent the dynamic conversion. It was shown that Lac/Py was significantly lower ($p<0.01$) in the drug-treatment group compared to the control group suggesting a response. ADC values within tumor ROIs were normalized and estimated using the within-subject correlation coefficient (wCV). The treatment group has significantly increased ADCs ($p<0.05$) compared to the control group (Figure 1). This is consistent with the fact that LDHA inhibition caused cell death creating more cellular space for water molecule movement, therefore increasing the ADC values. Furthermore, HP ^{13}C MRS has a higher area under curve (AUC) from the receiver operating characteristic (ROC) plot. This indicates a better ability to identify the response (Figure 2).

Conclusions Hyperpolarized MRS using ^{13}C pyruvate is a novel biomarker of metabolic activity and response to treatment. This result was further confirmed by DW-MRI. Both biomarkers are clear indicators of response; however, hyperpolarized ^{13}C MRS demonstrates higher sensitivity and accuracy as a potential clinical imaging biomarker.

Reference:

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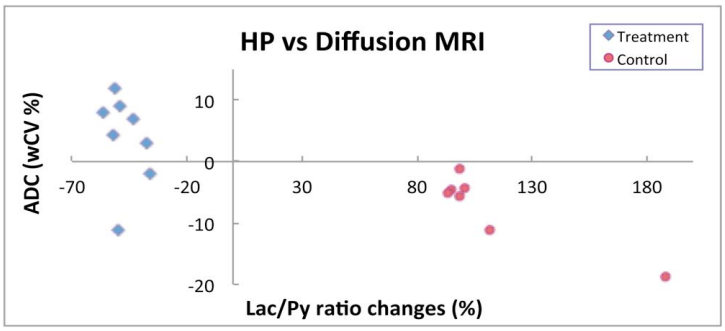

Figure 1. Lac/Py ratio measured from hyperpolarized ^{13}C MRS was present as a percentage of change for the X-axis. The treatment group (blue diamond) showed reduced rate of flux (negative) while control group (red circle) had increased rate of flux (positive). ADC value from tumor ROIs of DW-MRI was present as wCV for the Y-axis. The treatment group (blue diamond) had increased ADC values as a result of positive wCV while the control group (red circle) had decreased ADC values as a result of negative wCV.

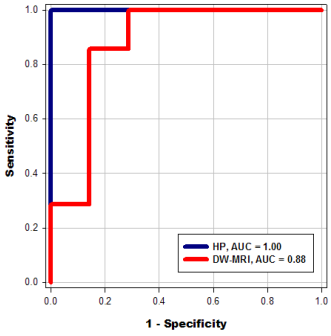

Figure 2. ROC curves were used to compare the sensitivity and specificity of two imaging biomarkers. In this study, HP ^{13}C MRS has highest AUC of 1.00, DW-MRI has slightly lower AUC of 0.88.