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## Hyperpolarized 1-<sup>13</sup>C-Pyruvate Magnetic Resonance Imaging Detects an Early Metabolic Response to Androgen Ablation Therapy in Prostate Cancer

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Hyperpolarized (HP) <sup>13</sup>C magnetic resonance spectroscopic imaging (MRSI) is a novel imaging technique that allows rapid and noninvasive monitoring of dynamic pathway-specific metabolic and physiologic processes [1] with unprecedented gain in sensitivity (10 000–200 000 fold increase) for imaging of <sup>13</sup>C-labeled biomolecules that are endogenous, nontoxic, and nonradioactive [2,3]. We previously reported the first-in-human phase 1 clinical study of HP [<sup>13</sup>C]-pyruvate MRSI in patients with prostate cancer on active surveillance, and confirmed the feasibility of capturing regions of accelerated HP pyruvate-to-lactate flux in high-grade versus low-grade cancer versus benign tissue [4].

Here we describe the first results demonstrating the metabolic response to androgen deprivation therapy (ADT) using HP [<sup>13</sup>C]-pyruvate MRSI. The patient presented with serum prostate-specific antigen (PSA) of 25.2 ng/ml and Gleason 4 + 5 prostate adenocarcinoma on biopsy. Cross-sectional imaging demonstrated metastases within the pelvic nodes and osseous structures. Baseline multi-parametric (mp) <sup>1</sup>H MRI of the prostate (anatomic imaging, diffusion-weighted imaging [DWI], dynamic contrast-enhanced [DCE] imaging, and 3D <sup>1</sup>H MRSI) with HP [<sup>13</sup>C]-pyruvate revealed a bulky tumor involving the left apex, mid gland, and base peripheral and transition zones, and right apex, mid gland, and base peripheral zone, measuring 4.5 × 1.5 × 5.1 cm<sup>3</sup>. T2-weighted MRI showed a well-defined focus of low signal intensity (T2 score 5/5; Fig. 1A). The lesion also had marked restricted diffusion (DWI score 5/5; apparent diffusion coefficient [ADC] 930) and was DCE-positive, with increased uptake and washout of contrast agent, and MRSI-positive, with elevated choline and reduced citrate on <sup>1</sup>H MRSI. The overall Prostate Imaging-Reporting and Data System v.2 score was 5.

Figure 1A shows the HP <sup>13</sup>C spectral array for the baseline scan, with markedly elevated lactate peaks within tumor-containing voxels. A color scale map of dynamic pyruvate-to-lactate metabolic flux ( $k_{PL}$ ) values likewise shows markedly elevated flux levels in the tumor compared to adjacent normal tissue in the baseline HP [<sup>13</sup>C]-pyruvate MRI.

At 6 wk after initiation of ADT, repeat imaging demonstrated nearly complete abrogation of elevated HP lactate peaks on HP <sup>13</sup>C MRI (Fig. 1B) and associated near complete

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diminution of intratumoral  $k_{PL}$  values on dynamic imaging ( $k_{PL}$  max  $0.025\text{ s}^{-1}$  at baseline and  $0.007\text{ s}^{-1}$  on follow-up). Notably, there was negligible change in size of tumor on T2-weighted MRI and only a modest change on ADC imaging, supporting the ability of HP  $^{13}\text{C}$  MRI to detect early metabolic responses before such a response can be ascertained using standard radiographic criteria. Concordant with these findings, the patient subsequently achieved a marked clinical response, with an undetectable serum PSA nadir at 6 mo after ADT initiation.

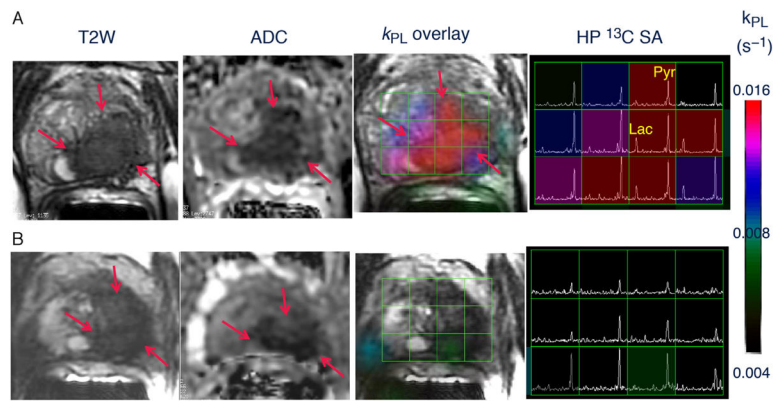
This first patient example illustrates the potential of HP [ $^{13}\text{C}$ ]-pyruvate imaging as a metabolic biomarker of response. Further clinical studies investigating the association between metabolic changes on HP  $^{13}\text{C}$  MRI and response and resistance to treatment are ongoing.

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**Fig. 1.** Representative axial T2-weighted (T2W) anatomic image and corresponding water apparent diffusion coefficient (ADC) image and T2W image with an overlaid pyruvate-to-lactate metabolic flux ( $k_{PL}$ ) image and corresponding hyperpolarized (HP)  $^{13}C$  spectral array (SA) for a 52-yr-old prostate cancer patient with extensive high-grade prostate cancer (A) before therapy and (B) 6 wk after initiation of androgen ablation and chemotherapy. Before treatment, the region of prostate cancer can be clearly seen (red arrows) as a reduction in signal on the T2W and ADC images, and increased HP lactate and associated  $k_{PL}$  flux on HP  $^{13}C$  MRI. After initiation of androgen deprivation therapy there was a significant reduction in reduction in HP lactate and  $k_{PL}$  to normal levels, with only a modest treatment effect on prostate volume and ADC.