

Hyperpolarized Carbon-13 Magnetic Resonance Spectroscopic Imaging of Metabolism in a Mouse Model of Breast Cancer

Roberta M Strigel¹, Erin Adamson², David J Niles², Amy Rapaich Moser^{3,4}, Jeremy W Gordon², Elizabeth S Burnside^{1,4}, and Sean B Fain^{1,2}

¹Radiology, University of Wisconsin, Madison, WI, United States, ²Medical Physics, University of Wisconsin, Madison, WI, United States, ³Human Oncology, University of Wisconsin, Madison, WI, United States, ⁴Carbone Cancer Center, University of Wisconsin, Madison, WI, United States

Target Audience: Scientists developing hyperpolarized ¹³Carbon MRI techniques and scientists/clinicians interested in tumor metabolism and breast cancer tumorigenesis.

Purpose: An improved understanding of tumorigenesis is necessary to accurately predict tumor progression and design novel, individualized treatments for breast cancer. We utilized hyperpolarized (HP) carbon-13 (¹³C) magnetic resonance spectroscopic imaging (MRSI) to test the feasibility of detection and characterization of the metabolic features of tumorigenesis in a mouse model of mammary malignancy. Since cancers have a high rate of lactate production due to the Warburg effect¹, we hypothesize that HP ¹³C-pyruvate MRSI and dynamic contrast-enhanced (DCE) MRI can be used to identify metabolic and vascular imaging features that are characteristic of breast cancer.

Methods: We included mice that carry a mutation in the Apc gene on the FVB/Tac background (FVB.B6-Apc^{Min/+}) which develop mammary adenocarcinomas after treatment with ethylnitrosourea (ENU). We imaged 7 mice with endogenous tumors that developed after ENU treatment, and 4 syngeneic mice (FVB/Tac) which were injected with tumor lines derived from FVB.B6-Apc^{Min/+} mice into the bilateral axillary fat pads. Mice were imaged on a 4.7T small animal MR system using a ¹³C/¹H dual-tuned volume coil (Doty Scientific, Columbia, SC). HP [1-¹³C]-pyruvate with ~20% polarization was produced by dynamic nuclear polarization (HyperSense, Oxford Instruments, Tubneywoods, Oxfordshire, UK). Non-contrast sequences included 3D T1-weighted SPGR (0.25 mm isotropic), and T2-weighted FSE (0.25 mm in-plane). Dynamic ¹³C imaging was performed immediately following intravenous tail injection of 10 µl/g of 80 mM HP ¹³C-pyruvate using a single-interleaved 2D spiral GRE multi-echo sequence with ~5 second(s) temporal resolution. For the first 4 mice, a single 10 mm slice was acquired (2 mm in-plane), and for the remaining 7 mice multiple 5 mm slices were acquired (3 mm in-plane). Spectral images of pyruvate and lactate were reconstructed using a linear least squares minimization of the signal model². Next, DCE MRI was performed with 2D T1-weighted SPGR sequences before and for up to 10 min after injection of 0.15 mmol/kg of gadodiamide contrast (0.25 mm in-plane; 2mm ST, 5s per image). In this feasibility study, imaging timing and experiments were not controlled for tumor size or aggression.

Results: We developed techniques to image HP ¹³C-pyruvate and DCE MRI in the same imaging session and successfully identified lactate as a metabolite of HP ¹³C-pyruvate and glycolysis. Two (of 11) mice had tumors demonstrating HP ¹³C-lactate production with heterogeneous spatial distribution (Fig. 1); the remaining 9 tumors did not show lactate production. Heterogeneous perfusion was demonstrated with DCE MRI, including in those mice with tumors without lactate production (Fig. 2). Adequate delivery of the substrate pyruvate was confirmed by the presence of DCE perfusion in all cases.

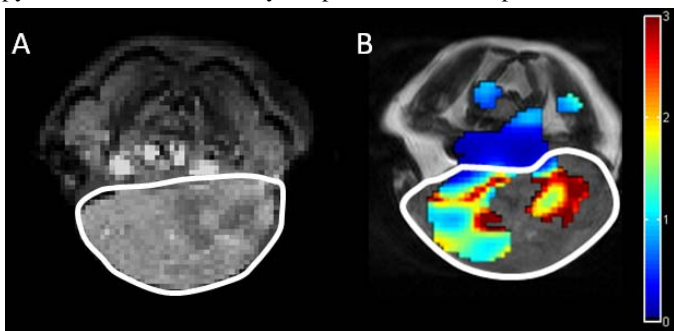


Figure 1: (A) Axial T1-weighted contrast-enhanced MRI of a mammary adenocarcinoma (white outline) in a mouse demonstrating heterogeneous contrast enhancement. (B) ¹³C-lactate:pyruvate ratio map (color) overlaid on an anatomic image (gray) with a pattern of intense lactate production in focal areas distinct from contrast enhancement.

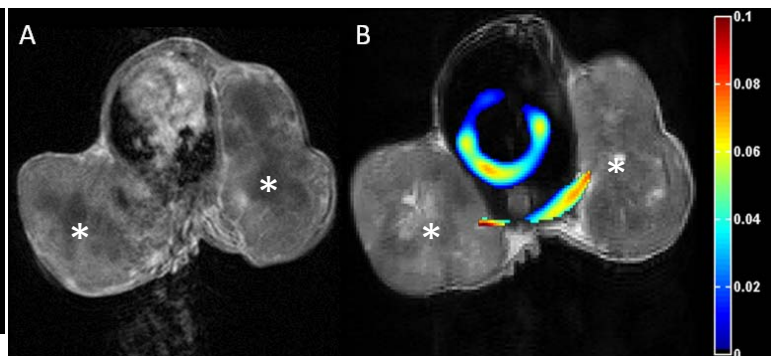


Figure 2: (A) Axial T1-weighted contrast enhanced MRI of bilateral mammary adenocarcinomas (*) in a mouse demonstrating heterogeneous contrast enhancement. (B) ¹³C-lactate:pyruvate ratio map overlaid on an anatomic axial MR image (gray) confirms no lactate production within the tumor.

Discussion: We applied a novel methodology, HP ¹³C-pyruvate MRSI, to image real-time cancer metabolism, in vivo, by observing the exchange of the HP ¹³C label of pyruvate substrate relative to its glycolytic metabolic product lactate. Our results demonstrate inconsistency between regional maps of contrast-enhanced perfusion and HP ¹³C-lactate. These preliminary results suggest that HP ¹³C imaging may identify spatial heterogeneity in metabolism, within and between different tumors, which differs from patterns of perfusion with DCE MRI.

Conclusion: We successfully imaged mice with mammary adenocarcinomas using DCE MRI and ¹³C-pyruvate metabolic imaging in a single imaging session and demonstrated differences in perfusion versus metabolism within and between different tumors. These preliminary results will next be compared to tumor histopathology to relate functional imaging features to markers of tumor aggression.

References 1. Sotgia F, et al. Breast Cancer Research. 2011;13(4):213; 2. Reeder SB, et al. J Magn Reson Imaging. 2007;26(4):1145-52.

Acknowledgments: This project was supported by the Department of Radiology, Research & Development Fund at the authors' institution.