Combined metabolic and perfusion imaging by hyperpolarized ^{13}C MR can evaluate early and dose-dependent tumor response to radiotherapy

Hecong Qin[1,3], Vickie Zhang[1], Robert A. Bok[1], Adam Cunha[2], I-Chow Hsu[2], Romelyn Delos Santos[1], Daniel B. Vigneron[1,3], David M. Wilson[1], Renuka Sriram[1], and John Kurhanewicz[1,3]

1. Department of Radiology and Biomedical Imaging, 2. Department of Radiation Oncology, 3. UC Berkeley - UCSF Graduate Program in Bioengineering

Highlights: We found combined metabolic and perfusion imaging by hyperpolarized MR with [1- ^{13}C]pyruvate and [^{13}C]urea could assess early tumor response to radiotherapy within a week post-therapy in a transgenic prostate cancer model, and that changes in tumor lactate production were associated with radiation dose applied.

Purpose: Radiotherapy (RT) is the mainstay treatment for many cancers, but timely and accurate assessment of RT response is still a clinical challenge. We investigated using combined hyperpolarized (HP) MR with [1-^{13}C]pyruvate (metabolism) and [^{13}C]urea (perfusion) to assess early and dose-dependent tumor response to radiotherapy in the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model. Our hypotheses are that since radiation causes cell cycle arrest, senescence, apoptosis, and eventual cell death resulting in decreased metabolism as well as complex tissue responses including altered cellularity and perfusion, combined HP ^{13}C metabolic and perfusion MR, coupled with multiparametric ^{1}H MR, could characterize these post-therapy physiologic changes, and that the magnitude of these changes might be associated with radiation dose.

Methods: TRAMP mice (n=15) was irradiated once using a clinical brachytherapy system and imaged using HP [1-^{13}C]pyruvate + [^{13}C]urea MR with a 3D GRadient And Spin Echo (GRASE) sequence6 and multiparametric ^{1}H MR including high-resolution T_2-weighted, dynamic contrast-enhanced (DCE) and diffusion-weighted imaging (DWI) at pre-RT, 1 day, 4 days, and 7 days post-RT on a 14T scanner. CT-based radiation dose maps were also generated and subsequently co-registered to MR scans. Tissues were collected at Day 4 and Day 7 post-RT to evaluate the biologic effects of radiotherapy. A linear mixed model with small sample size correction was used to analyze longitudinal data; dose-dependent effects were evaluated by repeated measures ANOVA or paired t-tests.

Results and Discussion: Mice were sub-grouped based on volume change at Day 4 post-RT measured on T2 weight images: growing tumor (n=11, 70.3±16.7% of baseline) and shrinking tumor (n=4, 115.5±7.1% of baseline). The shrinking tumors showed significantly decreased lactate production ($p=0.002$) and increased urea perfusion ($p=0.005$), represented in Fig 1a; in contrast, the opposite changes were observed for growing tumors ($p=0.021$ for lactate increase, $p=0.004$ for urea decrease) (Fig 1B). These post-radiation changes measured by HP MR revealed a metabolism-perfusion mismatch - as cancer progresses, aerobic glycolysis and lactate production increase despite decreased perfusion, indicative of aggressive phenotype; while responding to therapy, metabolism decreases and perfusion normalizes. Moreover, the magnitude of post-RT ^{13}C-lactate reduction was associated with radiation dose, where high-dose tumor regions showed significantly higher magnitude of lactate reduction than low-dose regions as early as Day 1 (ANOVA: Day 1, $p=0.045$; Day 4, $p=0.0395$; Day 7, $p=0.0003$; high vs. low: Day 1, $p=0.038$, effect size Cohen's $d=0.71$; Day 4, $p=0.042$, $d=0.75$; Day 7, $p=0.0022$, $d=1.22$) (Fig 1C). Correspondingly, the high-dose regions showed a lower proliferation by Ki-67 staining ($p=0.0002$), LDH enzyme activity ($p=0.042$), and LDHA gene expression ($p=0.0221$) (Fig 1D). Additionally, DCE MR perfusion parameters showed a strong correlation with HP [^{13}C]urea (area under the curve: $r=0.73$, $p<0.0001$; wash-in slope: $r=0.71$, $p<0.0001$). The apparent diffusion coefficient (ADC) generated from DWI increased in the high-dose regions while decreased in the lower-dose regions.

Conclusion: Combined HP [1-^{13}C]pyruvate + [^{13}C]urea MR can assess early and dose-dependent tumor response to RT in a mouse prostate cancer model, suggesting that it could facilitate designing patient-specific RT protocols and provide timely treatment evaluation. These results also demonstrated the potential of HP MR in cancer diagnosis and therapy monitoring and provided novel scientific premises for its application in the clinical setting.

(A)

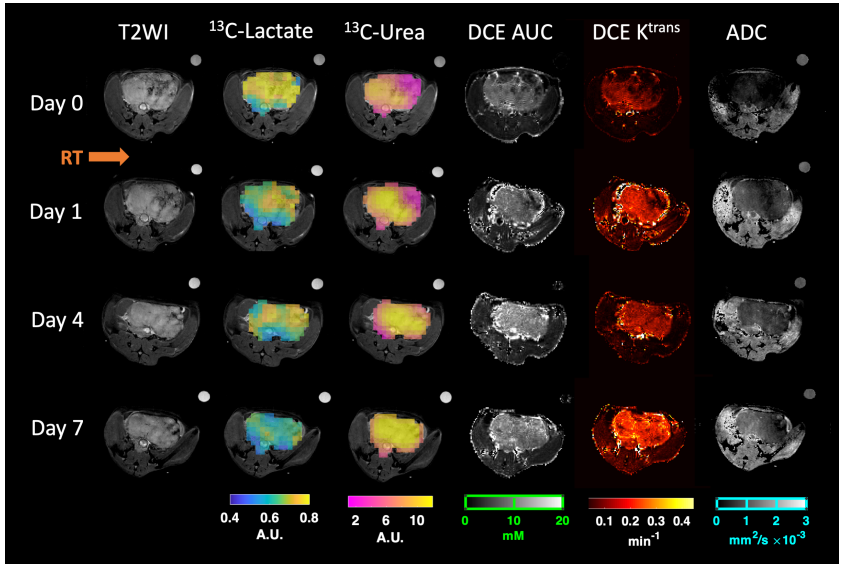


Fig A: A panel of representative images showing tumor volume and metabolism (^{13}C-Lactate) decreased after radiotherapy, while perfusion (^{13}C-Urea, DCE AUC, DCE K^{trans}) and ADC (inversely correlated with cellularity) increased.

(B)

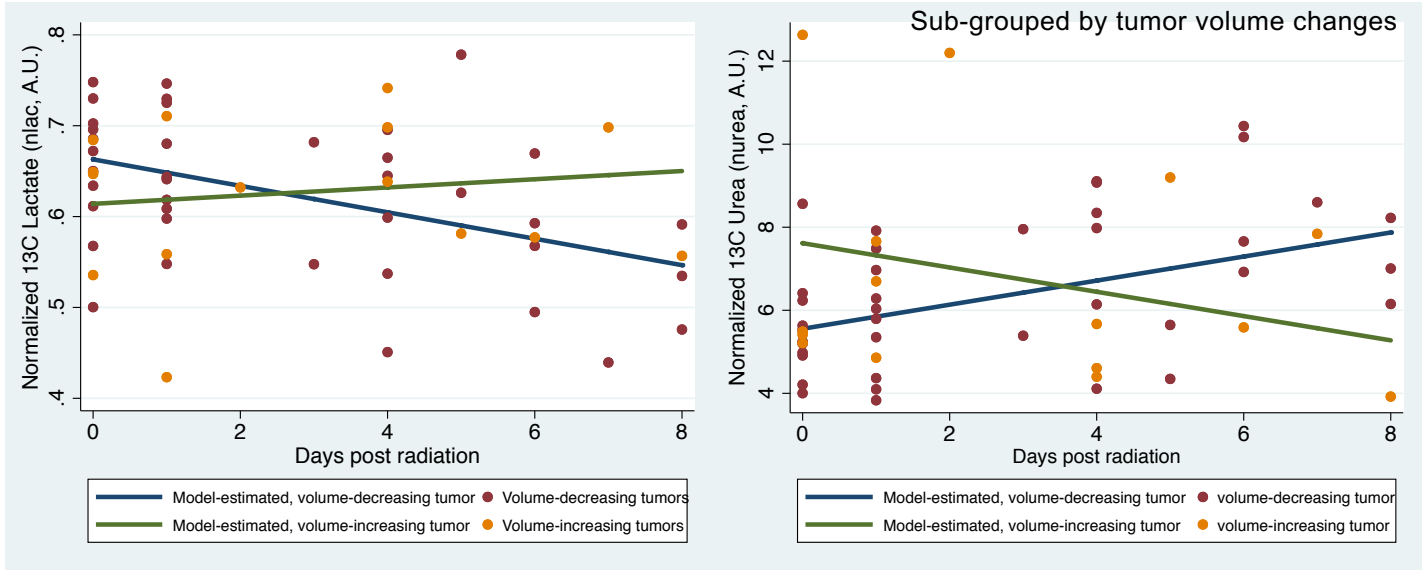
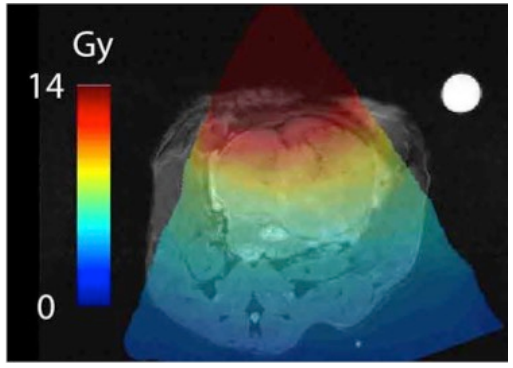


Fig B: Combined metabolic and perfusion imaging with hyperpolarized ^{13}C MR revealed sharp contrast between growing (n = 4) and shrinking tumor (n = 11) post radiotherapy: As cancer progresses, lactate production increases despite decreased perfusion, indicative of aggressive phenotype; while responding to therapy, lactate production decreases and perfusion improves. Moreover, metabolism and perfusion change in the opposite directions, providing additional contrasts.

(C)



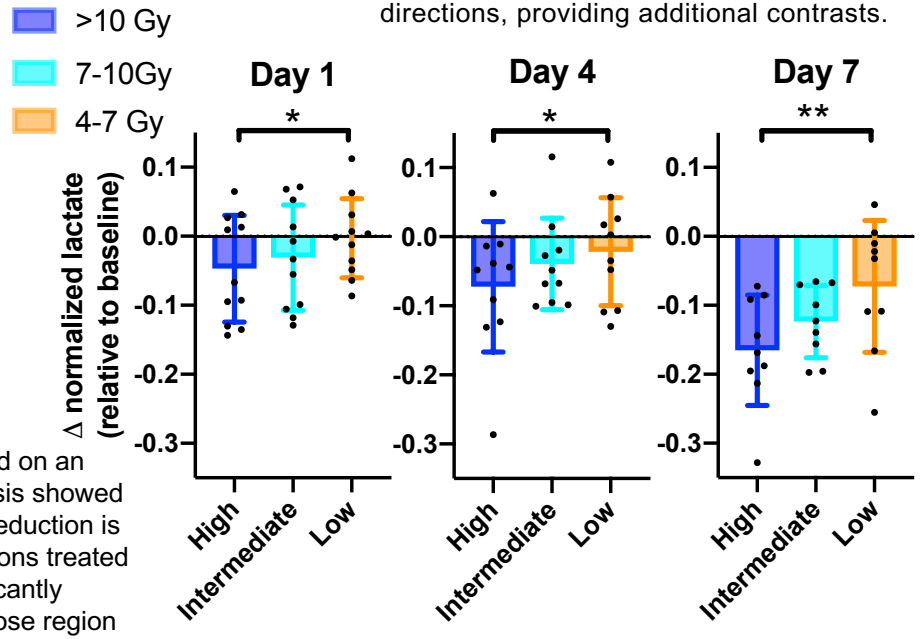


Fig C: An example of radiation dose map overlaid on an axial T2 weighted image. Dose correlation analysis showed that the magnitude of post-radiation ^{13}C-lactate reduction is associated with radiation dose, where tumor regions treated with high-dose radiation (> 10Gy) showed significantly higher magnitude of lactate reduction than low-dose region (4 -7 Gy) as early as Day 1 (plots showing mean ± standard deviation, * p< 0.05, ** p < 0.01).

(D)

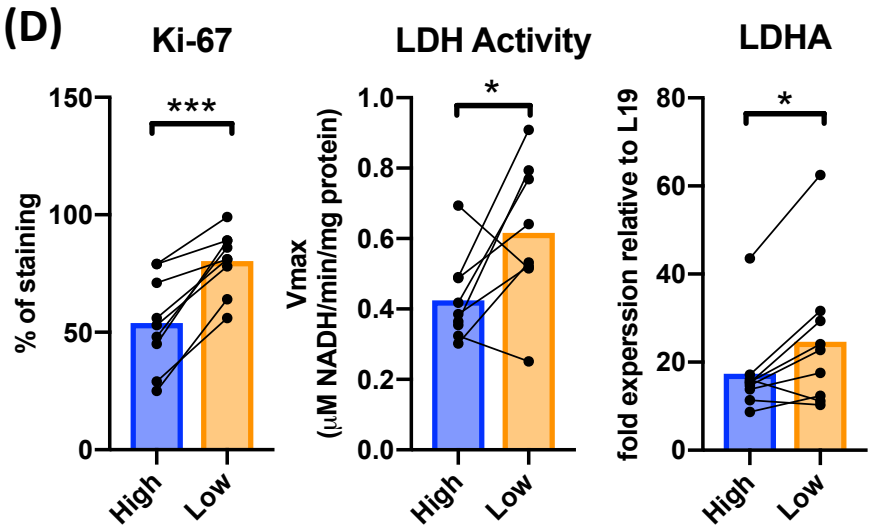


Fig D: Histopathology and *in vitro* assays showed tissue treated with high-dose radiation showed lower Ki-67 staining (proliferation), and lower lactate dehydrogenase (LDH) activity and LDHA expression than low-dose regions. (* p< 0.05, *** p<0.001)