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Department of Radiology & Biomedical Imaging

Role of Multiparametric ^{1}H and Hyperpolarized ^{13}C Metabolic Imaging in the Personalized Care of Prostate Cancer Patients

Osher Mini Medical School for the Public

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Imaging and Precision Medicine

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National Research Council explains: Precision Medicine refers to the tailoring of medical treatment to the individual characteristics of each patient.

Topic of this lecture: Hyperpolarized ^{13}C MR imaging and it's combination with mp-^{1}H MRI and PET to tailor the treatment of individual prostate cancer patients.

Multiparametric (mp) - ^{1}H MRI

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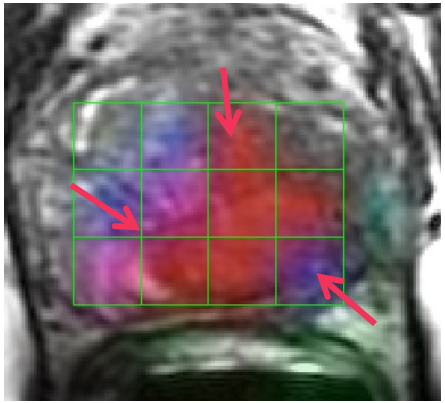
*"one picture is worth ten thousand words" **



mp-^{1}H MRI and hyperpolarized ^{13}C MRI

*"Multiple concordant pictures – provide the most confident identification and characterization of prostate cancer in individual patients." **

- 24 years of continuous NIH funding - multiparametric ^{1}H MRI
- Integration with PET – PET/MRI
- Over 200 publications
- ≈ 1,200 patients scanned in 2017
- Targeted biopsies and therapy

** 1926 Time Magazine advertisement for a children's encyclopedia*

** UCSF approach to imaging prostate cancer*

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Multiparametric ^{1}H MRI + PET

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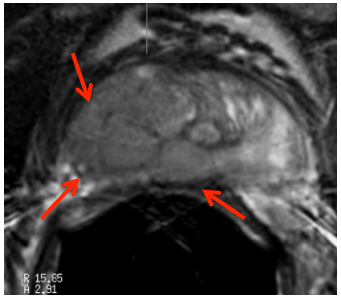
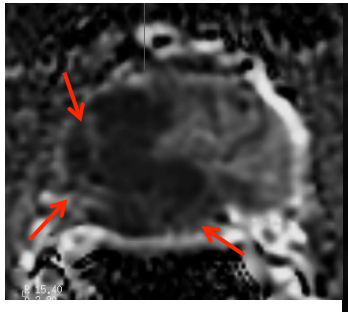
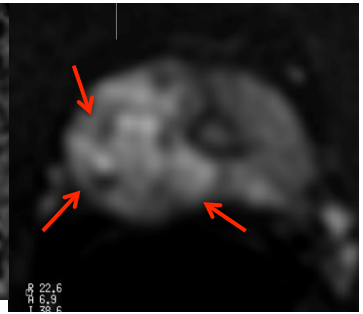


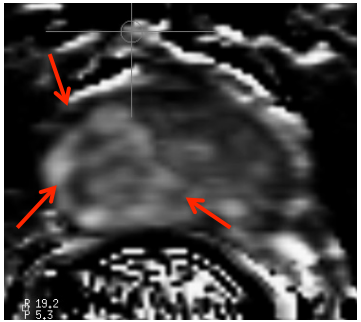
T2 wt. MRI



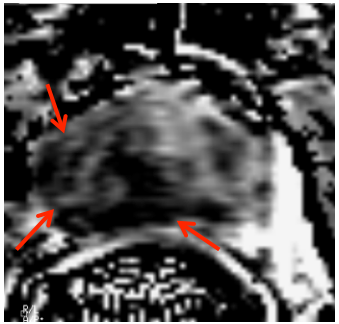
ADC



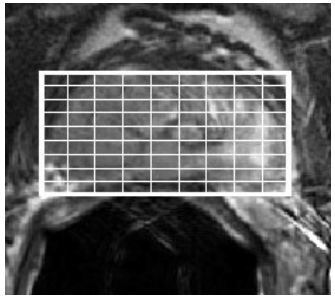
High-b DWI



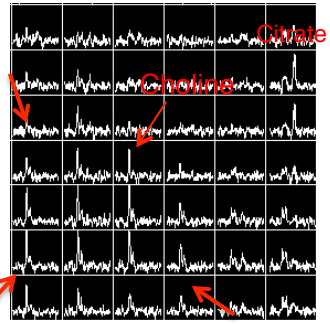
DCE Uptake



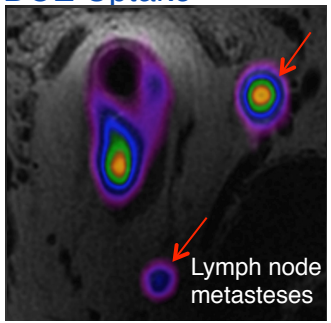
DCE Wash-out



T2 + ^{1}H MRSI grid



^{1}H Magnetic Resonance Spectroscopic Imaging



PSMA -PET

- mp-^{1}H MRI primary approach to assessing localized disease
- PET - assessing metastatic disease(^{68}Ga and ^{18}F PSMA, ^{18}F and ^{11}C choline, ^{68}Ga citrate
- Addition of HP ^{13}C MRI

Aggarwal, R, Kurhanewicz, J. Prostate cancer in 2013: The changing role of imaging in clinical care. Nature Reviews Urology. 2014 Feb;11(2):75 -7. PMCID: PMC4057014

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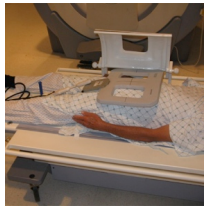
Hyperpolarized (HP) ^{13}C MRI

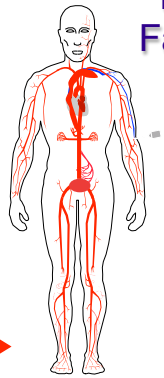
- DNP polarization ⇛ ≥ 10^5 signal enhancement relative to conventional MRI ⇛ measure real time metabolism in patients[1,2]
- Use clinical MRI scanner with multi-nuclear capabilities (hardware and RF coils)
- Injected i.v. like other contrast agents
- Fast HP ^{13}C imaging + mp-^{1}H MRI in prostate cancer patients[3]

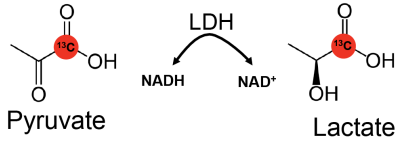
[1-^{13}C]pyruvate 40,000 increase in MR signal at 3T[1]

Clinical MR Scanner

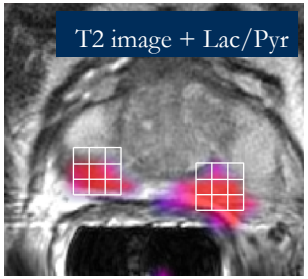


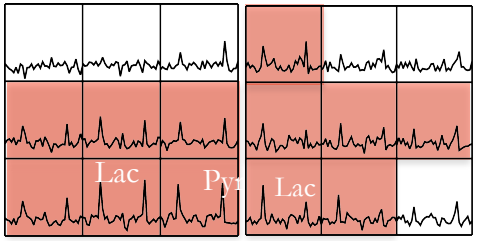
Inject i.v. – Fast ^{13}C MRI





Volume ^{13}C MRI in 10's of secs[3]





[1]Ardenkjaer-Larsen et al. *PNAS*. 2003
[2]Kurhanewicz et al. *Neoplasia*, 2011

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Hyperpolarized ^{13}C Metabolic Imaging

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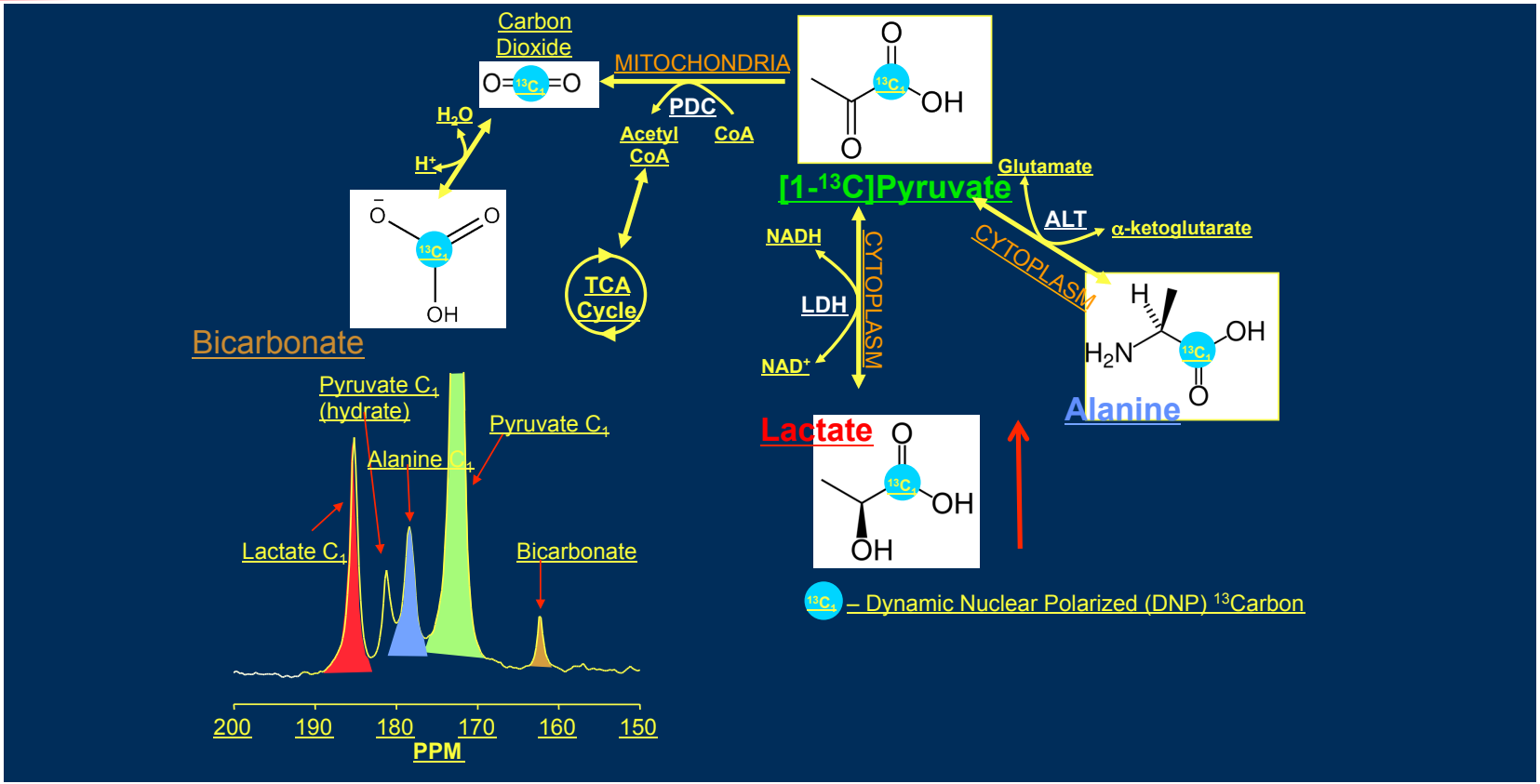
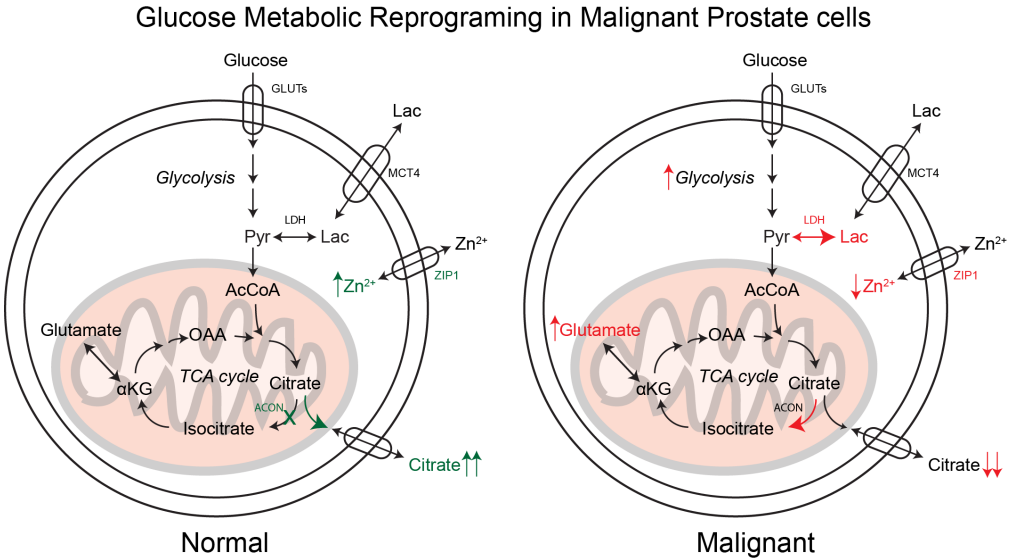


Metabolic Reprogramming – Prostate Cancer

Prostate cancer metabolism

- Both Benign and malignant prostate exhibits high glycolytic metabolism limiting FDG PET imaging[1-3]
- Fundamental switch in prostate cancer is the utilization of carbons not the uptake of Glucose.



- Use fast ^{13}C MR of HP ^{13}C pyruvate to measure this metabolic switch and its relationship to cancer aggressiveness and therapeutic response.

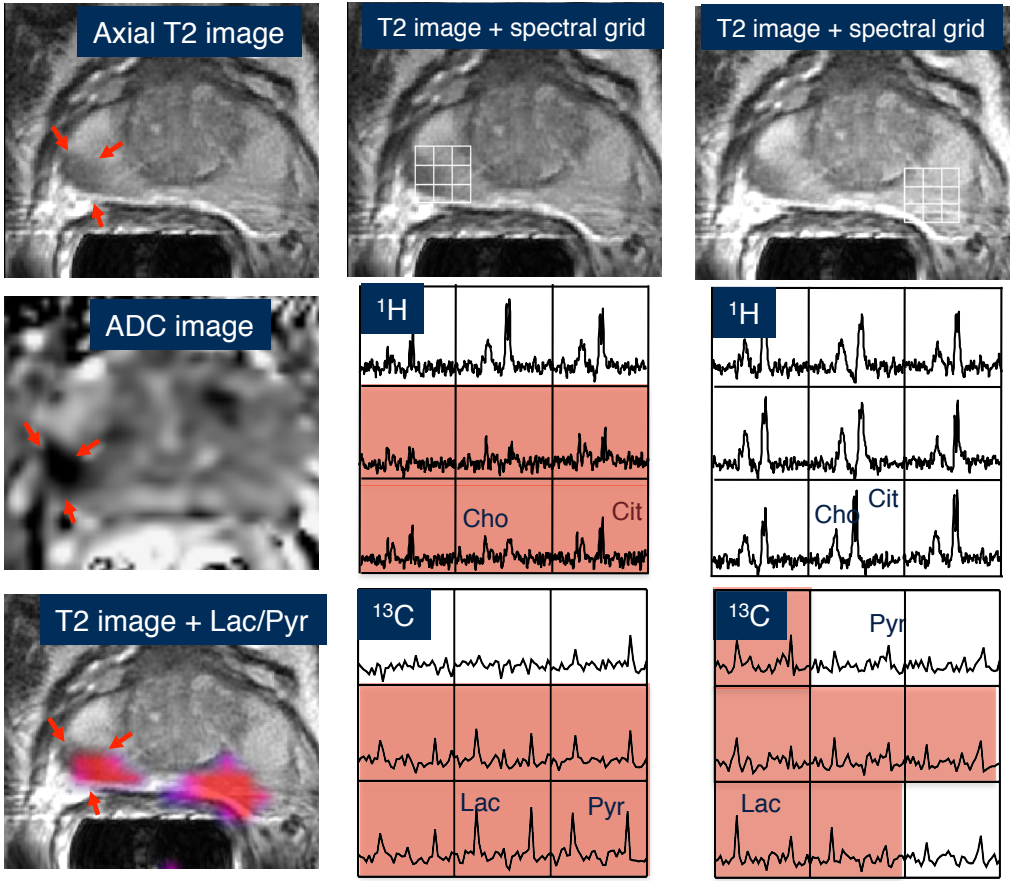
Important Clinical Questions

- *At Diagnosis* -Identification of indolent versus aggressive disease – *individualized therapeutic selection*

- *Advanced Disease* - Therapeutic response and development of therapeutic resistance – *selection of new therapeutic approaches at a earlier more effective time point*

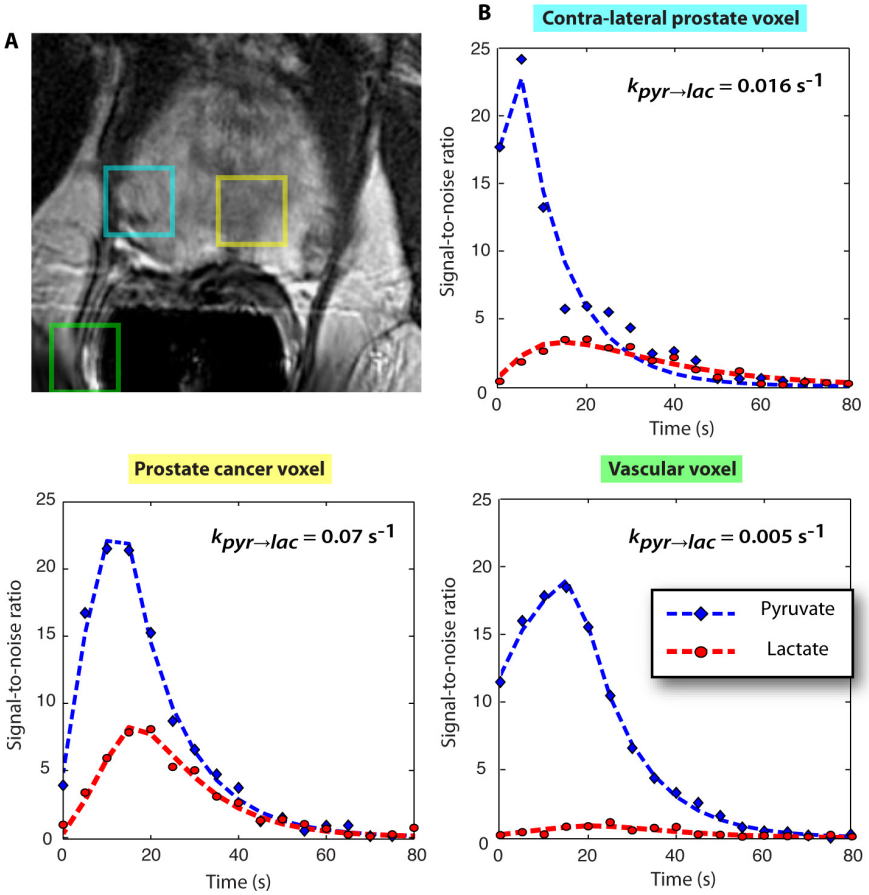
UCSF Phase 1 Trial of ^{13}C Pyruvate in Localized Prostate Cancer

- Dose escalation safety and imaging feasibility study – *Demonstrated Safety and Feasibility*
- 3D single time point HP ^{13}C MRI - identified cancer missed on mp-^{1}H MRI – *need for full pathologic correlations*



Nelson, Kurhanewicz, Vigneron et al. Science Translation Medicine, 2013; 5(198).

Phase 1 Trial - Localized Prostate Cancer



- Quantitative measurements of cancer metabolism in individual patients
- High metabolic flux of [1-^{13}C]pyruvate to [1-^{13}C]lactate (k_{PL}) in prostate cancer
- Is k_{PL} pathologic grade dependent ?

Phase II study of HP ^{13}C pyruvate imaging to Detect High Grade Prostate Cancer

Pre-Radical Prostatectomy (50 patients): Correlate 3D HP ^{13}C MRI biomarkers with whole-mount step-section pathology in order to:

- Investigate the association between HP pyruvate-to-lactate conversion with histologic grade of prostate cancer
- Investigate the association between HP pyruvate-to-lactate conversion and clinical outcomes - extracapsular extension, positive nodal involvement, and failure to achieve undetectable PSA nadir following prostatectomy.

Phase II study of HP ^{13}C pyruvate imaging to Detect High Grade Prostate Cancer

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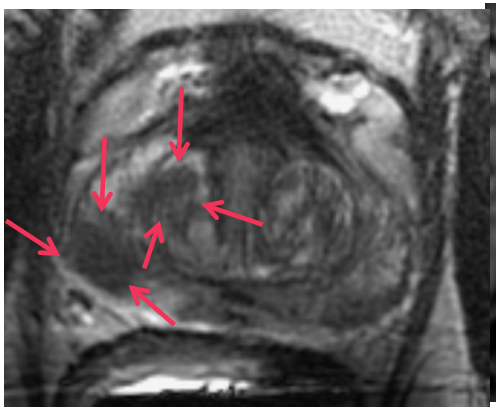
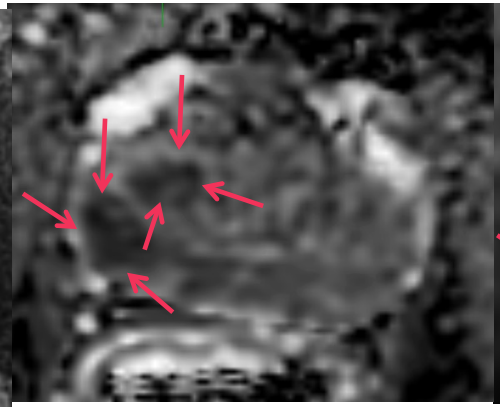
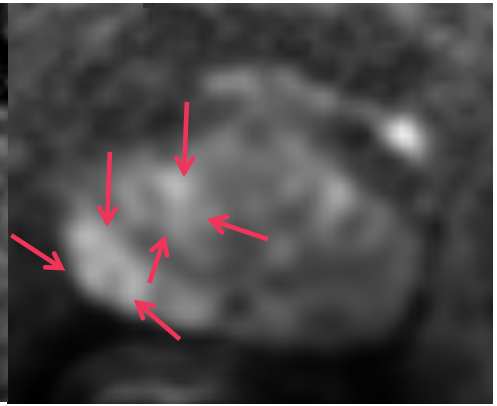
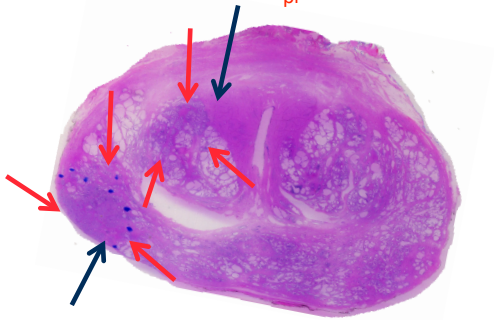




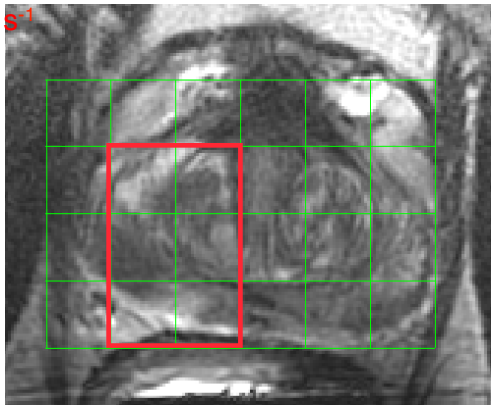


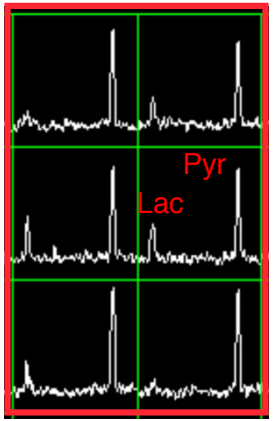
Correlation of 1 Section out of 3D MRI vloume

Gleason 3+3 – K_{pl} = 0.02 ± 0.005 s^{-1}



Gleason 4+3 – K_{pl} = 0.04 ± 0.003 s^{-1}





Pathologic Correlations on 16/50 patients thus far

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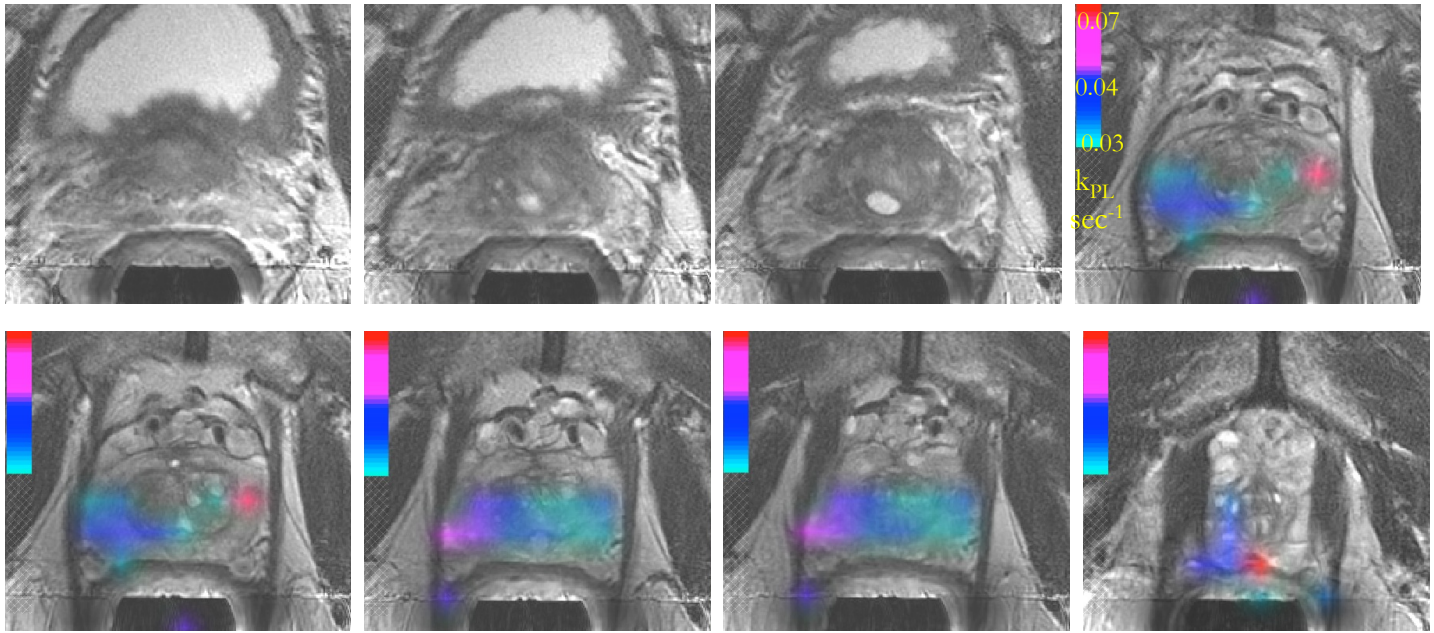
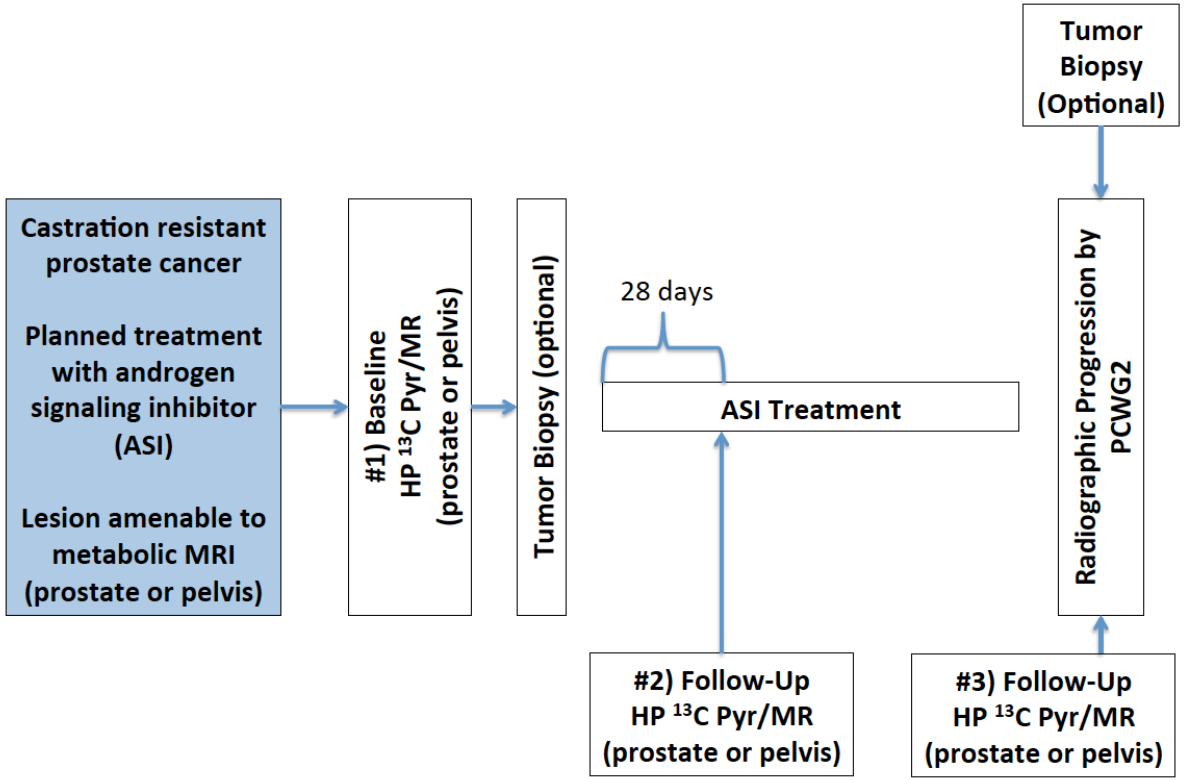
Phase 2 Trial – Detection of High Grade Cancer



Regions of Gleason 4+4 - 4+3 cancer correlated with area of high k_{PL} (pink to red on the overlays), whereas regions of Gleason 3+4 and 3+3 cancer correlated with the lower k_{PL} (dark to light blue on the overlays).

- Pyruvate to lactate flux images (k_{PL}) images overlaid on anatomic images of a patient with multi-focal prostate cancer

HP ^{13}C pyruvate MRI as a Biomarker of Response/ Resistance to Androgen Signaling Inhibition



- 75 patients prior Androgen Deprivation Therapy

Phase 2 Trial - [1-^{13}C]pyruvate as a Biomarker of Response/Resistance to Androgen Signaling Inhibition

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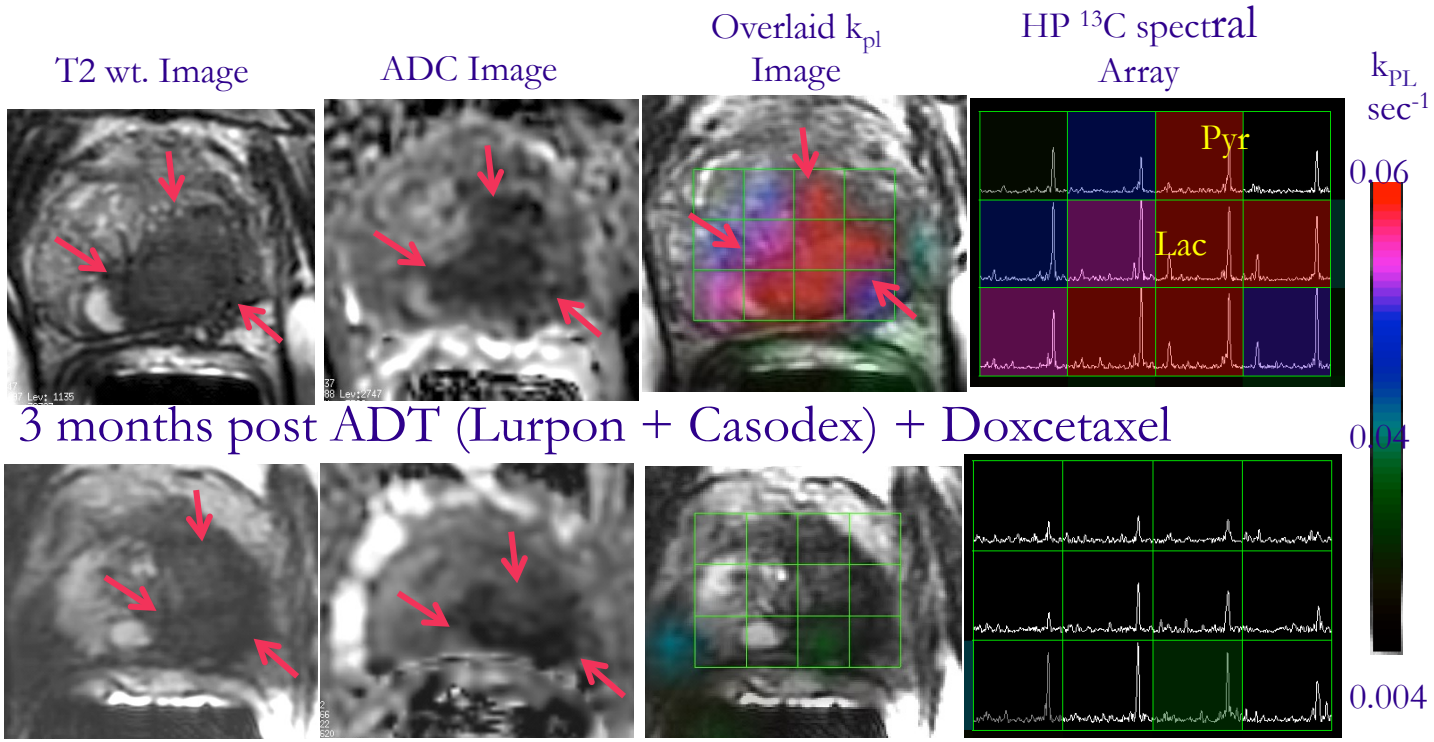

- A significant reduction in k_{PL} predicted therapeutic response

Aggarwal, R., Vigneron, D.B., and Kurhanewicz, J, Hyperpolarized 1-[13C]-Pyruvate Magnetic Resonance Imaging Detects an Early Metabolic Response to Androgen Ablation Therapy in Prostate Cancer, Eur Uro, July 23, 2017 e-pub

Phase 2 Trial - [1-^{13}C]pyruvate as a Biomarker of Response/Resistance to Androgen Signaling Inhibition

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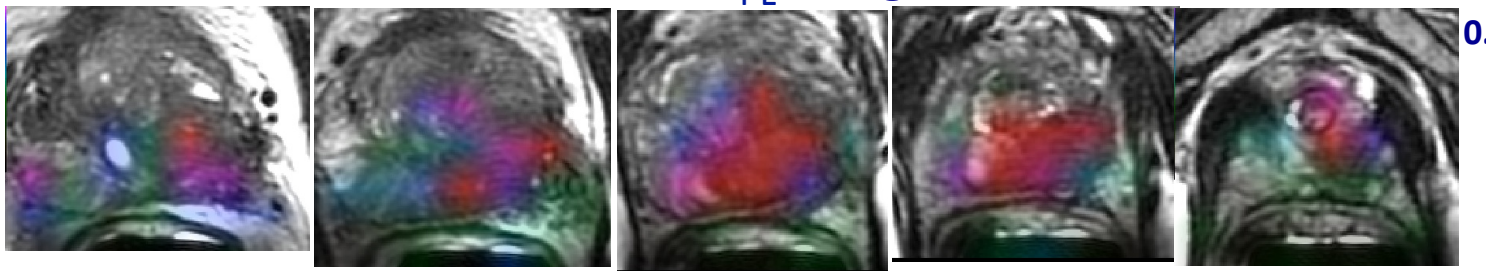
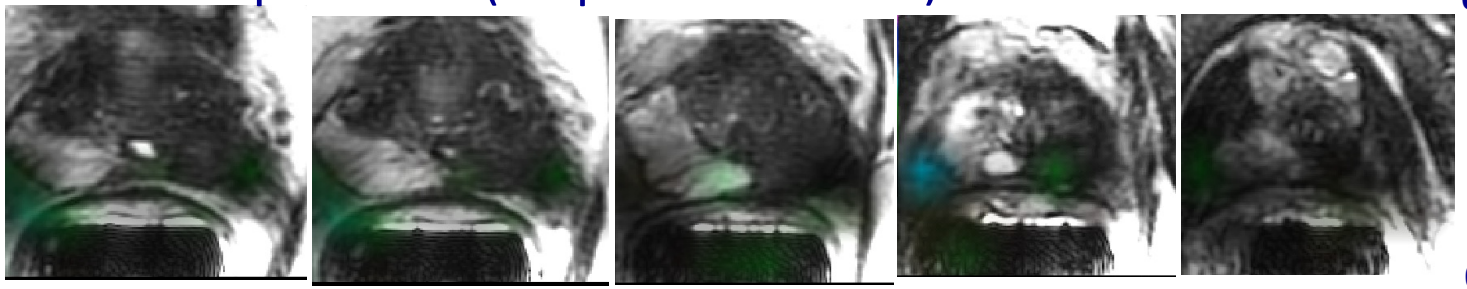
Pre-treatment

Overlaid k_{PL} Images



3 months post ADT (Lurpon + Casodex) + Doxcetaxel



- After treatment PSA decreased from 25.7 to 0.78 and 1 year out the patient's PSA remains undedectable

Aggarwal, R., Vigneron, D.B., and Kurhanewicz, J, Hyperpolarized 1-[13C]-Pyruvate Magnetic Resonance Imaging Detects an Early Metabolic Response to Androgen Ablation Therapy in Prostate Cancer, Eur Uro, July 23, 2017 - In Press

THANK YOU!

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