

Molecular Imaging of Prostate Cancer for Diagnosis and Therapy

Peter Choyke, MD

Molecular Imaging Program

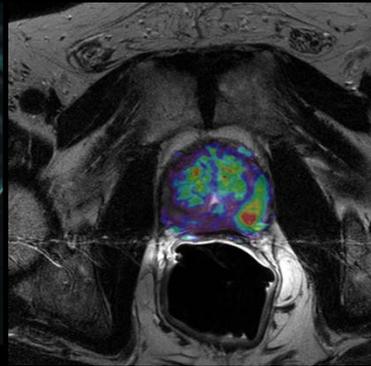
National Cancer Institute



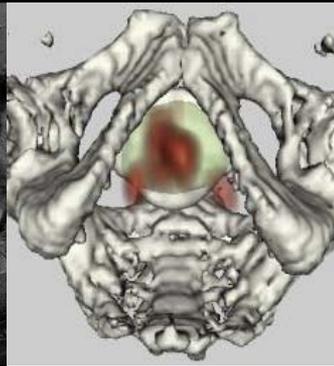
What Modalities Will Guide Future Therapies?



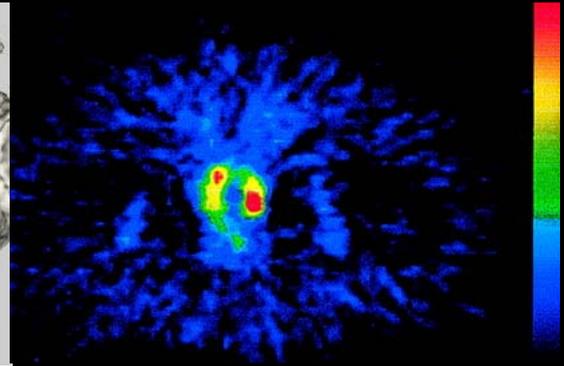
Ultrasound
Microbubble
Color doppler



MRI
DCE-MRI
MR Spectroscopy
Iron Oxides
DWI

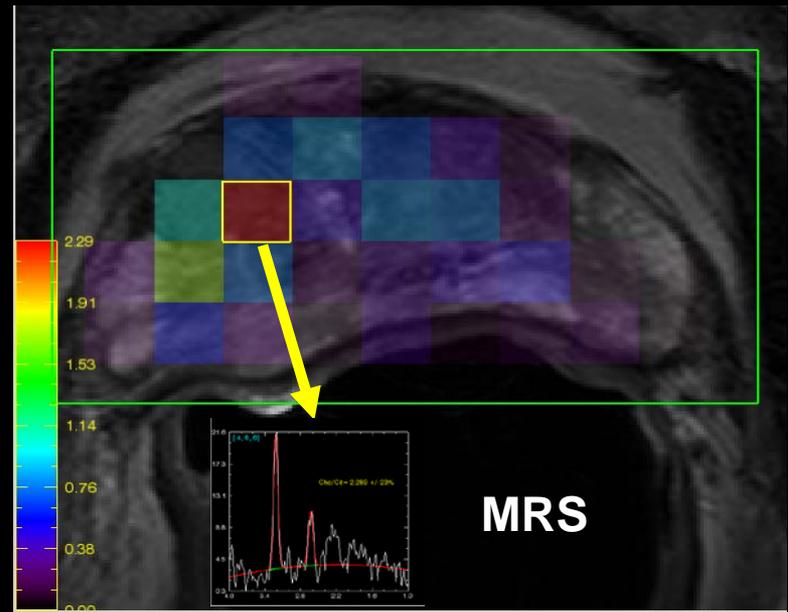
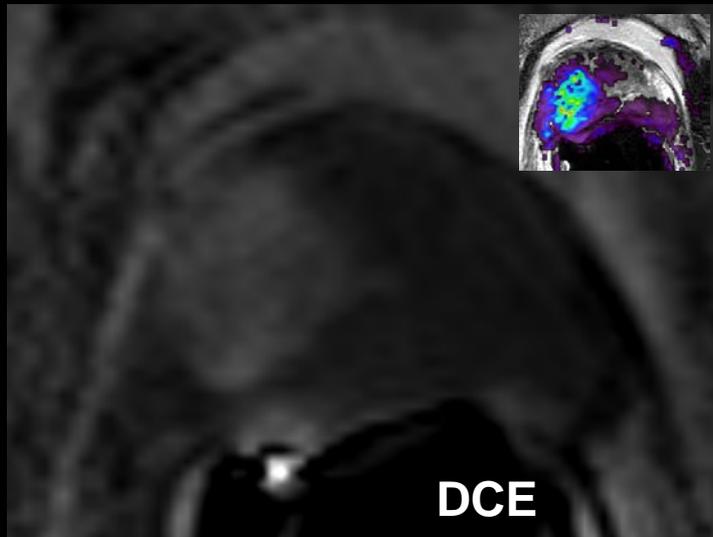
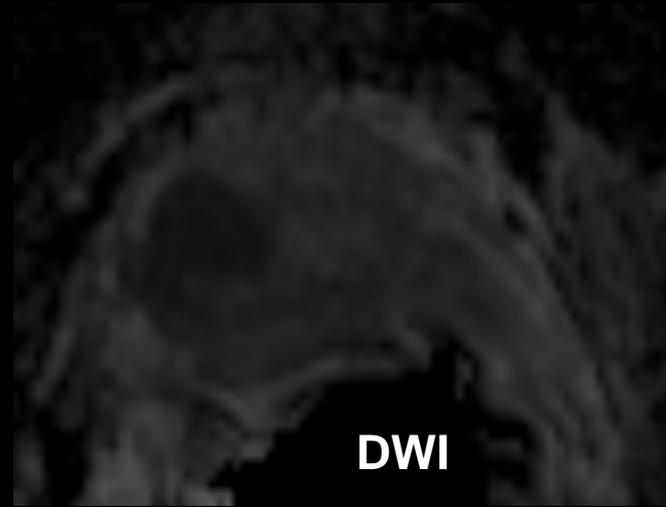
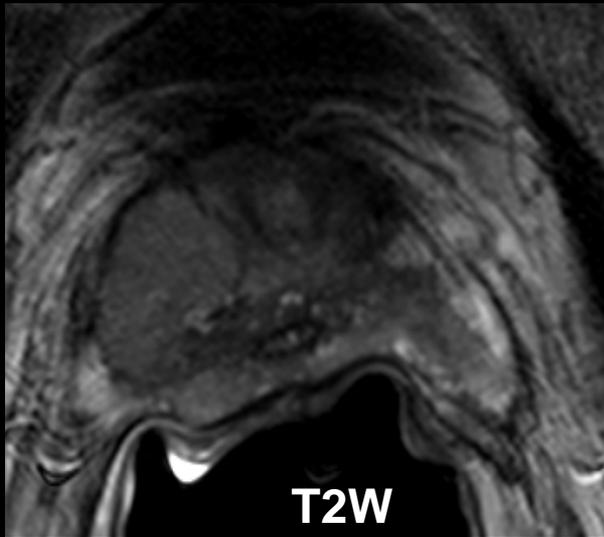


Radionuclide
Prostascint
PSMA antibodies
Aptamers



PET
11C Choline
11C Acetate
18F Choline
18F ACBC
18F AR analog

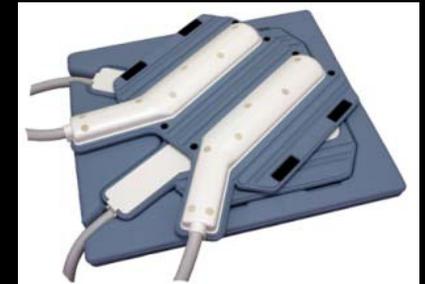
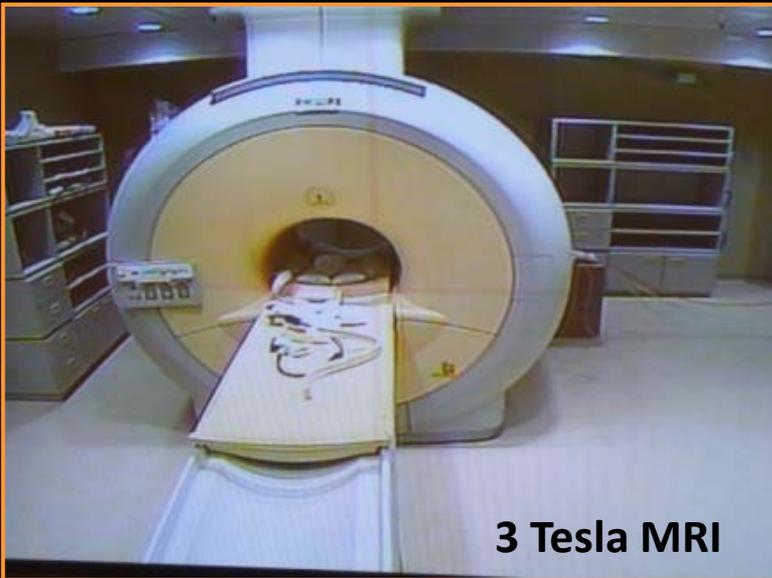




Multi-parametric Prostate MRI

- 510 patients/3 years
- 10 patients/week

T2W, ADC, MRSI, DCE



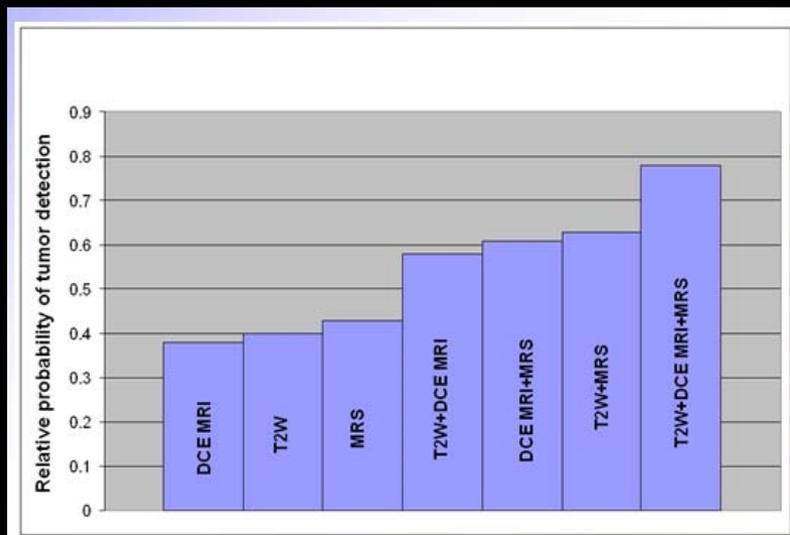
Prostate Cancer: Value of Multiparametric MR Imaging at 3 T for Detection—Histopathologic Correlation¹

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 Yuxi Pang, PhD
 Yolanda L. McKinney, RN
 Kiranpreet Khurana
 Gregory C. Ravizzini, MD
 Paul S. Albert, PhD
 Maria J. Merino, MD
 Peter L. Choyke, MD

Purpose: To determine utility of multiparametric imaging performed at 3 T for detection of prostate cancer by using T2-weighted magnetic resonance (MR) imaging, MR spectroscopy, and dynamic contrast material-enhanced MR imaging, with whole-mount pathologic findings as reference standard.

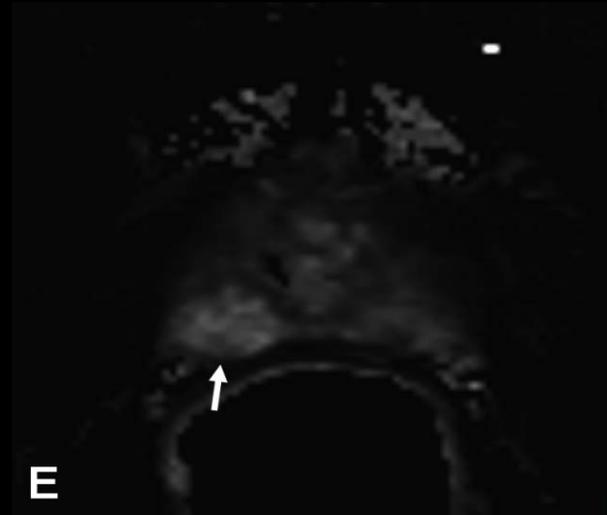
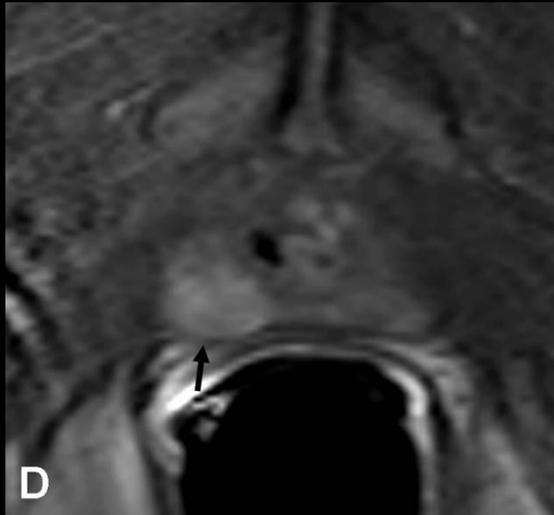
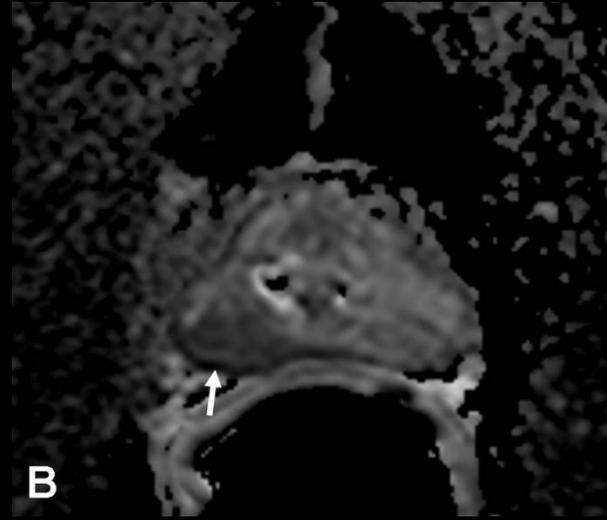
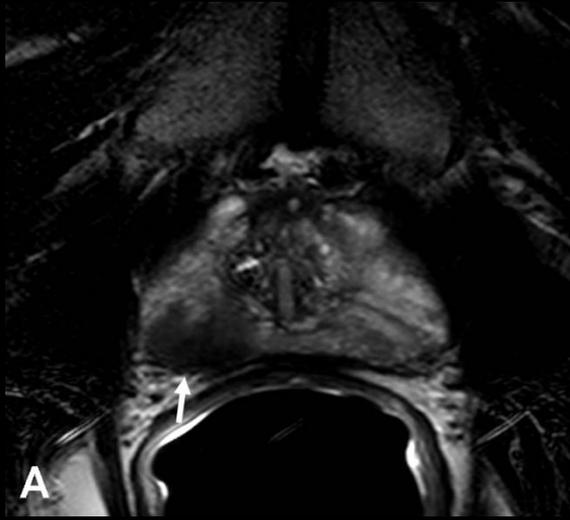
Materials and Methods: This prospectively designed, HIPAA-compliant, single-institution study was approved by the local institutional review board. Seventy consecutive patients (mean age, 60.4 years; mean prostate-specific antigen level, 5.47 ng/mL [5.47 $\mu\text{g/L}$]; range, 1–19.9 ng/mL [1–19.9 $\mu\text{g/L}$]) were in-

| Lesion characteristics | Sensitivity | | |
|------------------------|-------------|-------------|-------------|
| | T2W | DCE MRI | MRS |
| $\leq 3\text{mm}$ | 0.40 (0.87) | 0.12 (0.51) | 0.07 (0.28) |
| $> 3\text{mm}$ | 0.61 (0.94) | 0.28 (0.56) | 0.21 (0.39) |
| Gleason score ≤ 7 | 0.48 (0.86) | 0.20 (0.48) | 0.16 (0.33) |
| Gleason score > 7 | 0.67 (0.98) | 0.36 (0.74) | 0.25 (0.51) |

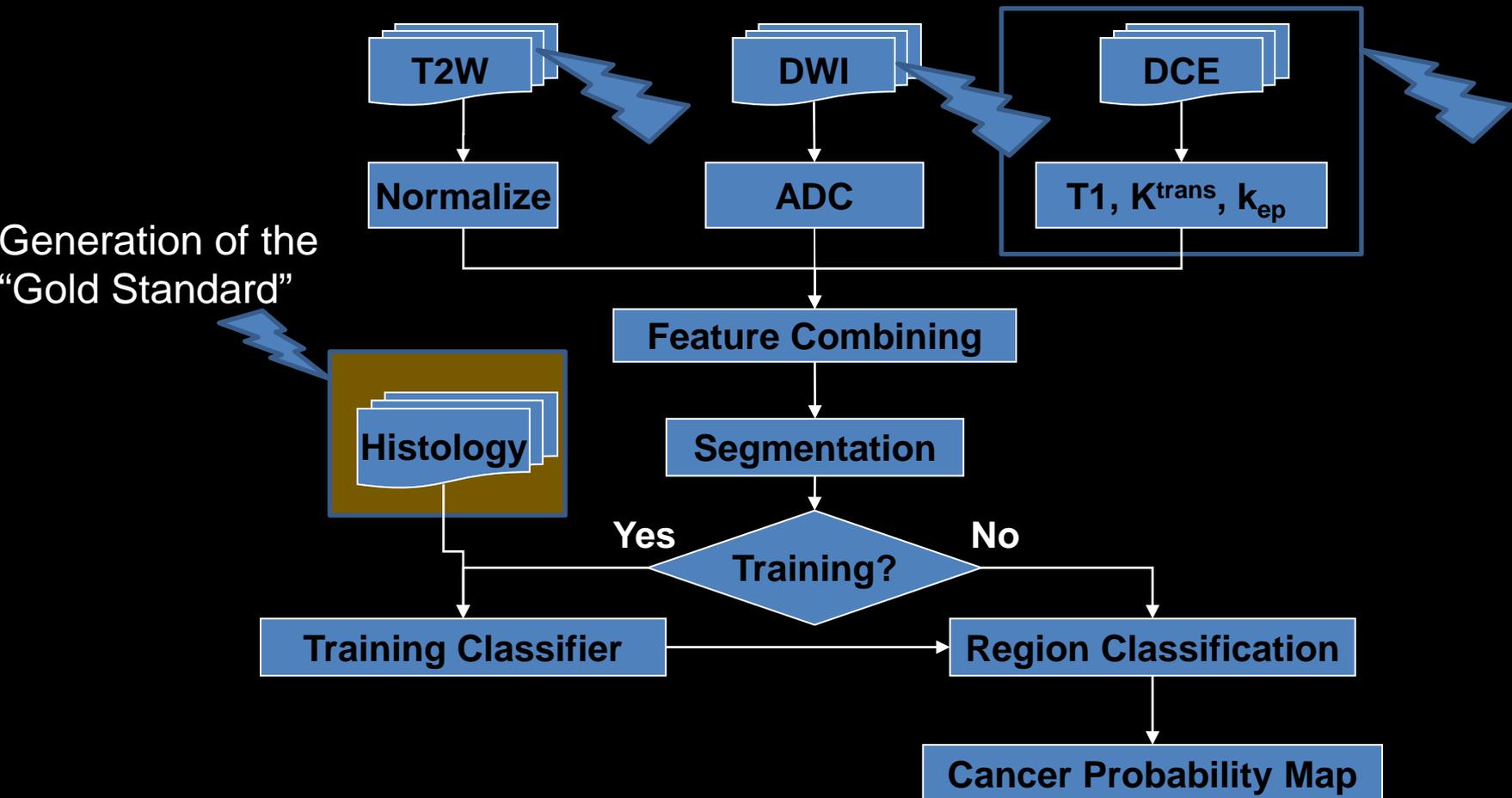


Turkbey B, et al. Radiology 2010





Design of Multi-parametric Analysis System



Improving Quantitation of T2 MRI

Conventional T₂-weighted Imaging

- **Qualitative**
 - ✓ Depends on pulse sequence and acquisition parameters.
 - ✓ Subjects to inter-scanner and intra-scanner variations.

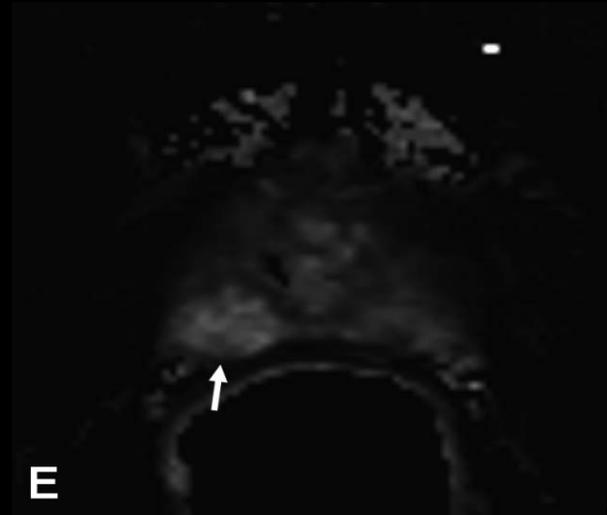
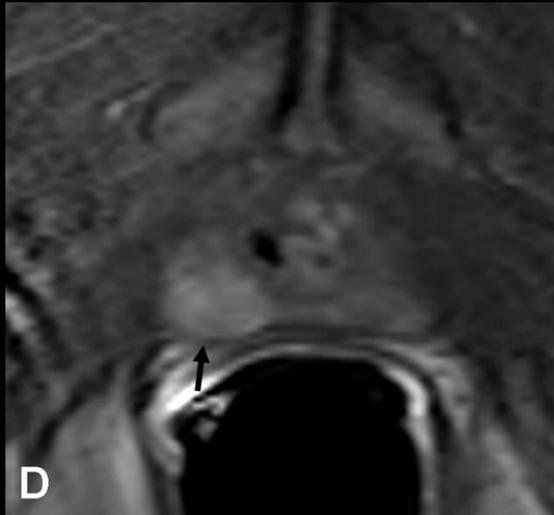
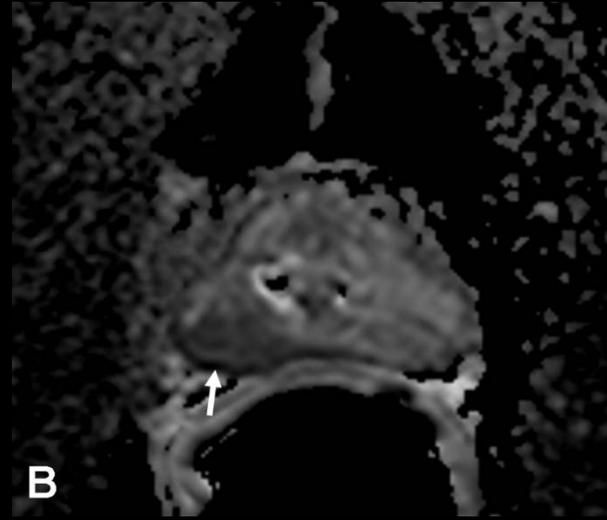
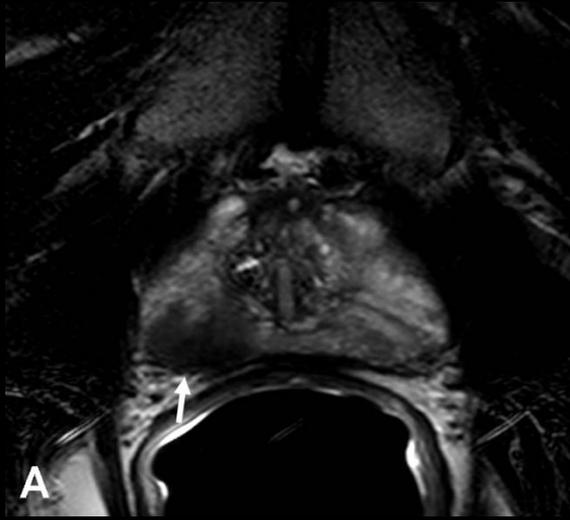
T₂ Mapping^{1,2}

- **Quantitative**
 - ✓ Generates reproducible results for longitudinal studies and inter- and intra-scanner comparisons.
 - ✓ Provides information for multi-parametric analysis (together with diffusion, DCE and MRS).
- **Prior iterations=long scan durations**

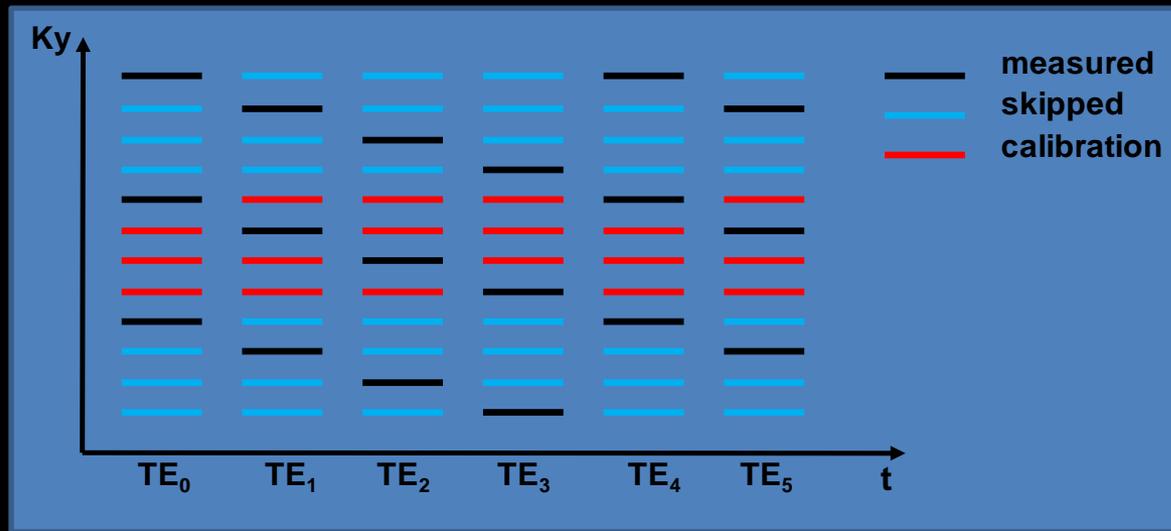
1. Storas, TH et al, 2008;28:1166-1172, J Magn Reson Imag.

2. Roebuck JR et al. 2009;27:497-502, Magn Reson Imag.





Fast T₂ Mapping Protocol



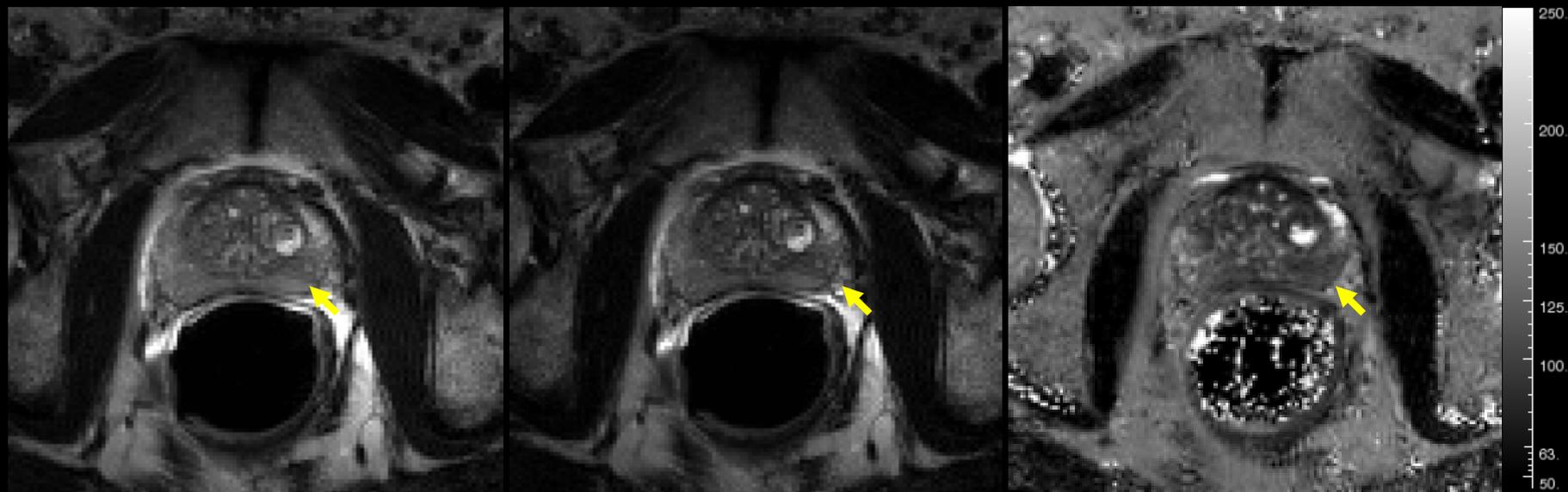
An accelerated TSE sequence

- Resolution = 1.09 mm \times 1.09 mm \times 3 mm
- Acquisition matrix = 256 \times 256
- Sixteen echoes with TE = 30, 45, 60, ..., 255 ms
- Undersampling factor = 4 with 24 calibration lines
- Scan time = 5 min 48 sec for 10 slices

Wei Liu PhD



Representative Images



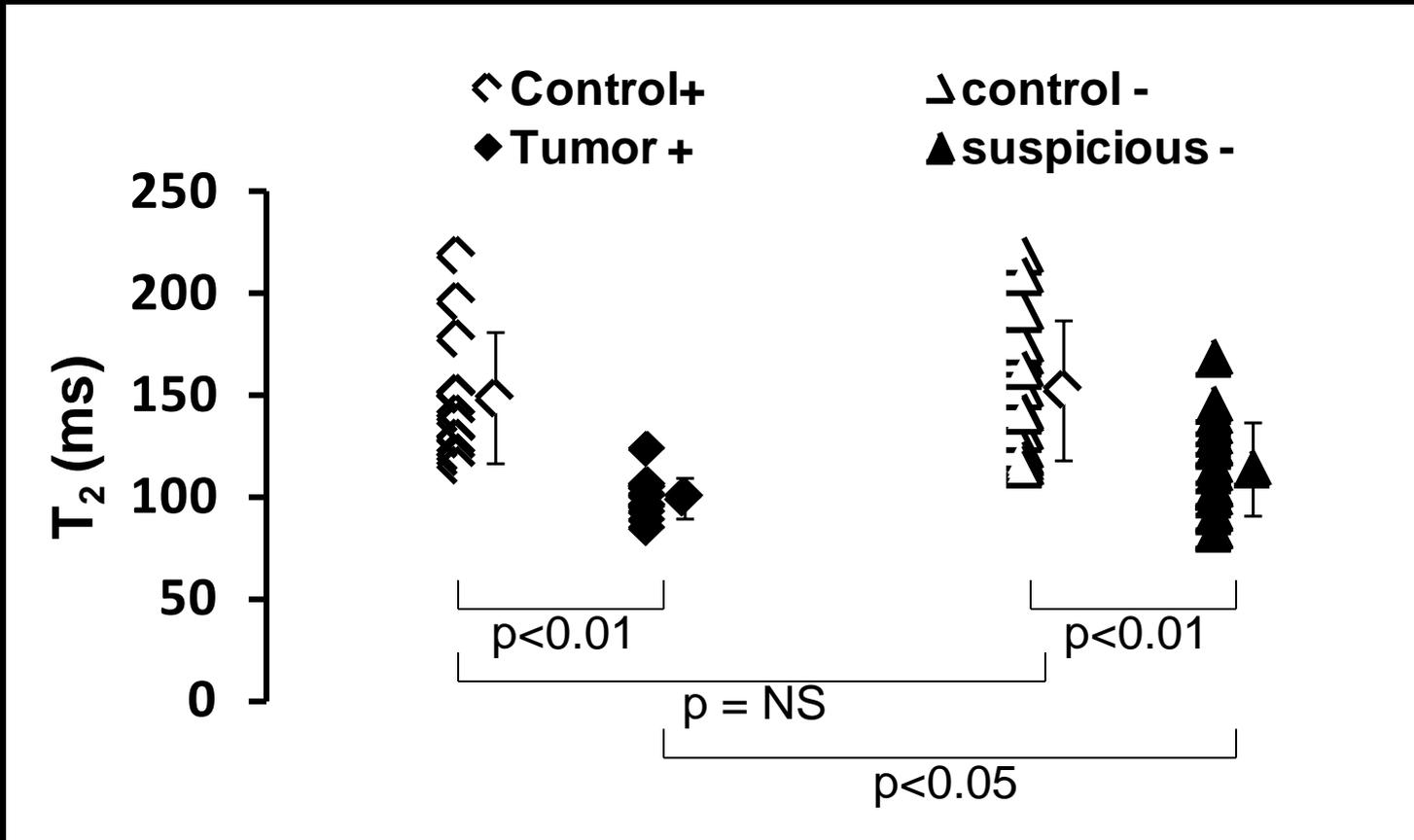
TE = 50 ms

TE = 80 ms

T₂ map



T₂ of Normal and Tumor Tissues

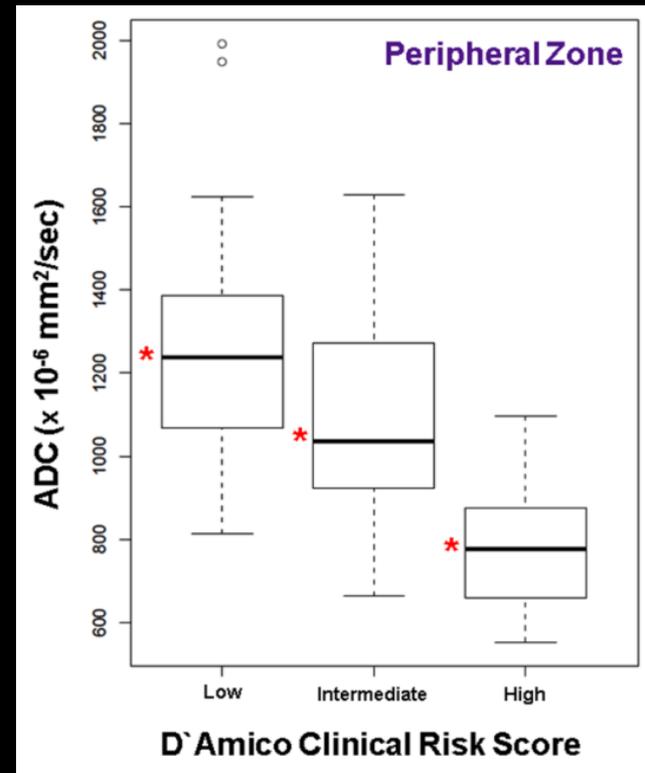
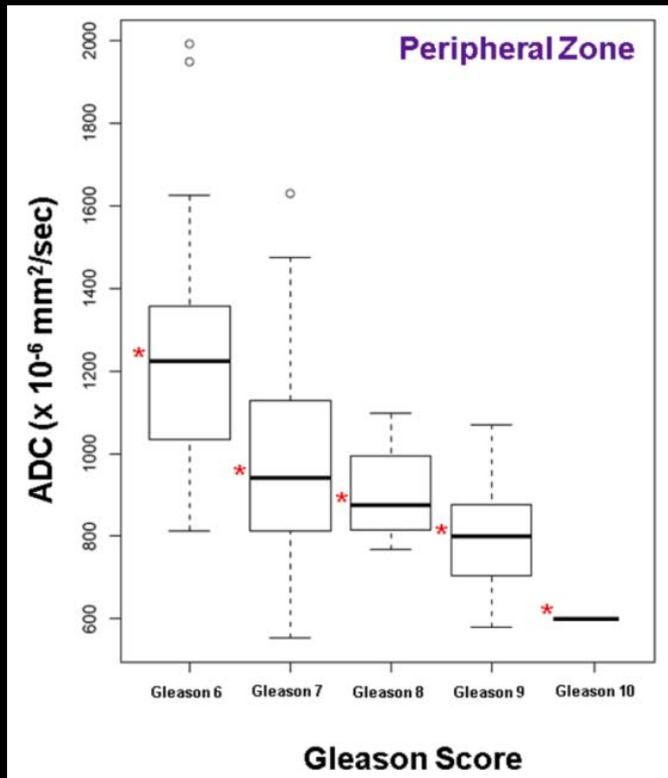


N = 7 for patients with tumor.

N = 11 for patients with lesions suspicious for cancer



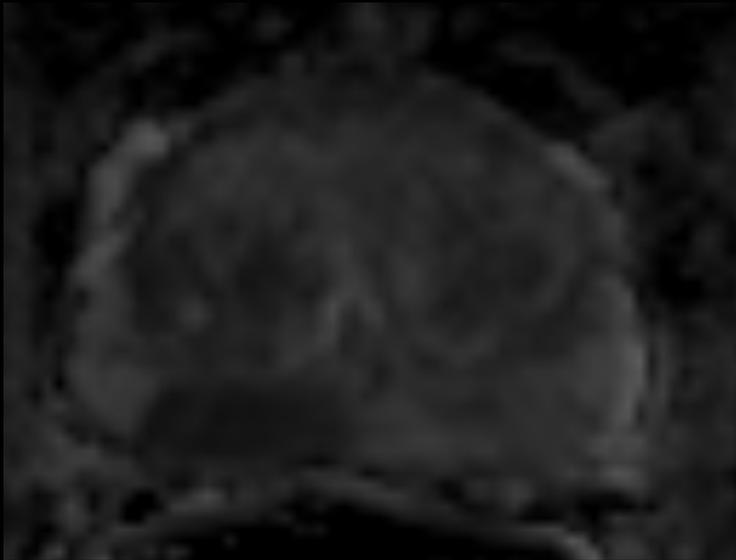
Quantifying Apparent Diffusion Coefficient



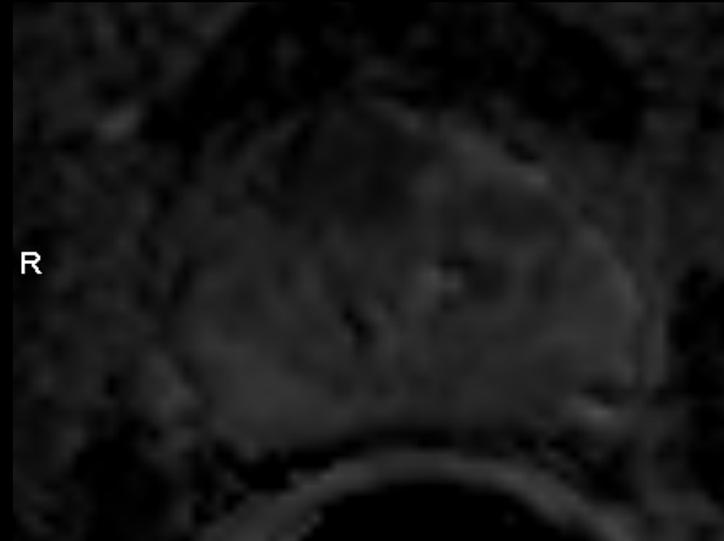
Turkbey B, et al. Radiology (in press)



Apparent Diffusion Coefficient



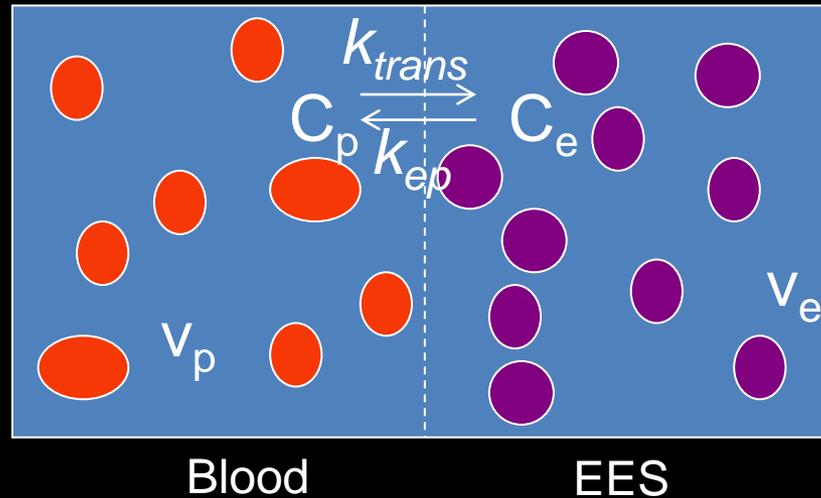
PSA 4.8 Gleason 3+3 5%



PSA 12.4 Neg Bxs



Quantitative pharmacokinetics maps from Dynamic Contrast Enhanced MRI



- Two Parameter Fit:

$$C_t(t) = k_{trans} \int_0^t C_p(u) \cdot e^{-k_{ep} \cdot (t-u)} du$$

- Three Parameter Fit:

$$C_t(t) = k_{trans} \int_0^t C_p(u) \cdot e^{-k_{ep} \cdot (t-u)} du + v_p \cdot C_p(t)$$

- Estimation of Pharmacokinetics parameter k_{trans} and k_{ep} depends on accurate estimation of concentration of agent in plasma C_p





PHILIPS

Load Bulk As Needed

Startup Dyn. Dyn. Time (sec)

3.0 3.10000

Temp. Smooth Spatial smooth

1 1

Blood T1 (ms) 1350

Tissue T1 (ms) 850

Save Current Series to Disk:

C:\DBIEX_Data\new

Signal Ratio (post/pre)

Delta R1

Conc. Only (mM)

Conc. + MTC (mM)

Re-Proc. AIF

Re-Proc. ROI

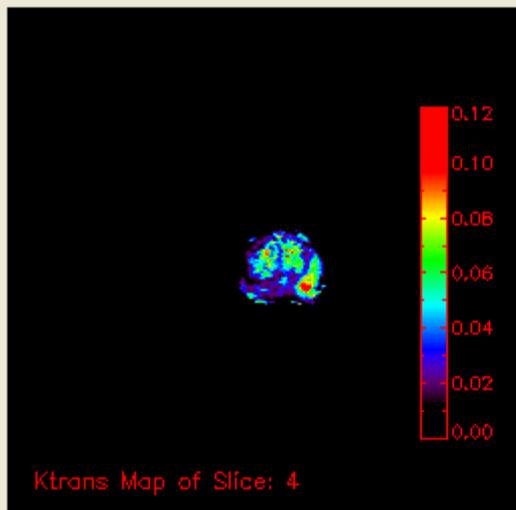
Process All

Exclude FPV

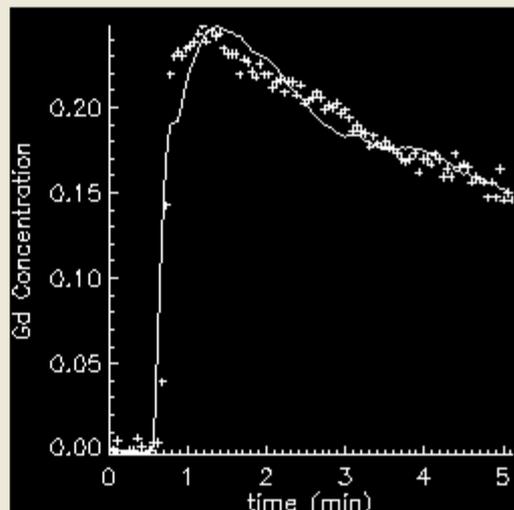
Include FPV

XROI

XROI_reload



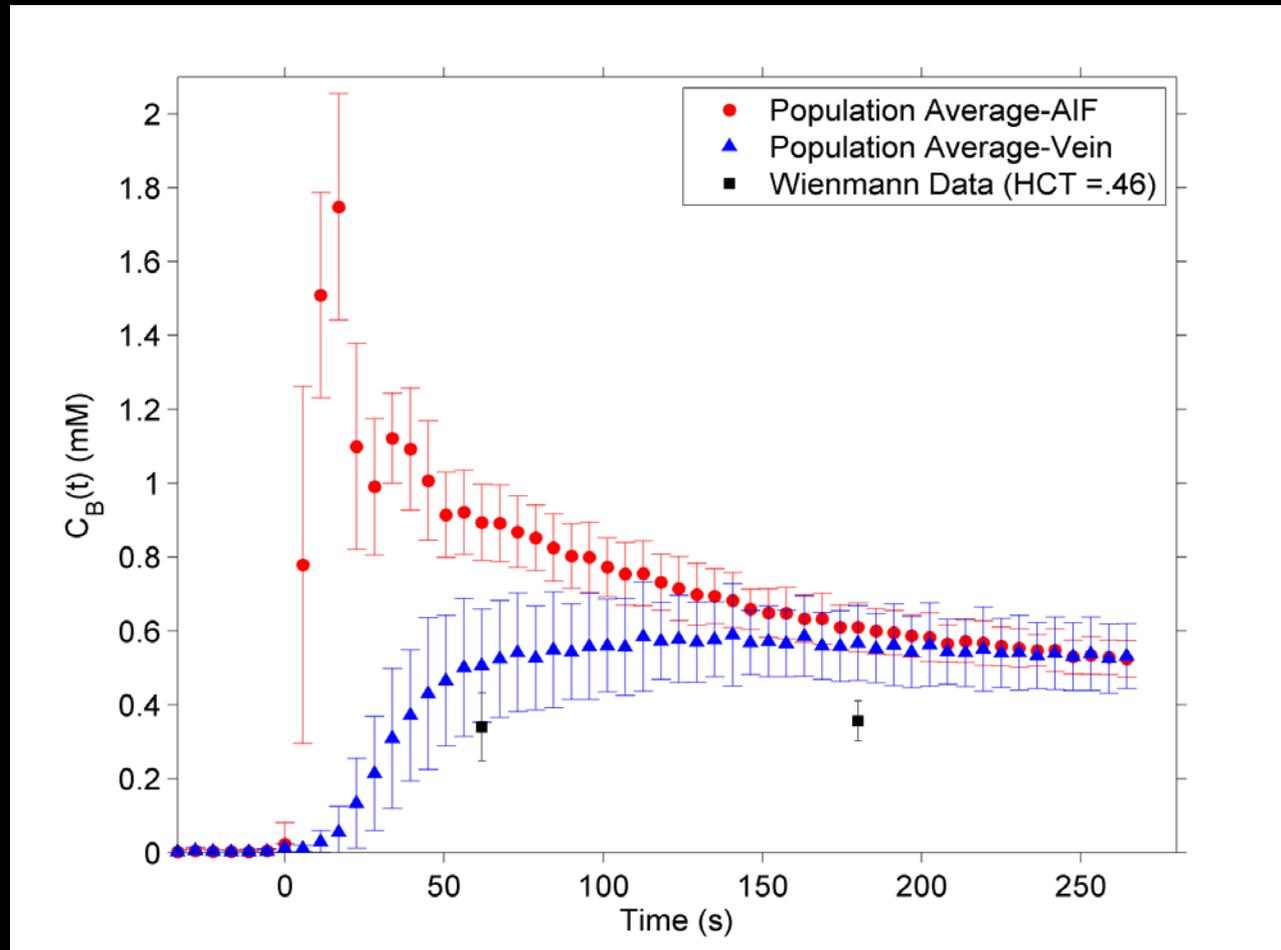
Ktrans Color R2 Thresh. 0.85



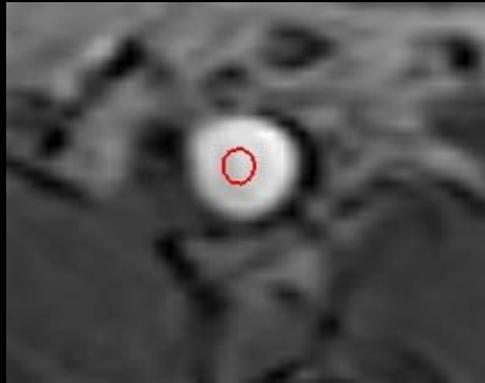
Attribute: Value(s):

Position(x,y)= (148, 141)
 Ktrans : 0.111359
 kep : 2.90820
 ve : 0.0382912
 AUGC : 16.8196
 fpv : 0.000000
 R2 : 0.955019
 T1 : 2355.5266

Inflow Suppressed Population Averaged Arterial Input Function



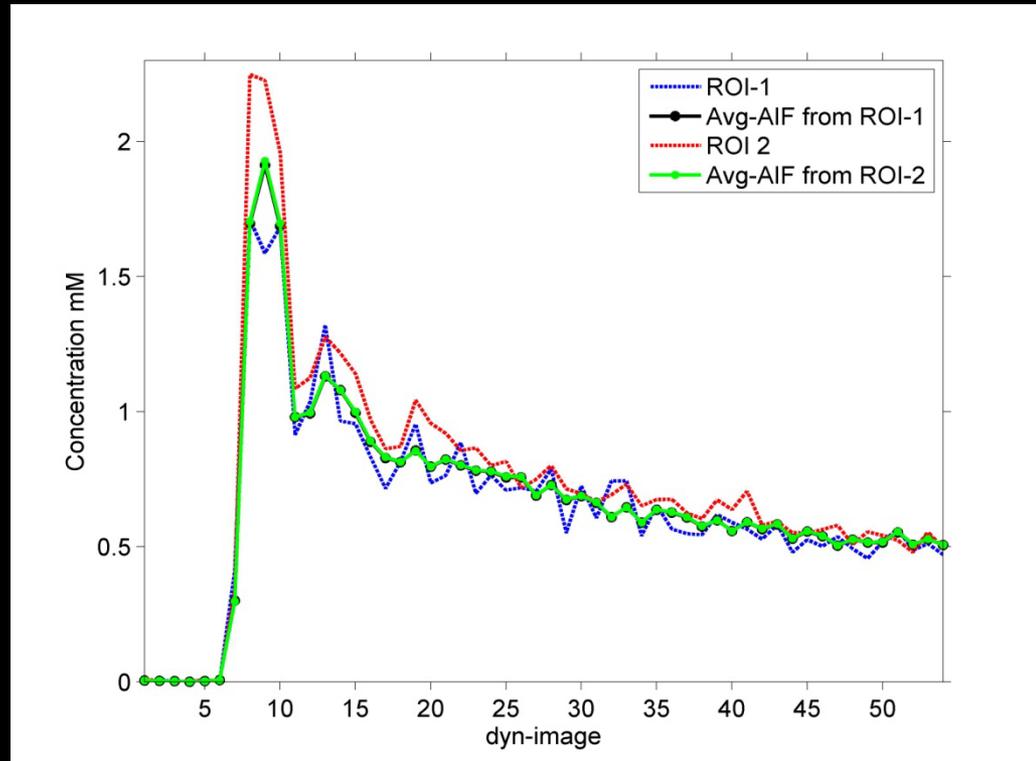
Automated Region of Interest Measurement



ROI-1 drawn on Slice 5

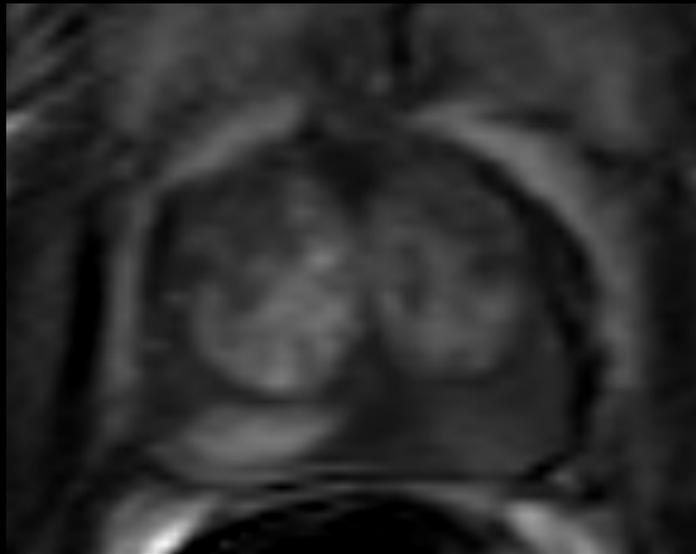


ROI-2 drawn on Slice 3



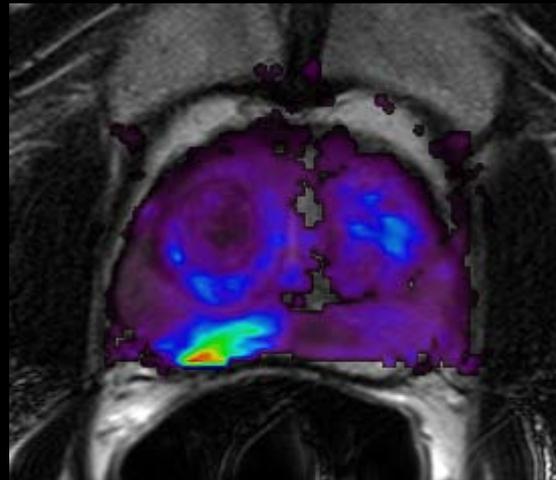
Avg-AIF obtained using our semi-automated algorithm is operator independent



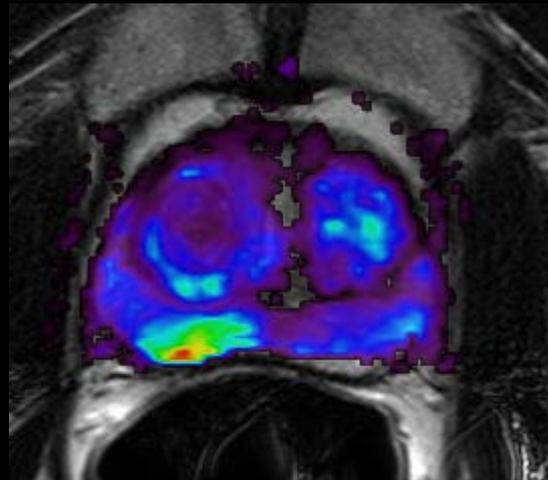


Raw DCE image: early enhancement

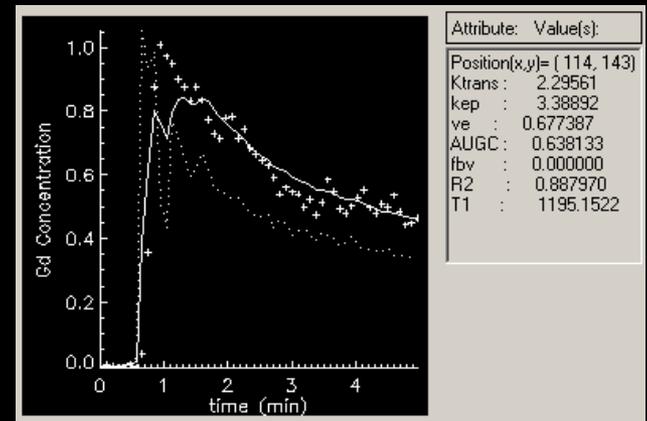
Permeability Maps using Quantitative arterial input function with population averaging and automated region of interest detection



Ktrans map

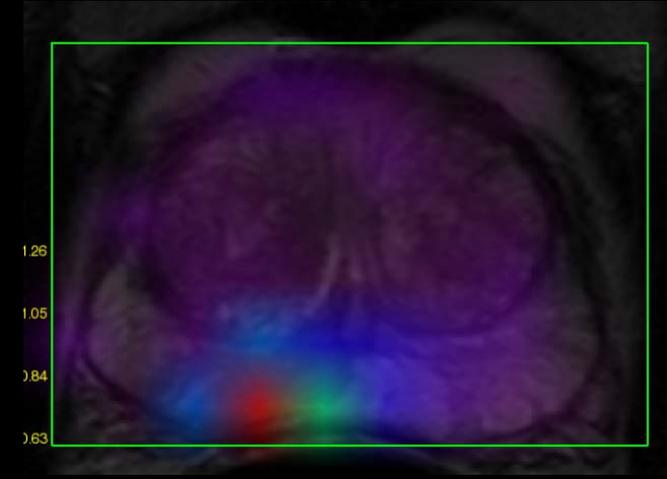
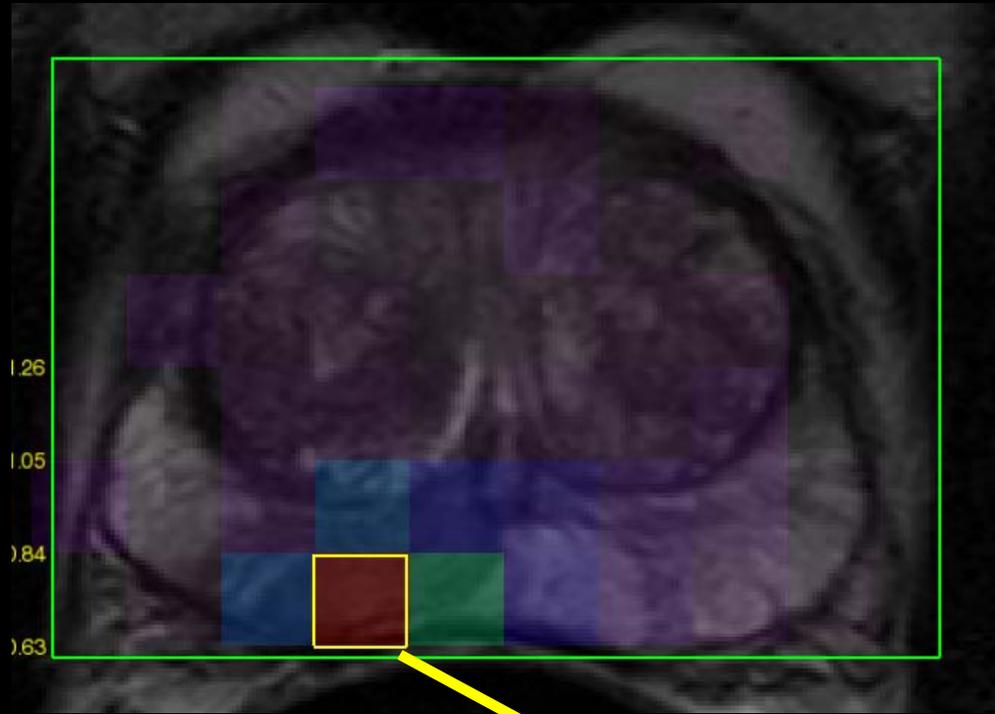


kep map



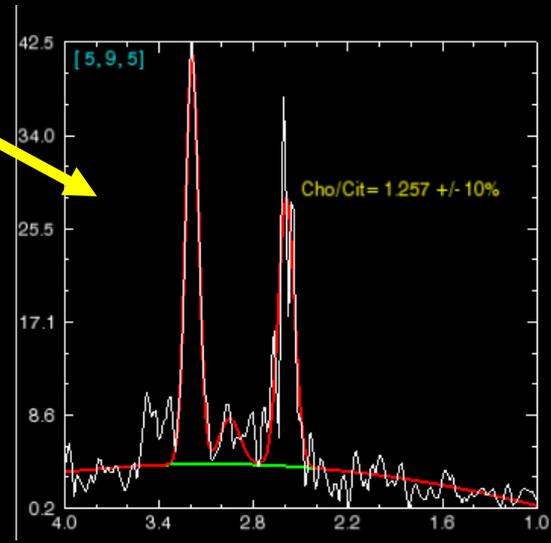
Gd-concentration curve of the lesion with the AIF overlay

MR Spectroscopy at 3T

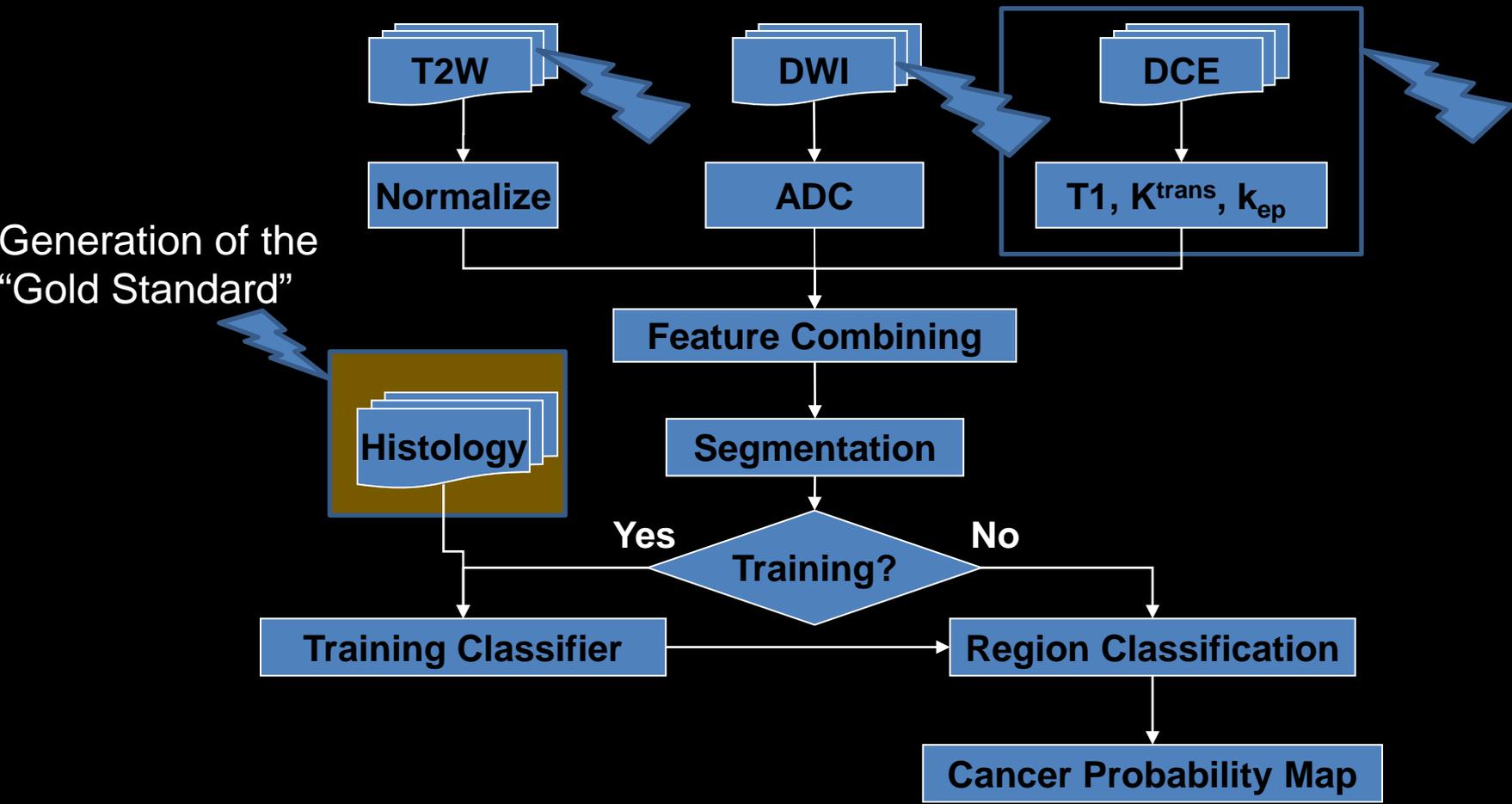


Interpolated MRS map

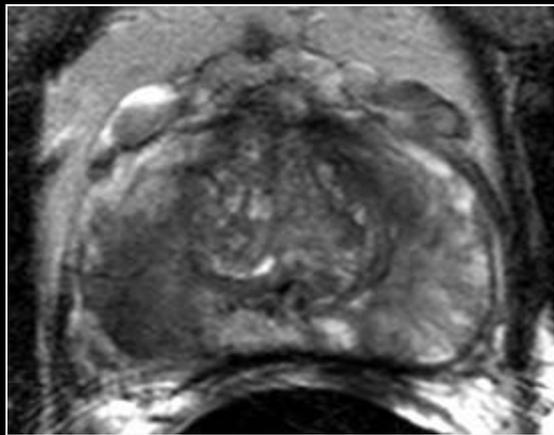
MRS shows highly positive lesion



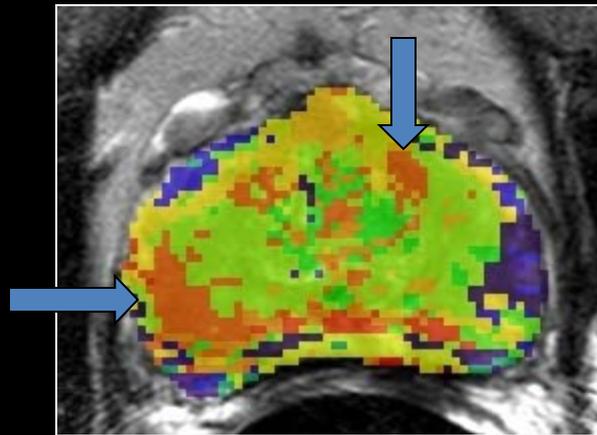
Design of Multi-parametric Analysis System



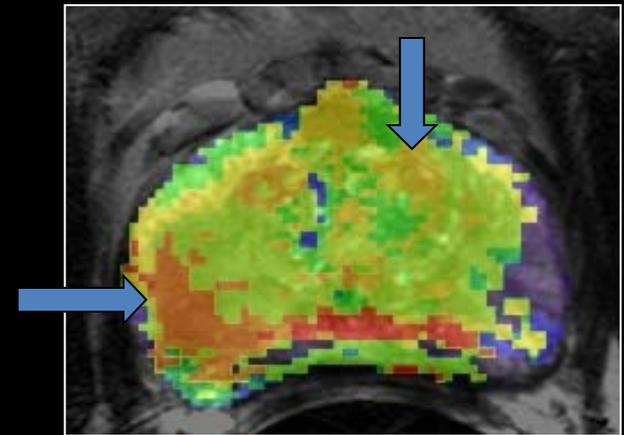
MR-Histology Correlation Solution



(a) T2W Image



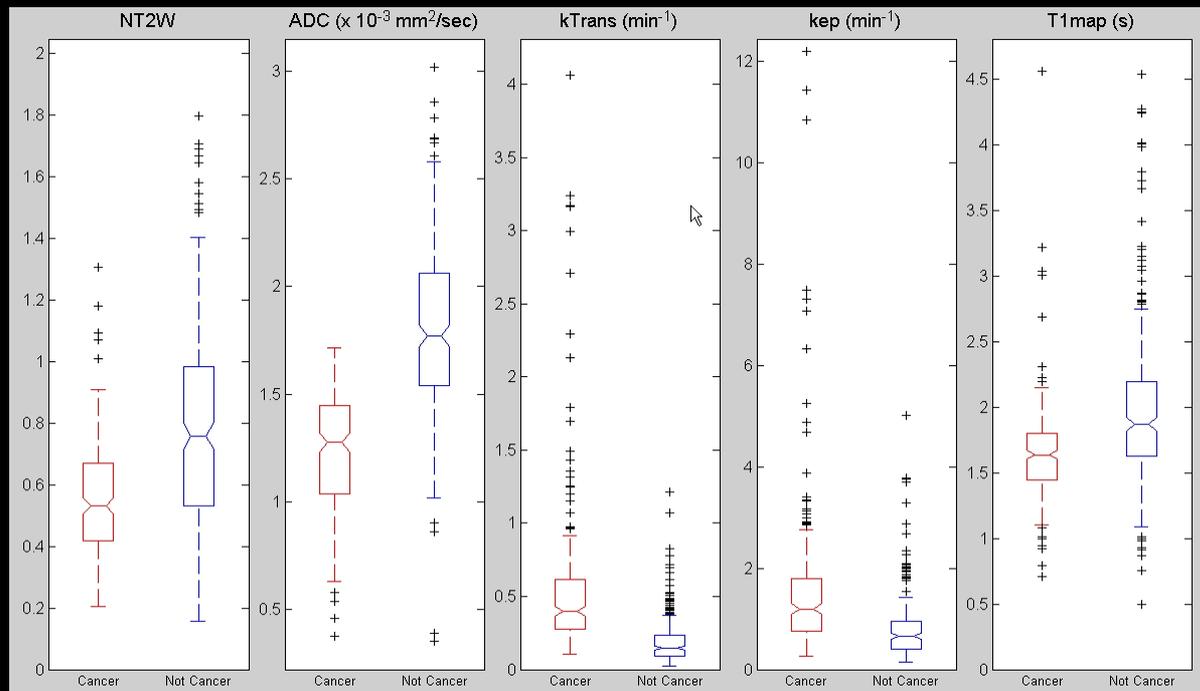
(b) Cluster Map



(c) Region Map

- Clustering is performed on MP-MRI
- Region map based on 3D-connectivity of voxels
- Correlate region map to histology to identify cancer and non-cancer regions

Quantitative values of Multiparametric-MRI for Cancer and Non-cancer Region



Patient Population consisted of 31 patients:

- 7 patients excluded due to motion artifacts, dce analysis problems, and/or specimen processing error

From 24 patients –

- 225 cancer region identified
- Observed GS 6 to GS 9 tumors
- 264 non-cancerous region identified

Optimized Results

| | Pathology Cancer | Pathology Not Cancer | Precision |
|-------------------------|----------------------|-------------------------|-----------|
| Predicted Cancer | 203 | 27 | 88% |
| Predicted Not Cancer | 22 | 237 | 92% |
| Class Recall | 90% [Sensitivity] | 90% [Specificity] | |

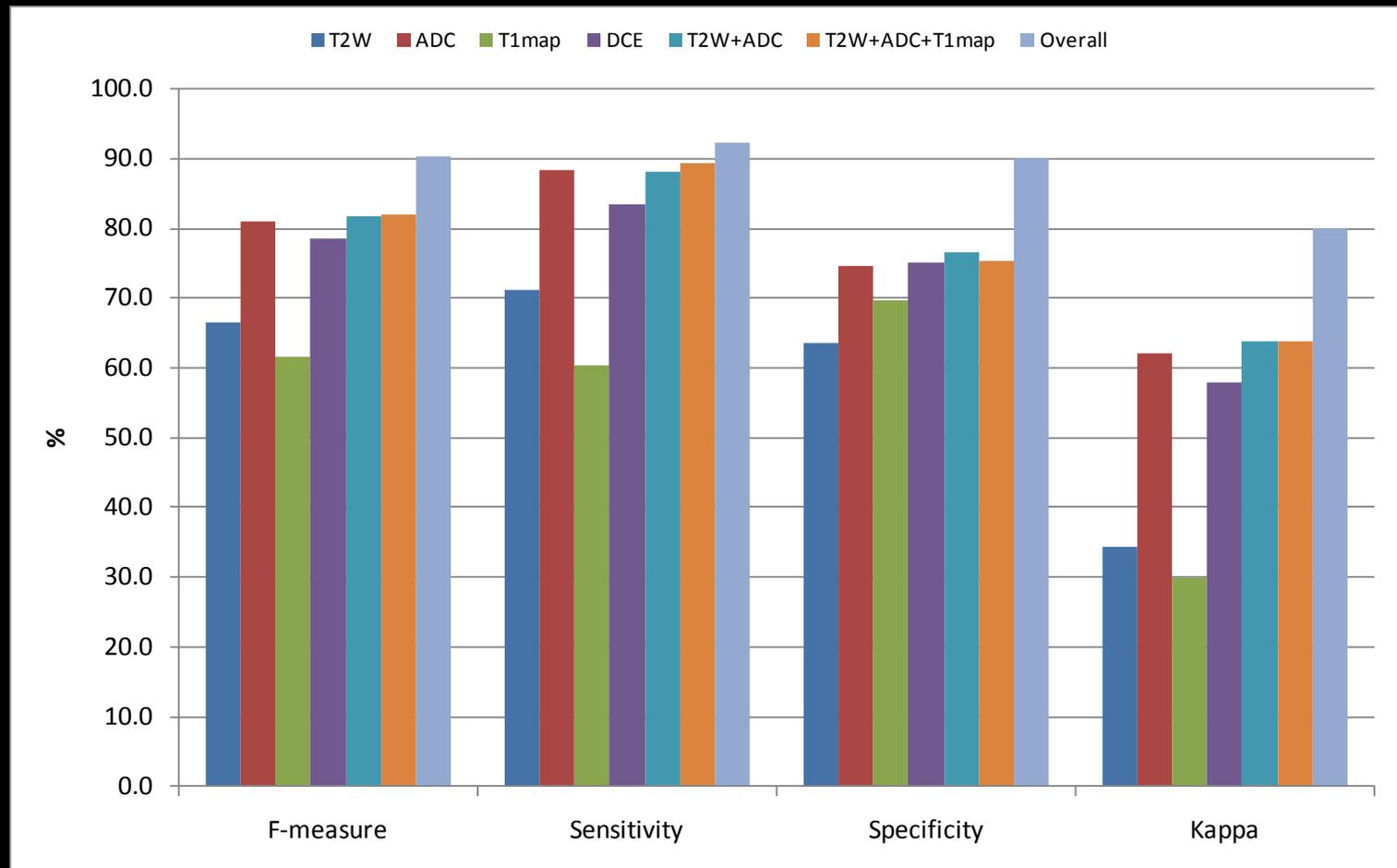
F-measure = 89% (also known as Positive agreement)

Kappa Coefficient = 80% (Rater's agreement)

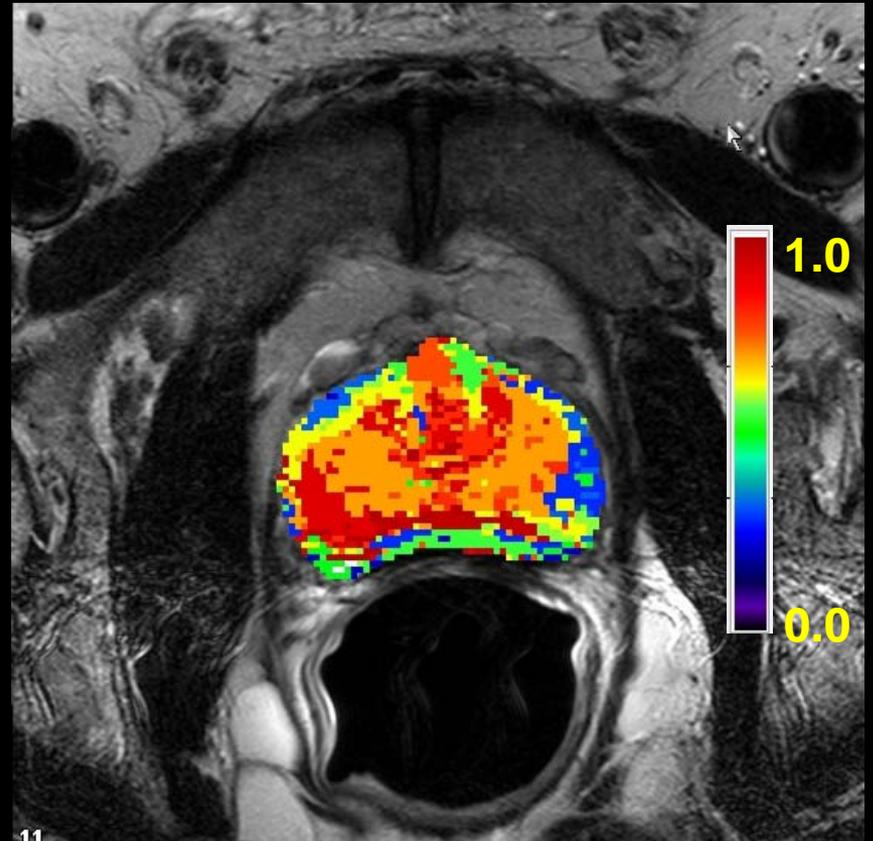
After Optimization : 5% increment in sensitivity and F-measure, while 20% increase in the Kappa coefficient



Comparison with Single Modality



Cancer Probability Map



Designated as "trade secret".



Molecular Imaging Program



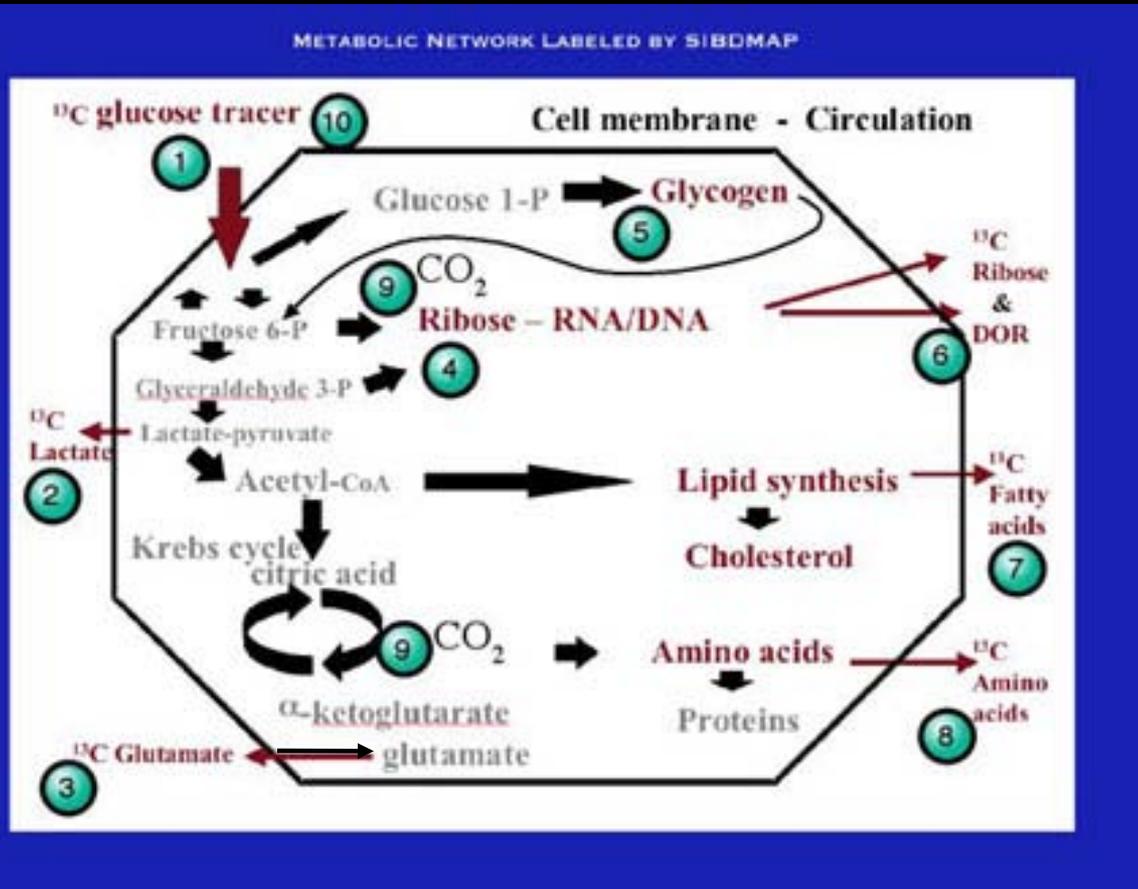
Molecular Imaging of Prostate Cancer: PET and SPECT



Metabolic Hallmarks



Warburg

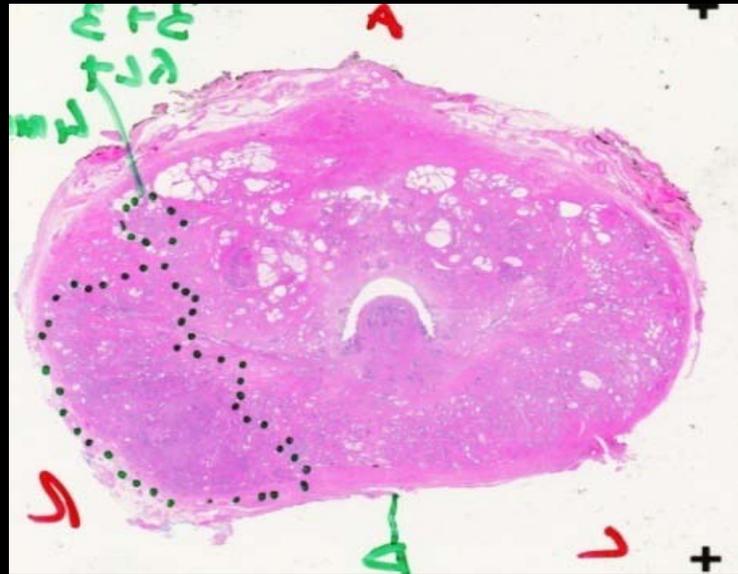
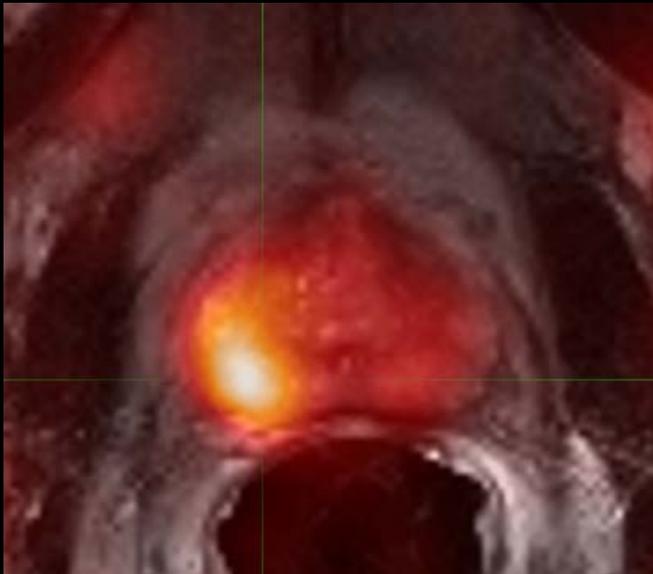
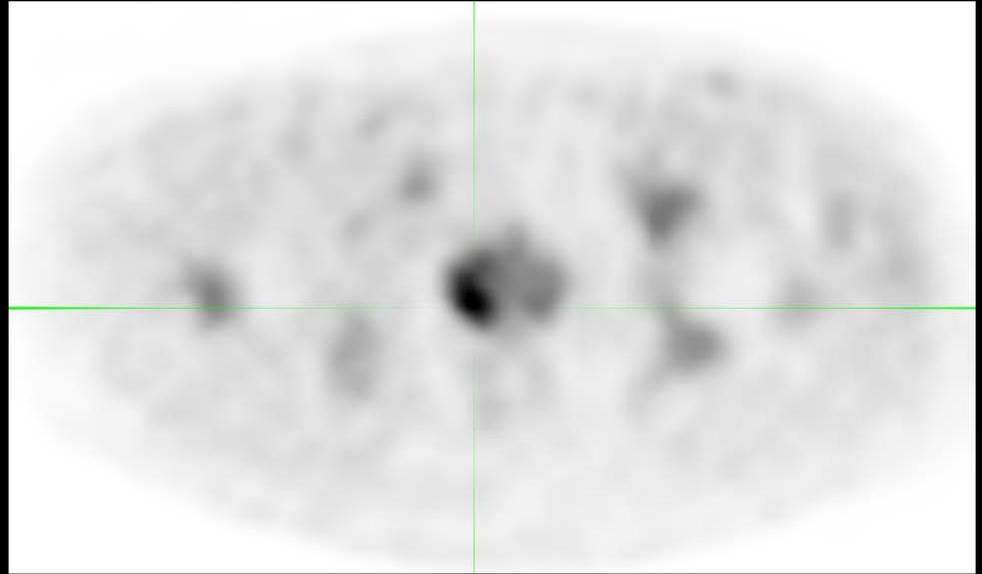
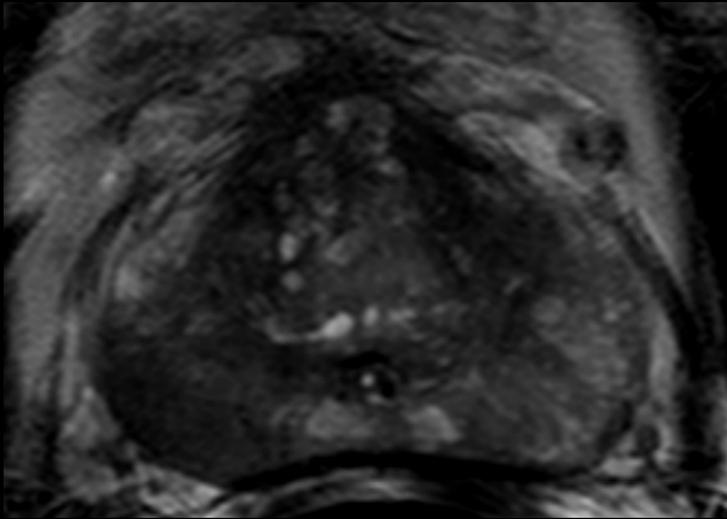


Fatty Acid Synthesis

Amino Acid Metabolism

^{11}C -Acetate PET/CT Imaging of Prostate Cancer

- Acetate: a fatty acid precursor
- Uptake may correlate with fatty acid synthetase
- A phase 2 trial of 40 patients
- ^{11}C -Acetate PET-CT synthesized in the PET Department NIH



58, M,
PSA=8.2
Gleason
3+4 tumor

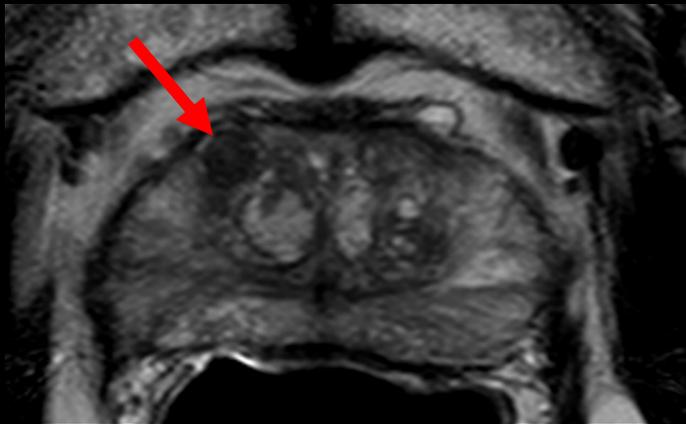
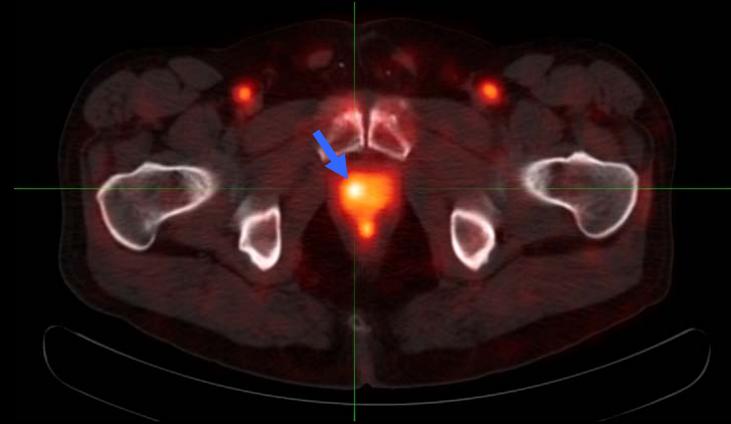
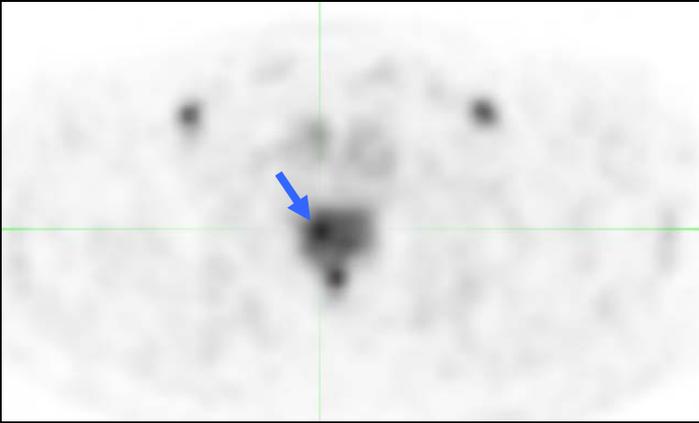


^{18}F -FACBC PET-CT Imaging of Prostate Cancer

- F-ACBC: A synthetic L-leucine analogue
- Increased amino acid transport within tumors
- A phase 2 trial of 30 patients
- ^{18}F -FACBC PET-CT vs. MP-MRI vs. histopathology
- Recently open to accrual (7/30 patients)
- *In collaboration with GE Healthcare: produced in Greenbelt, MD at Cardinal Health*



^{18}F -FACBC PET-CT Imaging of Prostate Cancer



57, M, PSA=5.41

Gleason 3+3 tumor

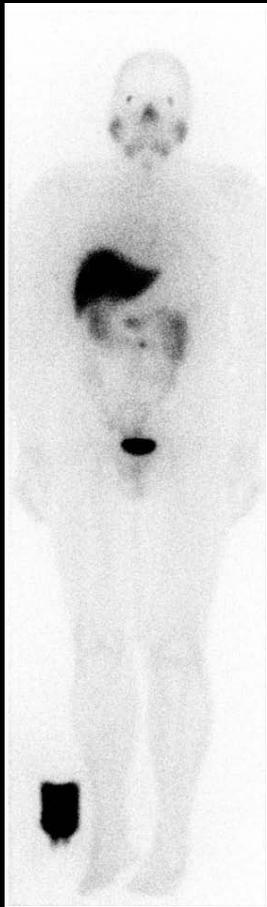
5-7min post-injection PET-CT



^{123}I -MIP-1072 (Trofex) SPECT Imaging of Prostate Cancer

- Small molecule targeting the extracellular domain of prostate specific membrane antigen (PSMA) for SPECT imaging
- A phase 2 trial of 20 patients in collaboration with Molecular Insight Pharmaceuticals
- 3- 6 hours post injection
 - Optional 1 day post injection
 - Optional compact endorectal gamma camera imaging

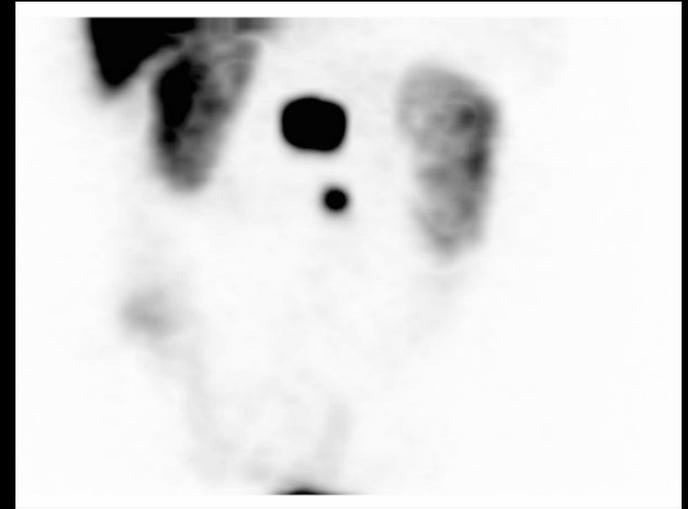
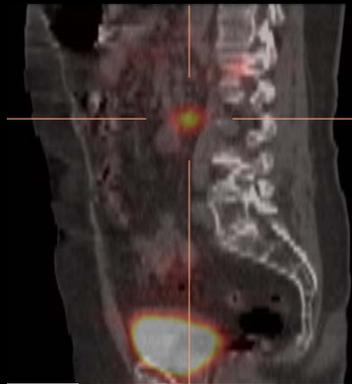




Anterior



Posterior



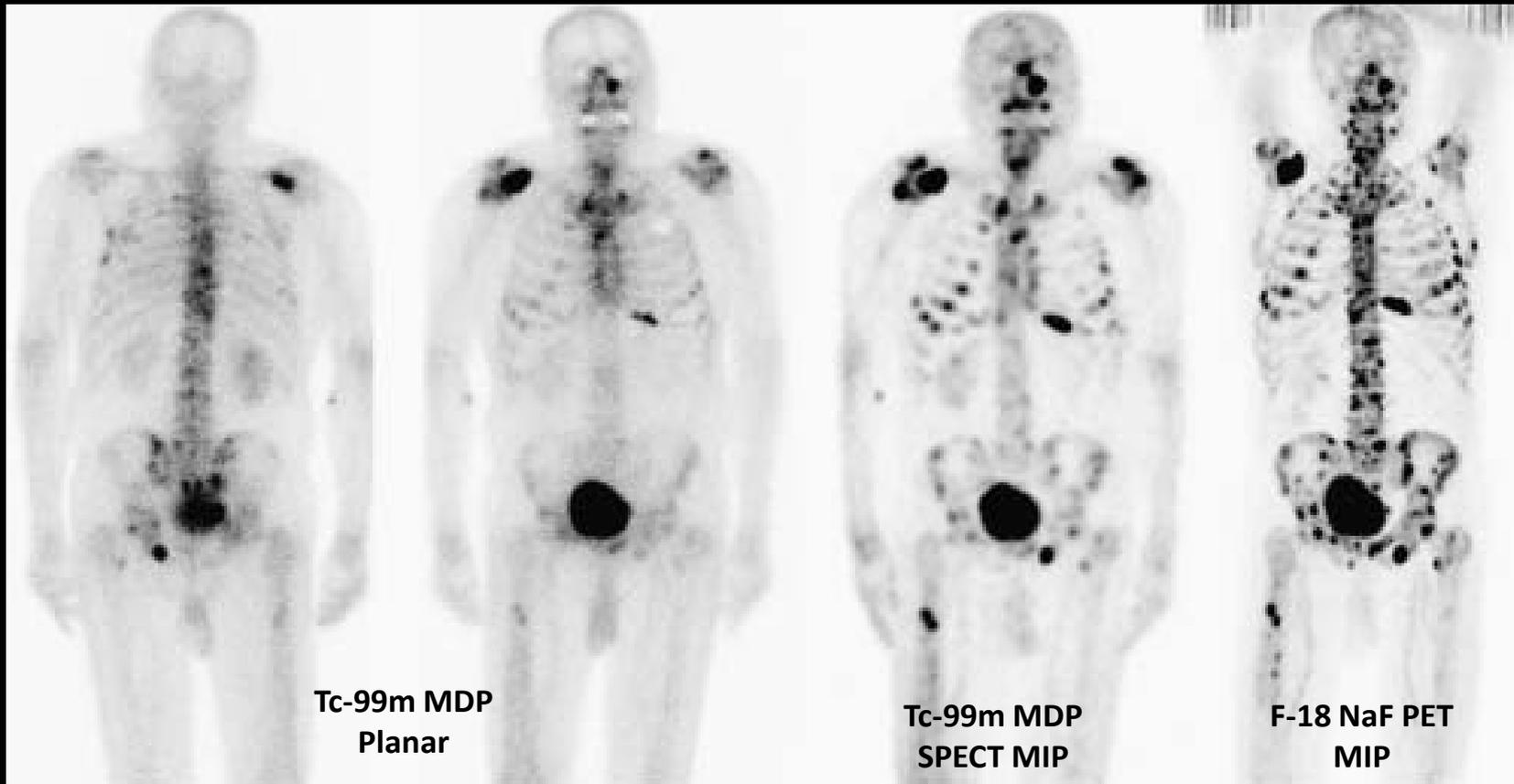
*Courtesy of Dr. J. Babich,
Molecular Insight
Pharmaceuticals*



^{18}F -Sodium Fluoride PET-CT

- ^{18}F -Sodium Fluoride: A calcium analogue
- Incorporated into hydroxyapatite
- A phase 2 trial of 60 patients
 - First 30 patients have reproducibility studies
- Recently opened to accrual (5/60 patients)
- *Produced by Cardinal Health*

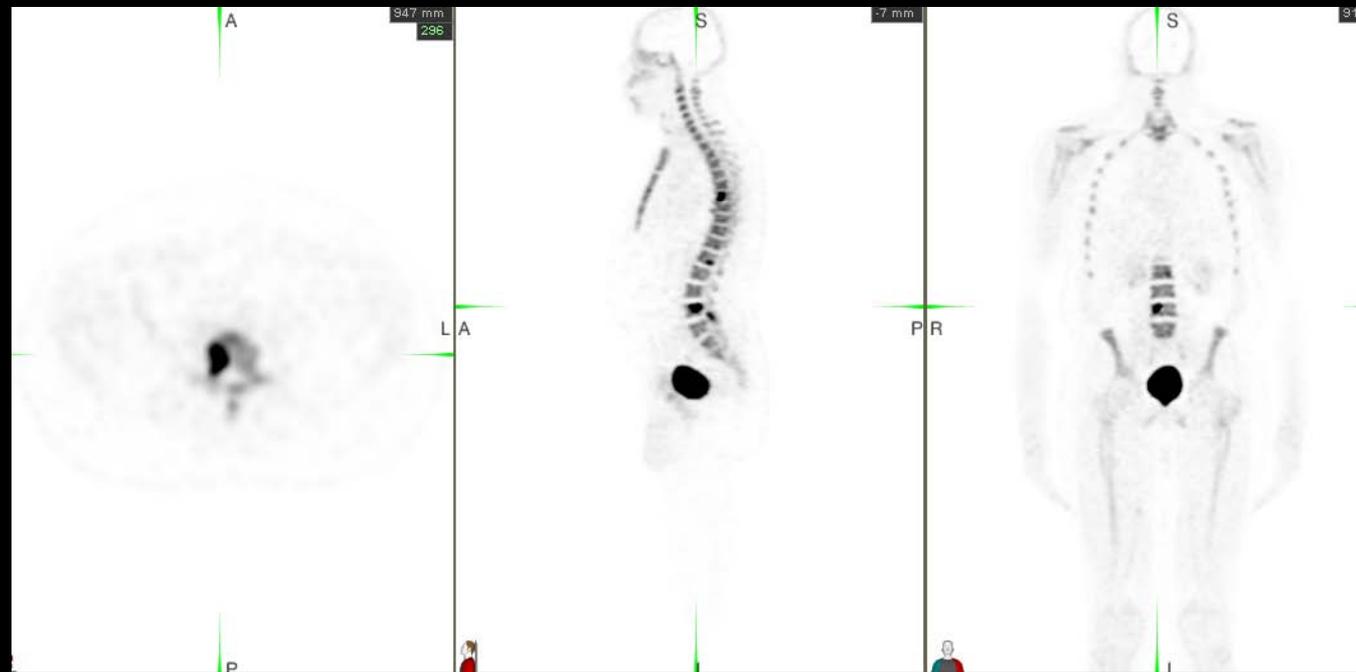
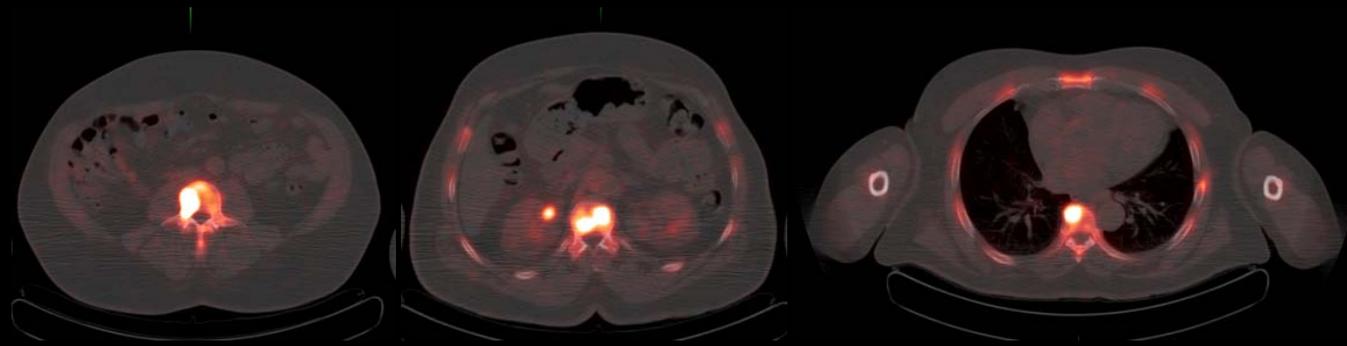
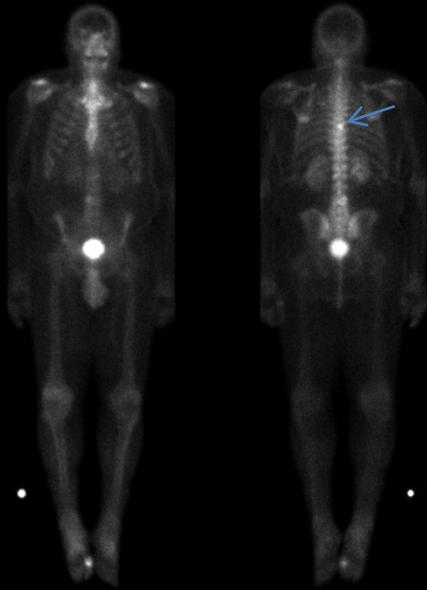
82-y-old patient with numerous bone metastases,



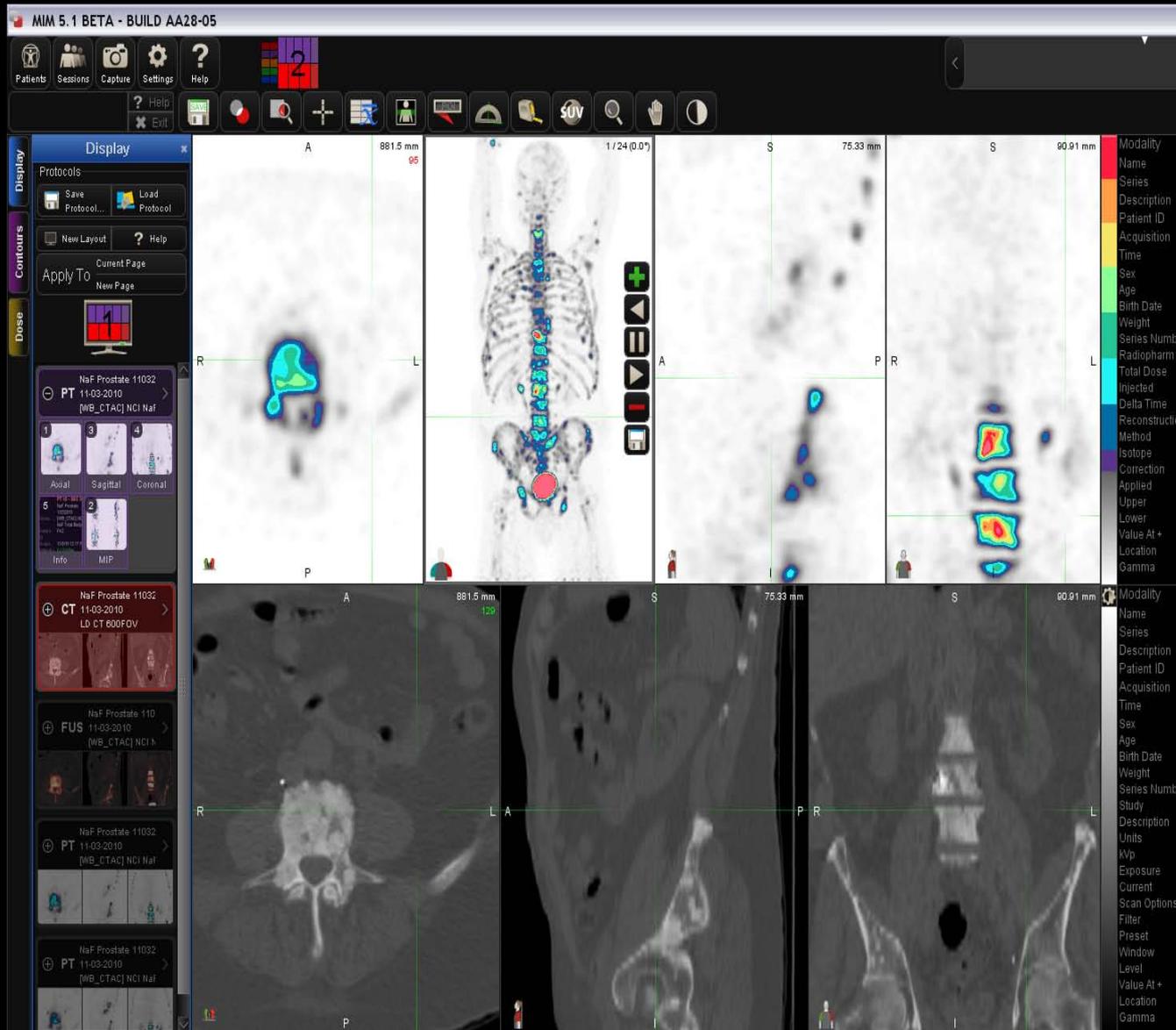
^{18}F -NaF PET/CT scan

64 yo, male with prostate cancer with elevated PSA level

$^{99\text{m}}\text{Tc}$ -MDP Bone scan



Automated Bone Lesion Detection



Summary

- Improving anatomical and functional prostate MRI
 - Improving H/P correlation
 - Quantitative MRI
 - Decision Support Systems
- Exploring PET and SPECT tracers for more accurate localization of prostate cancer
 - **Metabolomic Imaging:** Fatty Acid and Amino Acid
 - **Molecular Imaging:** Prostate Specific Membrane Antigen, Sodium Fluoride
- Unique features:
 - Resource intense, multidisciplinary, integrated



Future Directions

- Continue to improve quantitation of MRI parameters
- Increase sophistication of Decision Support System to incorporate tumor aggressiveness
- Develop and compare additional molecular imaging probes (EpCAM, ferumoxytal)
- Translate diagnostic information into image guided biopsy and therapy (Dr. Pinto)

Acknowledgements

MIP

- Baris Turkbey
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- Karen Kurdziel
- Vijay Shah
- Steve Adler
- Yolanda McKinney
- Revia Wade
- Dagane Daar
- Gideon Kwarteng
- Philip Eclarinal
- Liza Lindenberg
- Mirna Martinez

NIH

- Peter A. Pinto/UOB
- Marston Linehan, UOB
- Maria Merino/Lab of Pathology
- William Dahut/MOB
- Bradford Wood/DRD, NCI
- Paula Jacobs/NCI
- Aradhana Kaushal/ROB
- James Gulley/MOB
- Joanna Shih/NCI
- Thomas Pohida/NIH

Outside collaborators

- ☐ Philips Medical Systems
- ☐ GE Healthcare
- ☐ Molecular Insight Pharmaceuticals

