Surgical Planning Laboratory
Brigham and Women's Hospital
Boston, Massachusetts USA

a teaching affiliate of
Harvard Medical School

Quantitiative MRI of prostate cancer as a biomarker and guide for treatment

Fiona Fennessy, MD PhD (PI)

Sandeep Gupta, PhD

Andrey Fedorov, PhD

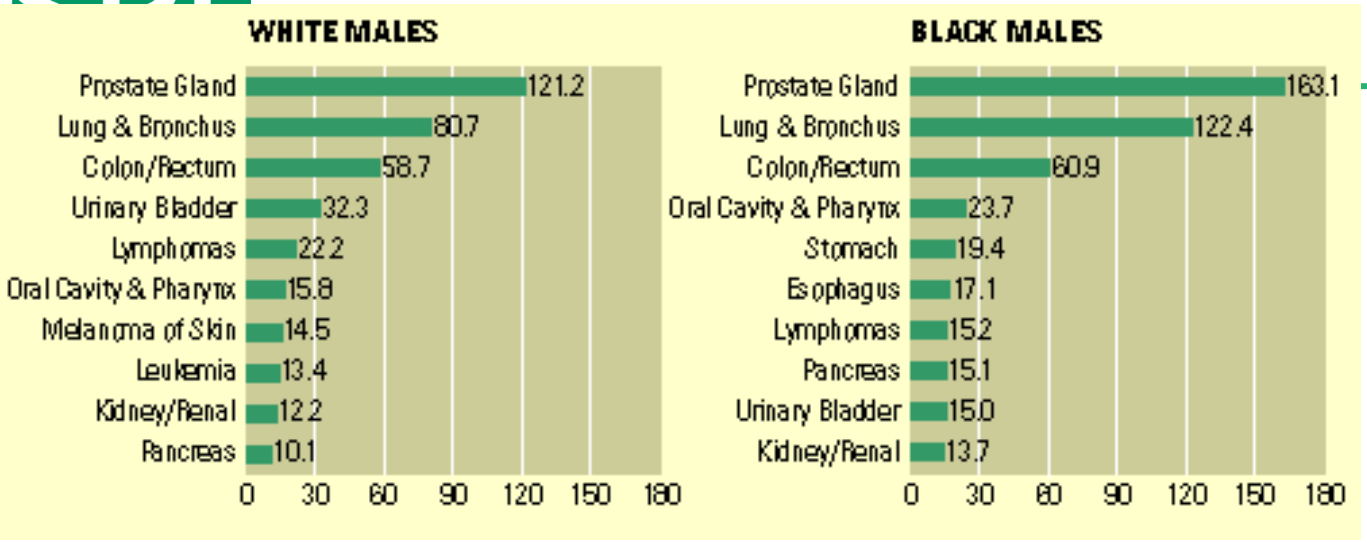
Michelle Hirsch, MD

Robert Mulkern, PhD

Ehud Schmidt, PhD

Clare Tempany, MD

Clinical problem: Localized Prostate Cancer



NCI: **Age-Adjusted Cancer Incidence Rates, 1987-1991**

(per 100,000)

	New cases	Deaths
2006	203,415	28,372
2010	217,730	32,050
2015	**450,000**	

Present: "Radical" treatment of the whole gland, watchful waiting

Future: Treatment tailored to individual patient

Role for MRI: Tumor detection, treatment planning & guidance, assessment of volumetric and functional response to therapy.

Clinical rationale

To develop quantitative pixel-wise tumor maps for focal prostate cancer

1. **Biomarker guide for focal therapy planning**
2. **Monitor tumor response in "low risk" localized prostate cancer group, post focal therapy**

   (Determine "expected" criteria for post-ablation margin and surrounding tissue, and determine if differentiation of residual tumor from peri-ablation enhancement possible using MP mapping)
3. **Monitor tumor response in "high risk" localized prostate cancer group, post neoadjuvant ADT**

   (Is multiparametric imaging (with the focus on DCE MRI) a predictor of pathological response?)

Specific aims

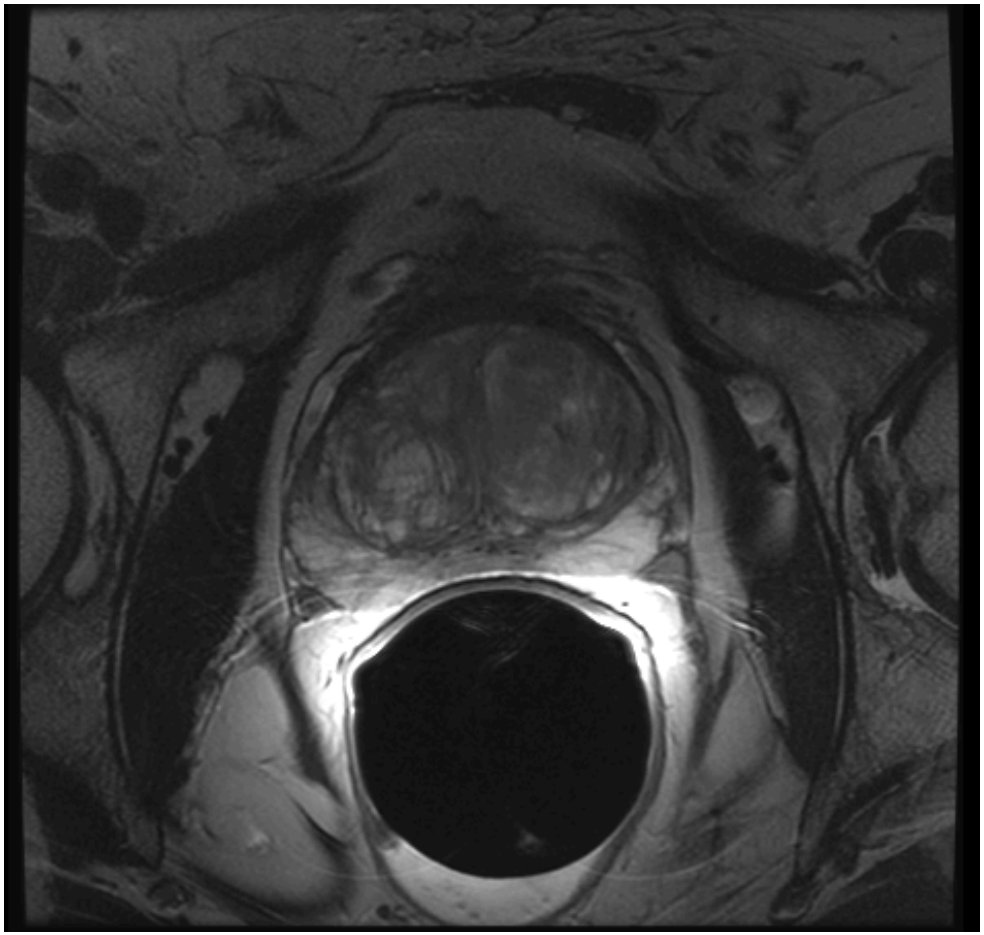
1. To optimize prostate MR analysis tools.
2. To clinically validate prostate MR quantitative analysis tools
3. To determine the clinical use of the analysis tools as a biomarker guide for targeted therapy and as a surrogate for disease recurrence in low-risk prostate cancer patients
4. To determine the clinical use of the analysis tools in evaluating tumor response to treatment with neoadjuvant androgen deprivation therapy (ADT) in patients with high-risk prostate cancer

MRI imaging protocol

- 3T GE magnet
- Medrad air-inflated endorectal coil
- Sequences include
  - T2w
  - T1w (pre- and post-contrast)
  - T1 mapping (variable FA and/or variable TR)
  - DCE (~4.6 sec time resolved)
  - DWI (b0-500 and b0-1400)
  - ADC maps calculated by scanner software

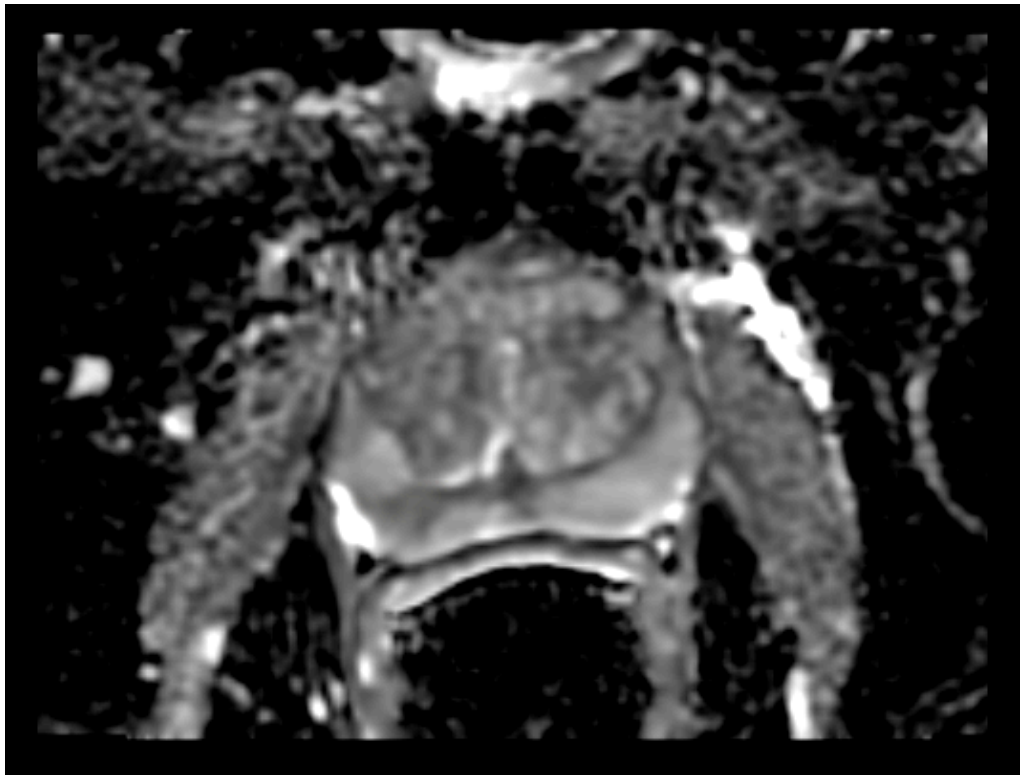
T2w MRI

- FRFSE sequence
- ~ 0.4x0.4x3 mm resolution
- Tumor cellularity/ extracellular water
- Qualitative assessment only



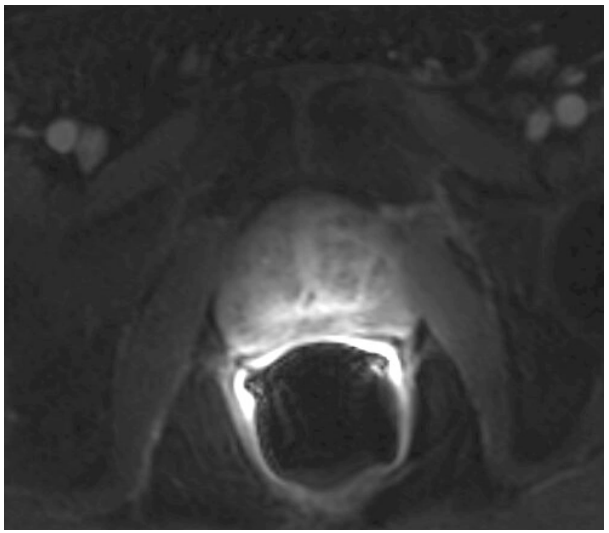
DWI MRI, ADC maps

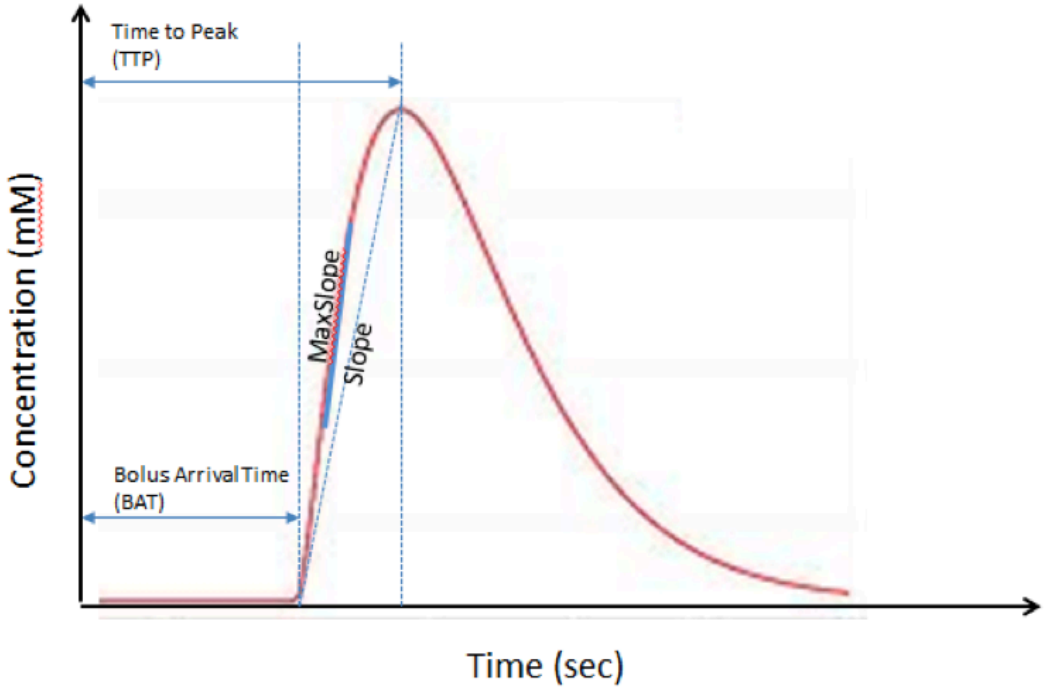
- Hypercellularity, enlargement of the cell nuclei
- ~0.7x0.7x3 mm
- b0-500, b0-1400



Dynamic Contrast Enhanced (DCE) MRI

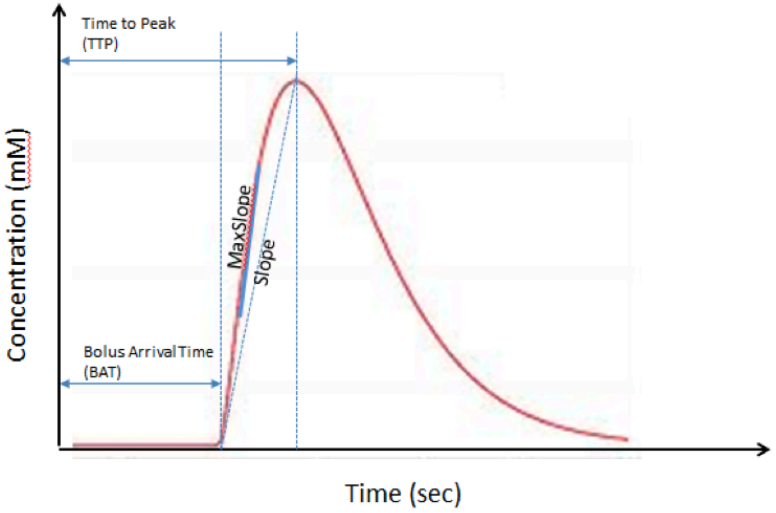
- ~0.9x0.9x6 mm, ~4.6 sec/frame
- Microvascularity of the tumor
- Qualitative assessment used in clinic
- Can be used for modeling and quantitative parameter estimation



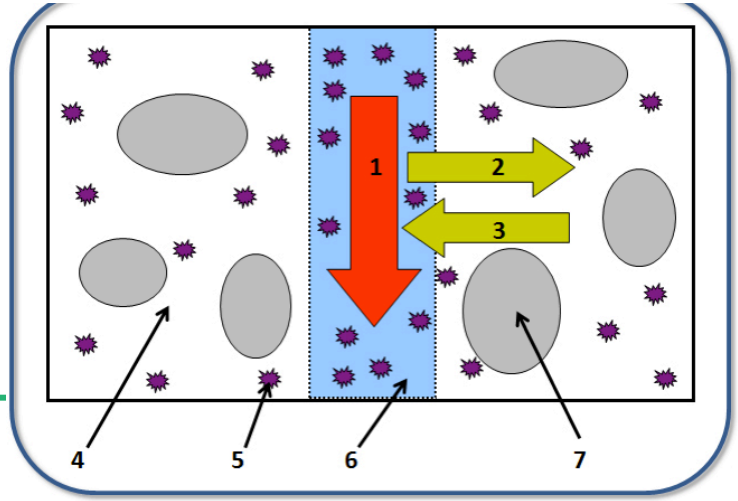


DCE post-processing (GE)

- "Empirical" parameters
  - Maximum slope of the uptake curve
  - Area under the curve (AUC)
  - Time to peak (TTP)
- "Derived" parameters
  - 2-compartment General Kinetic Model (Generalized Tofts-Kermode Model)
    - Extravascular extracellular space (ve), transfer rate from plasma to EES (Ktrans)



$$\frac{dC_{\text{tiss}}(t)}{dt} = K^{\text{trans}} C_{\text{p}}(t) - k_{\text{ep}} C_{\text{tiss}}(t)$$



DCE post-processing prerequisites

- "Empirical" and "Derived" parameters
  - Conversion of the signal intensity into concentration units
- "Derived" parameters
  - Estimation of Arterial Input Function (AIF)

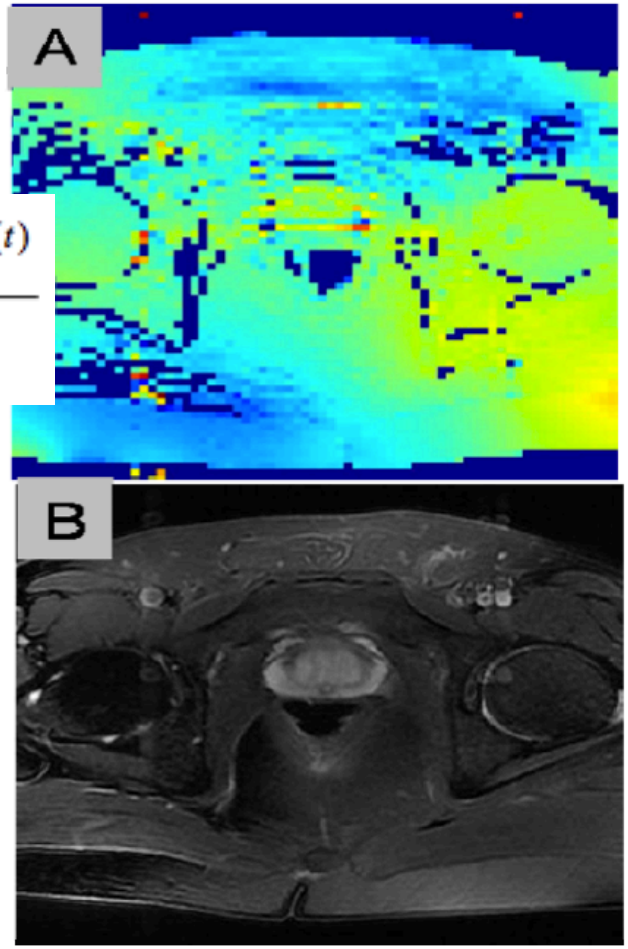
T1 mapping for PCa DCE

$$\frac{dC_{tiss}(t)}{dt} = K^{trans} C_p(t) - k_{ep} C_{tiss}(t)$$

$$\frac{SIpre}{SI(t)} = \frac{(1 - e^{-TR/T_{1pre}})}{1 - \cos\alpha e^{-TR/T_{1pre}}} \frac{1 - \cos\alpha e^{-TR/T_1(t)}}{(1 - e^{-TR/T_1(t)})}$$

Conventional approaches:

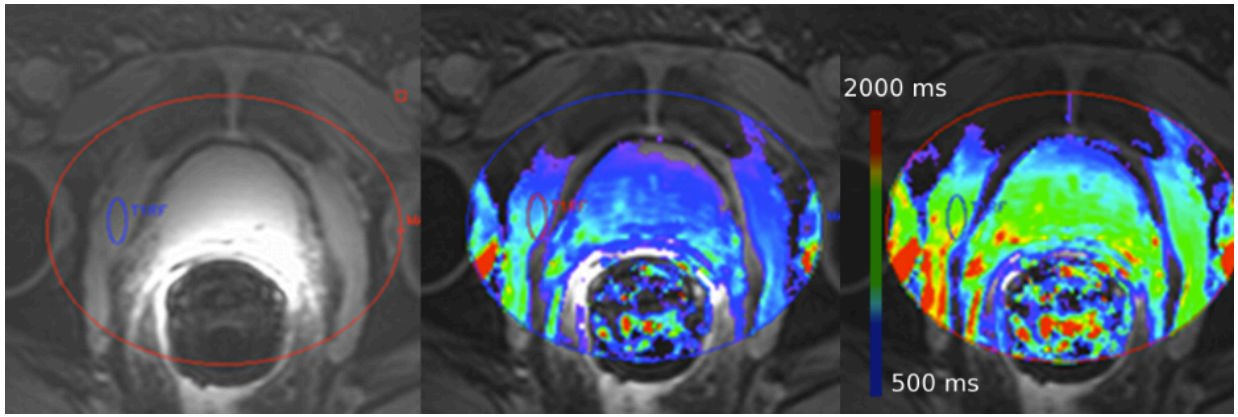
- Fixed T1 value for the whole gland
- Variable FA T1 mapping
  - Large errors in prostate at 3T



Gupta et al, ISMRM 2012

T1 mapping: alternative approaches

- Variable TR sequence
  - T1 mapping approach insensitive to B1 field inhomogeneity
- Reference-corrected variable FA approach

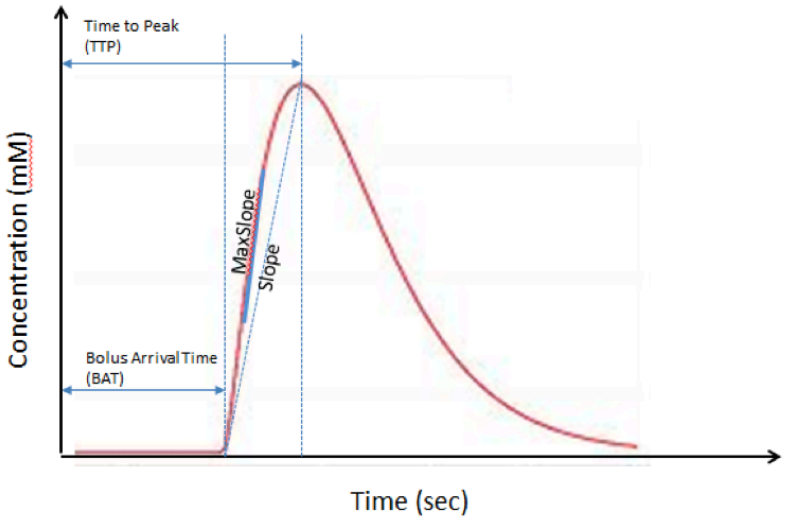


Gupta et al, ISMRM 2012

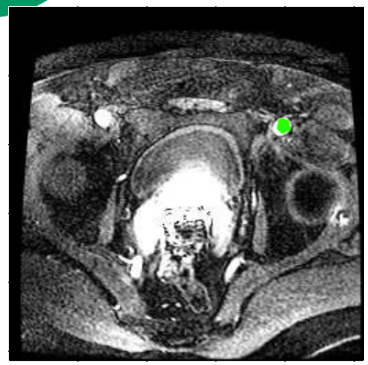
Arterial Input Function

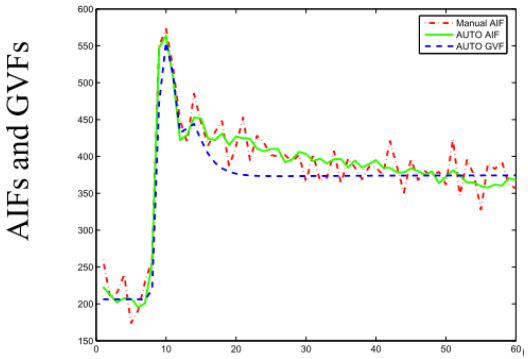
- Required for determination of rate of change of CA concentration in plasma
- Choices for AIF selection
  - Patient-specific (manual/automatic/automated)
  - Population-averaged
  - Model-based

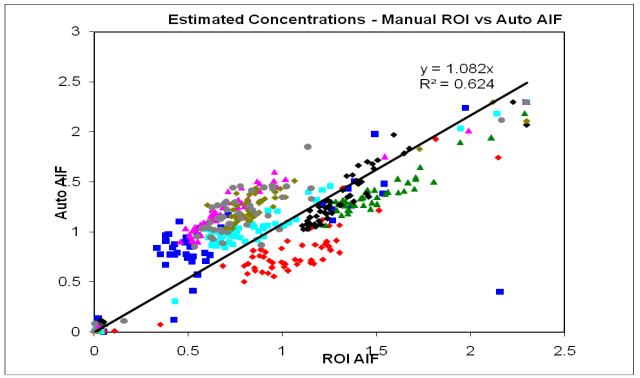
$$C_{\text{tiss}}(t) = K^{\text{trans}} C_{\text{p}}(t) \otimes \exp(-k_{\text{ep}} t)$$



Automatic estimation of AIF



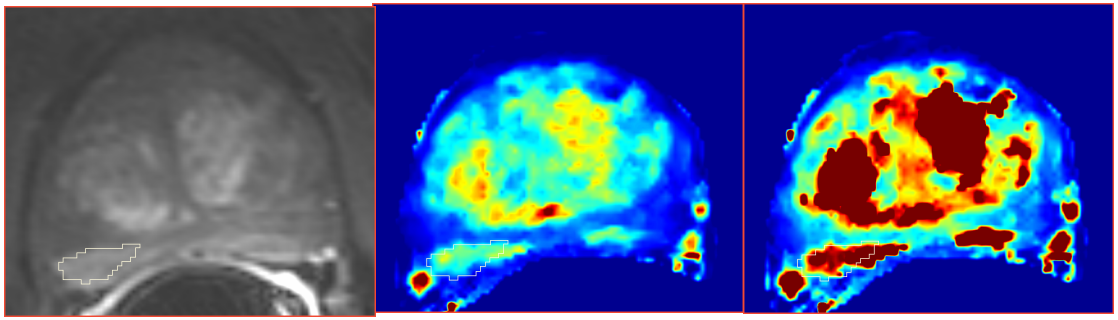


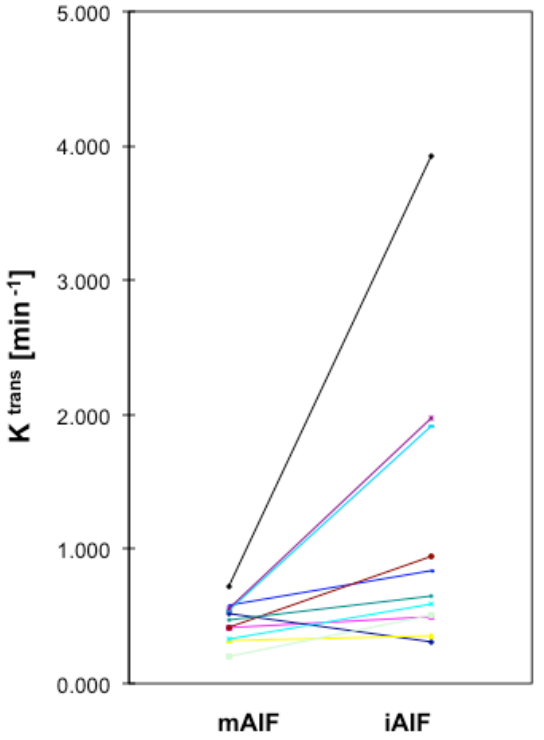


- AIF Shape prior Gamma-Variate Function
- Anatomical prior on voxel location
- Time- and space-domain filtering

Zhu et al. Automated determination of arterial input function for DCE-MRI of the prostate. In: Proc. SPIE Med Imag. Vol. 7963; 2011.

Automatic vs model AIF





- Large differences observed between parameters derived using model and individualized AIF

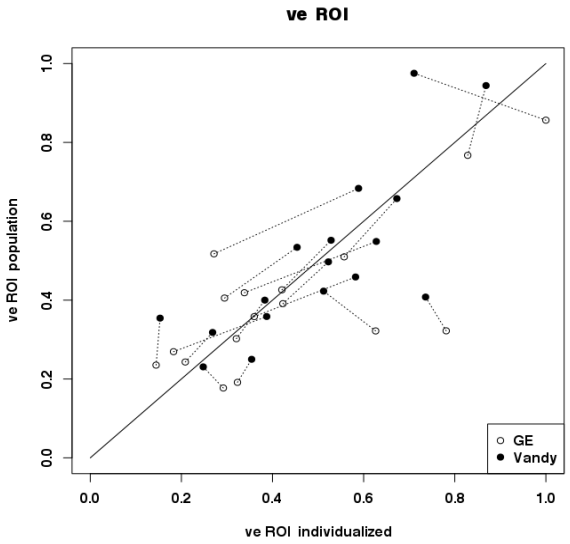
Fennessy et al, ISMRM 2011

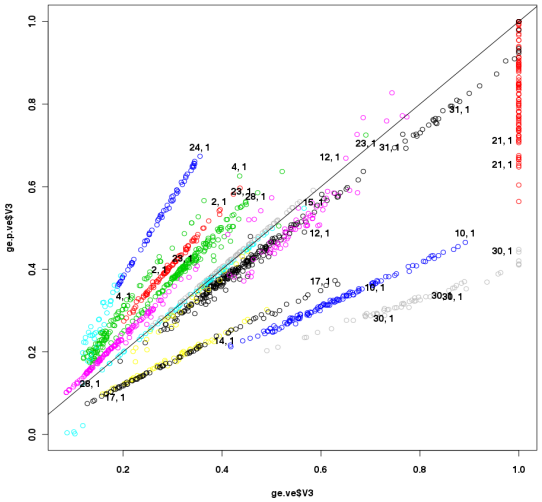
Comparison of individualized AIF estimation methods

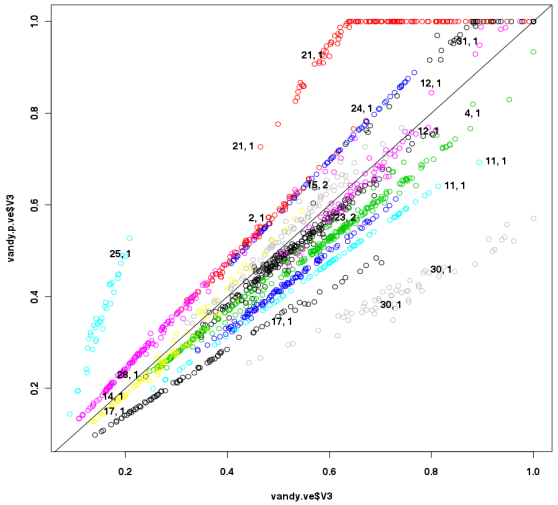
- Joint work with Vanderbilt QIN group (Tom Yankeelov)
- 17 patients with biopsy/prostatectomy-confirmed PCa
- Evaluate choices:
  - iAIF using one of the two methods
  - Population-averaged AIF

Zhu et al. Automated determination of arterial input function for DCE-MRI of the prostate. In: Proc. SPIE Med Imag. Vol. 7963; 2011.
Li et al. A novel AIF tracking method and comparison of DCE-MRI parameters using individual and population-based AIFs in human breast cancer. Phys Med Biology. 2011;56(17):5753-69.

Comparison of individualized AIF estimation methods







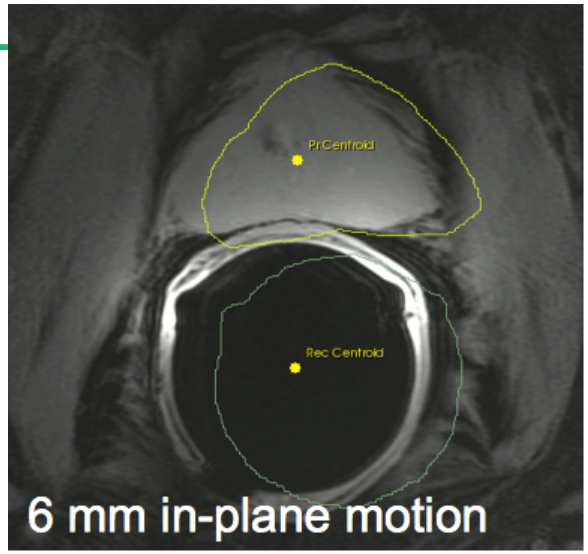
- ROI-based vs pixel-wise analysis
- iAIF-pAIF consistency does not imply correct results!

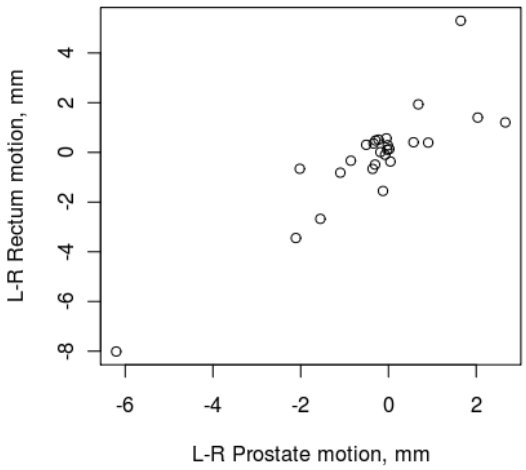
Co-registration

- Required for joint quantitative analysis of mpMRI
  - Same study, Inter-sequence co-registration
  - Inter-study co-registration
  - Co-registration with pathology

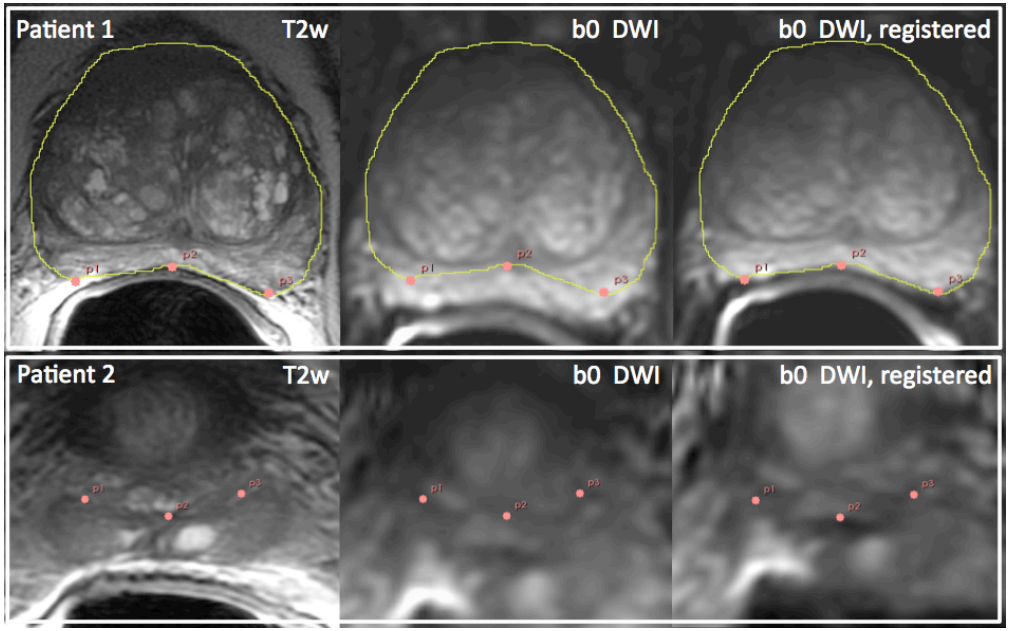
mpMRI inter-sequence co-registration

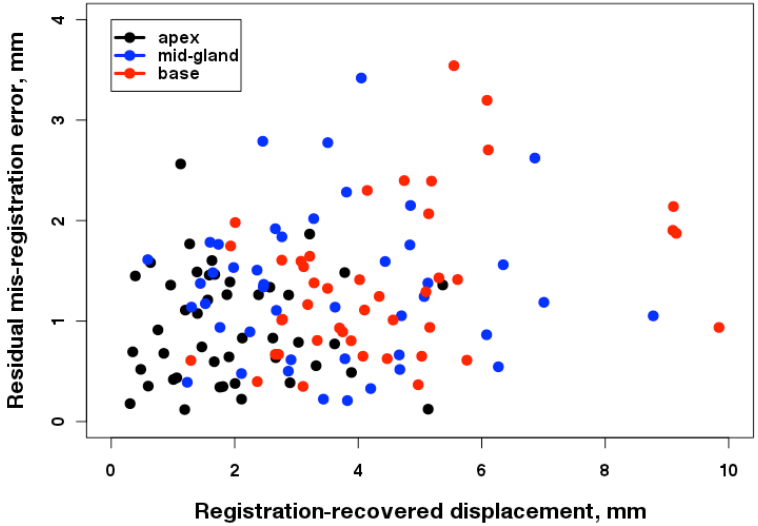
- 26 mpMRI exams analyzed retrospectively
- In-plane motion between pre- and post-contrast T1w study (10-20 min apart) quantified
- 4 patients motion > 3 mm
- Rigid registration to recover (3D Slicer)





DWI distortion correction

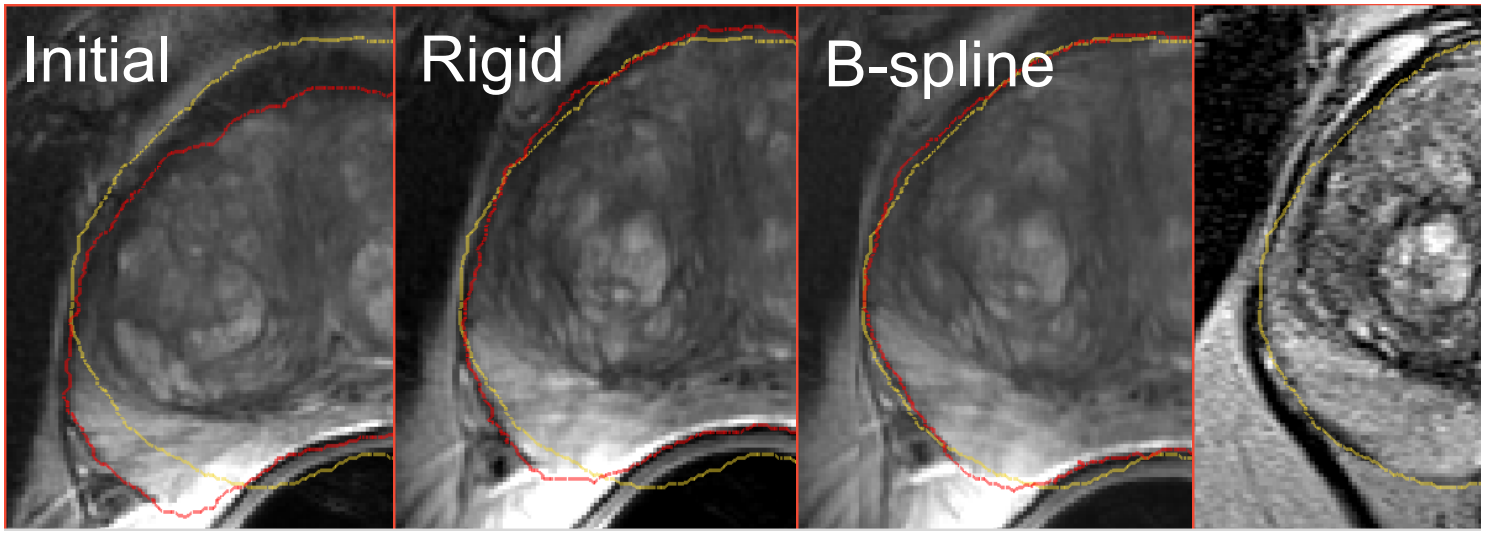




Fedorov et al, ISMRM 2012

- B-spline transformation model
- Inhomogeneity correction
- Optimizer tuned to favor A-P deformations

Registration across studies



Fedorov et al, ISMRM 2011

- Deformable registration to compensate for endorectal coil deformation
- Based on Iowa BRAINSFit tool (Hans Johnson)

Validation

- Overarching issue: no ground truth
- Possible options for validation
  - Radiology reports
  - TRUS biopsy results
  - MR-guided biopsy results
  - Repeat / “coffee break” studies
  - Whole mount pathology
  - Clinical outcome

Whole mount pathology correlation

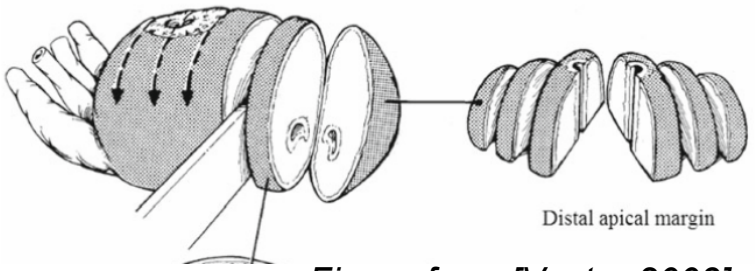
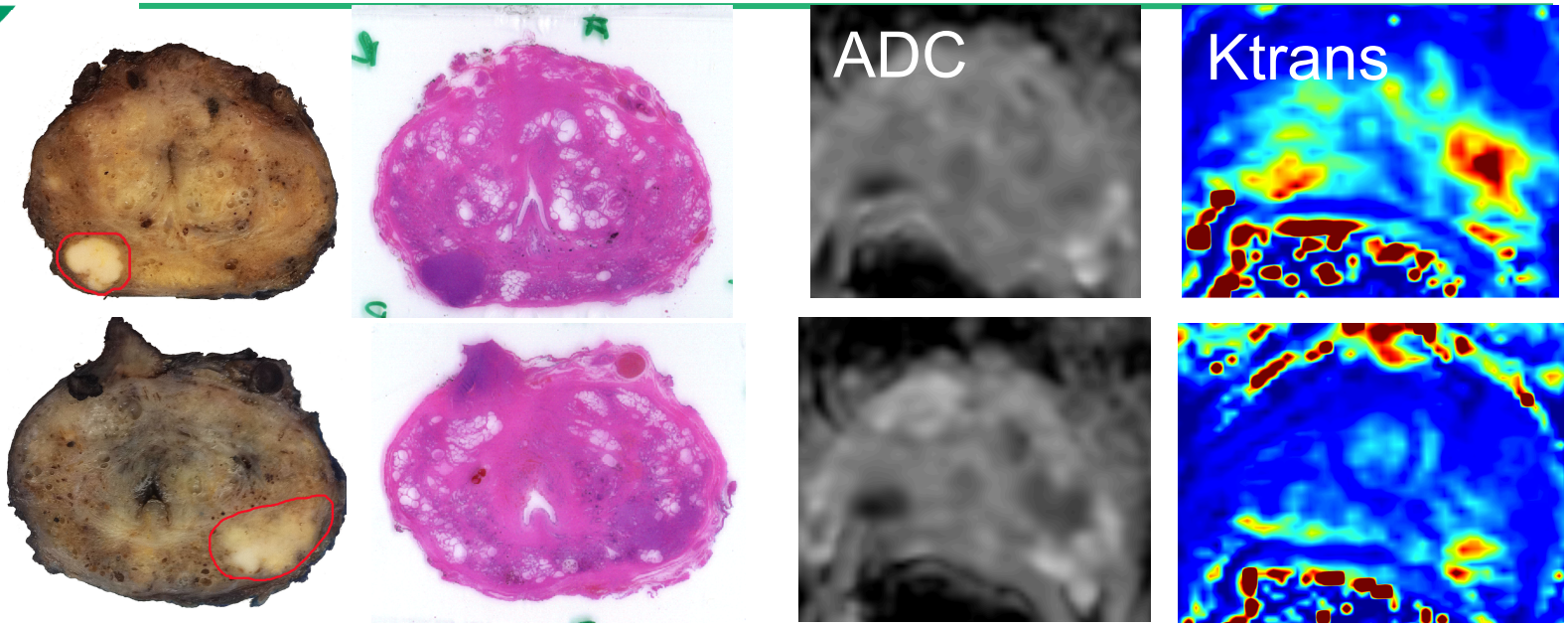


Figure from [Vestra 2003]

- Radical prostatectomy gland specimen
- Slide specimen shaved off 5-6 mm “slabs”
- Stained

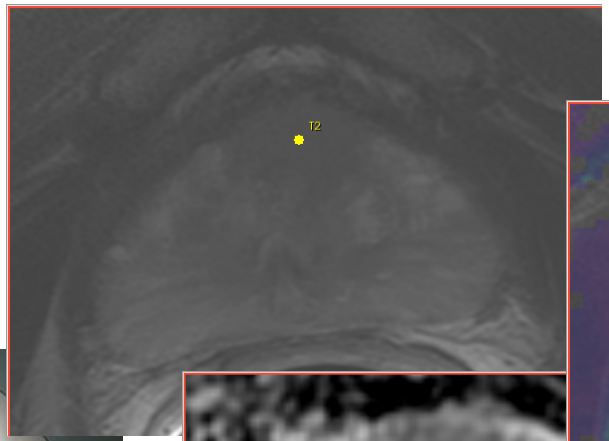
Whole mount pathology correlation

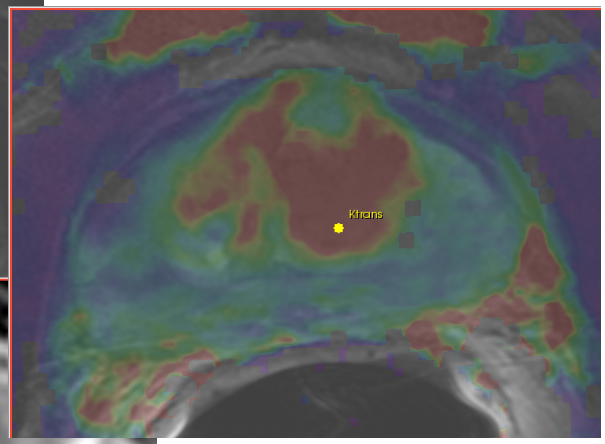


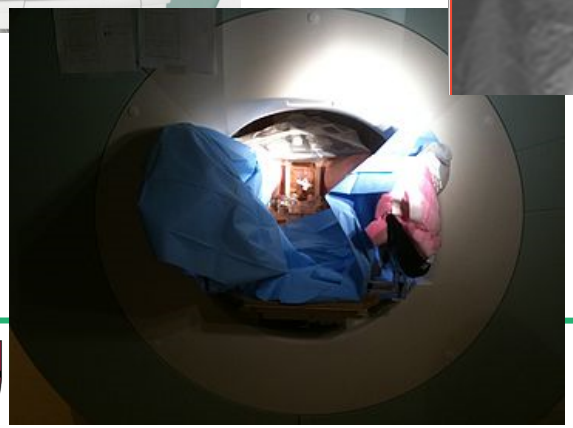
- Geometric differences: Slice/slab thickness, orientation, shape

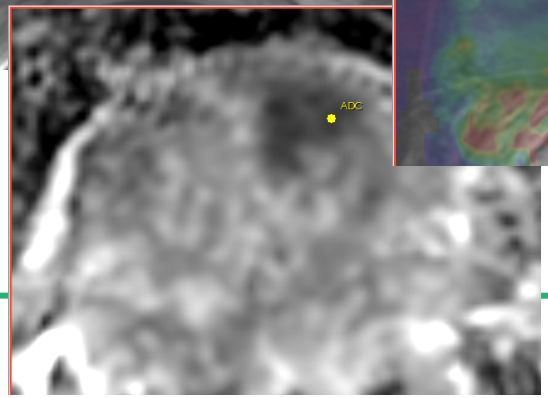
MR-guided prostate biopsy

- Direct transperineal sampling based on pre-biopsy MRI to define targets
  - Target sampling is guided by 3D Slicer
  - Targets defined based on DWI/DCE/T2W, guided by 3D Slicer





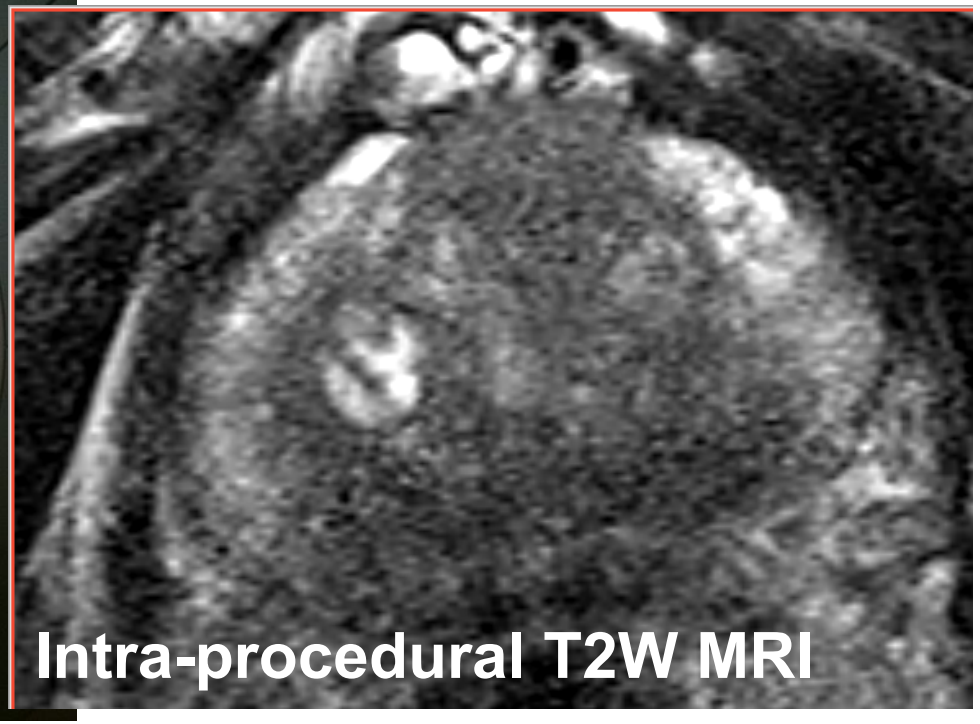




MR-guided prostate biopsy

- Closed bore scanner
- Surface and body coils used for imaging (no endorectal coil)
- Patient is in lithotomy position
- 35 cases completed to date


Patient setup in the scanner


Intra-procedural T2W MRI

BWH QIN Bioinformatics

Summary of the collected data

- Image data
  - Raw images (DICOM)
  - Derived maps and reconstructions (NRRD)
  - Segmentations (3D labels, NRRD)
  - Whole mount path slides
  - Organized on file system, Slicer MRML scene
- Clinical data (demographics, PSA, pathology)
  - Spreadsheet(s)

Other non-image data

- Pre-processing-related
  - transforms (rigid, B-spline)
  - Total gland segmentation
  - Intensity inhomogeneity correction results

Data organization

- Status quo: directories on file system
- Desired: XNAT – in the works
- XNAT open questions:
  - Organization of non-DICOM data
  - Usage scenarios
  - Integration with processing tools

Summary

- Our major focus
  - Acquisition of “good” data
  - Image analysis
  - Validation
- Bioinformatics is important
  - not yet for decision-making
- 3D Slicer as a platform for clinical research