Image Guided Biopsy of Prostate Cancer: Implications for Diagnosis and Therapy

Peter A. Pinto
Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health

National Cancer Advisory Board
December 7, 2010
Clinical Questions for Research

• Why is prostate cancer the only solid tumor that is diagnosed by randomly sampling the organ in the hopes of hitting the tumor?

• If organ sparing treatment has been developed for other cancers (breast, kidney, bladder, etc.) why not prostate?
Clinical Questions for Research

• Both of these questions were linked to the lack of reliable imaging for localizing tumors within the prostate and beyond it

• Can MRI, PET, and other imaging modalities change this?
Diagnosis

• Digital Rectal Exam (DRE)
• Blood Test – Prostate Specific Antigen (PSA)
• 12 core Prostate Biopsy
Prostate biopsy

• 1st described by Fergusson (1930): transperineally
• Astraldi (1937) described transrectal
• Use of TRUS first in 1955 (Wild & Reid), popularized by Watanabe et. Al. in 1970s
• Hodge proposed “sextant” biopsy model in 1989
• Estimated over a million biopsies annually in U.S.
• Despite technical advances, biopsies are still NOT based on imaging
Trans Rectal Ultrasound (TRUS)

• How is it clinically used today?
• Most urologists use TRUS to ensure the needle samples the prostate, few use TRUS to look for areas suspicious for cancer

Prostate Cancer

• Current detection suffers from low sensitivity and poor localization.
• 60% of ultrasound-morphologically suspicious lesions are biopsy negative\(^1\)
• Prostate cancer is the only solid-organ tumor currently diagnosed without routine imaging.

---

\(^1\)Loch, T. et al., Transrectal ultrasound-guided biopsy of the prostate: random sextant versus biopsies of sono-morphologically suspicious lesions, World J. Urol, **22**: 357-360, 2004
Cancer Detection Rate

- **6 core biopsy**
  - 20 to 30%

- **12 core biopsy**
  - 27 to 40%

When the biopsy is negative?

- “Physicians are frequently presented with the dilemma of a patient who has had one or more negative prostate biopsies yet continues to have an elevated PSA value or abnormal digital rectal examination of concern for prostate cancer.”

Cancer detection on repeat biopsies

<table>
<thead>
<tr>
<th>Prior Negative Biopsies</th>
<th>Sextant (%)</th>
<th>Saturation Biopsy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 prior negative biopsy</td>
<td>10-17%</td>
<td>36%</td>
</tr>
<tr>
<td>2 prior negative biopsies</td>
<td>5-14%</td>
<td>31%</td>
</tr>
<tr>
<td>3+ prior negative biopsies</td>
<td>4-12%</td>
<td>14-36%</td>
</tr>
</tbody>
</table>

Biopsy is not just for diagnosis

- Crucial to the management of patients on active surveillance (AS)
- Role of AS is increasing
- Without good imaging, yearly biopsy currently required for men on AS
Role of biopsy in active surveillance patients

• Active surveillance: distinguish clinically insignificant cancers from life-threatening cancers while still localized to delay definitive therapy

• Monitoring: interval PSA testing, repeated biopsies every 12 months
Role of biopsy in AS

- Carter et al, (2002): PSA not likely to reveal disease progression accurately, need annual surveillance biopsies

- Abnormal biopsy found to be most significant prognostic factor for progression (Patel et al, 2004)
Imaging

• Is improving ultrasound sufficient?
  – 3D ultrasound
  – Contrast enhanced ultrasound (black box)
  – 3D models: Imaging based on vascularity
  – Transurethral ultrasound: reduced anatomic coverage than TRUS but higher resolution
Improving ultrasound?

Ultrasound Contrast (black box warning)
Improving ultrasound?

- Hypervascularity is not an independent factor in distinguishing between various pathologic entities, and therefore cannot serve as a tool to decrease the number of prostate biopsies (Arger et al. 2004)

MRI of the Prostate ?
Multi-parametric 3Tesla endorectal MR Imaging of the prostate

T2  DWI  DCE-MRI

Spectroscopy
Clinical Questions

Can MRI detect and characterize cancer within the gland:

Location?
Size?
Grade?
Clinical Questions

• Can MRI allow better sampling of the prostate when biopsied?
Clinical Questions

• Can MRI increase our confidence in excluding cancer in patients with negative biopsies?
Clinical Questions

• Can MRI be used for men undergoing active surveillance?
Clinical Questions

- Can MRI be used to change how we treat prostate cancer?
  - Image guided focal therapy
Two Research Endeavors

- Develop a research platform to ensure the prostate MR Images correlates with pathology
- Develop a prostate biopsy platform that uses image guidance (MRI)
Prostate Cancer Localization with 3T erMRI: Correlation with Whole-Mount Histopathological Specimens
MRI and Histology Correlation for prostate cancer

Protocol 04-CC-0109: Comprehensive Prostate MRI for the Evaluation of Prostate Cancer at 3.0T

Men undergo multi-parametric 3T endorectal coil MRI prior to radical prostatectomy.

Prostate is whole mount sectioned and compared to MR’s axial images
MRI / Path Correlation
58-year-old male, PSA=7 ng/mL
Neighboring method

Prostate gland

Central gland

Base
Mid-base
Mid
Apex-mid
Apex

Right

Peripheral zone

Left

Superior

Inferior
This work raised another question

• How can we improve the MRI / Path correlation?
Prostate Segmentation
Prostate Mold

Suspected Tumor Target
Fresh Tissue Procurement
Printing the Mold
Printing the Mold
Printing the Mold
Prostate Cancer Localization with 3T erMRI: Correlation with Whole-Mount Histopathological Specimens
MRI correlation with radical prostatectomy specimens using the mold slicer for whole mount pathology

- Analyzed the data from the first 45 patients
NCI Results: Tumor Detection

Overall prostate gland

Positive Predictive Value

MRI parameters

T2W MRI
T2W MRI + DW MRI
DW MRI + DCE MRI
T2W MRI + DCE MRI
T2W MRI + DW MRI + DCE MRI
MRS + DCE MRI
T2W MRI + MRS
T2W MRI + DW MRI + MRS
DW MRI + MRS
T2W MRI + DW MRI + MRS + DCE MRI
T2W MRI + DW MRI + MRS + DCE MRI
NCI Results: Tumor Detection

Central gland

Positive Predictive Value

MRI parameters
To Improve current methods of detection / treatment of PCa:

• Diagnostic imaging
  – Improve MR Imaging sequences
  – Other imaging modalities

• Devices
  – If we have imaging that can see the tumor in the prostate can we “hit” it
Why image (MRI) guided biopsies?

- Lesion-targeted prostate biopsy
  - Increase biopsy yield
  - Reduce number of biopsies
  - Reduce number of failed biopsies
  - Locate cancers outside peripheral zone

- Lesion-targeted localized therapy
  - Eliminate side effects of radical treatment
In Gantry MRI-Guided Prostate Biopsies?

• Technically challenging
• Uncomfortable, unpleasant for patient
• COSTLY- Becomes hospital based procedure, not office base
• Time in MRI gantry at a premium; diagnostic tests take priority
  – Mean time 1.5-2.5 hours!
• Learning curve
• Patient acceptance low

MRI-TRUS Fusion Prostate Biopsies

• Office-based procedure.
• Minimal additional patient discomfort for significant additional diagnostic yield.
• Utilizes widely available imaging technologies
• Technically feasible with mature technology and proper instruction.
Why fuse MRI and Ultrasound?

**MRI**
- Temporal resolution: ✗
- Spatial resolution: ✔
- Sensitivity/Specificity: ✔
- Cost effective: ✗

**TRUS**
- Temporal resolution: ✔
- Spatial resolution: ✗
- Sensitivity/Specificity: ✗
- Cost effective: ✔
Why fuse MRI and Ultrasound?

- Fusing prior-acquired MRI with real-time TRUS brings diagnostic information to the urologist possibly improving office prostate biopsies.
- May lead to office-based image-guided focal therapy.
Image fusion guided prostate bx

• Work here at NIH leads the way in developing this technology with the help of interdisciplinary collaborative efforts
  – Urologic Oncology, Interventional Radiology, Diagnostic Radiology, Pathology, Engineering, Medical Oncology, CIT, Industry (CRADA Philips)
To Improve current methods of detection / treatment of PCa:

- **Diagnostic imaging**
  - Improve MR Imaging sequences
  - Other imaging modalities

- **Biopsy devices**
  - If we can see the tumor in the prostate can we “hit” it
Spatial Tracking System

EM sensors
MR-US prostate image fusion
Conclusions

- Feasible to fuse prostate MRI and US in real time
- Real-time electromagnetic tracking enables targeting of MR visible PCa lesions with an office based ultrasound platform, without the need to utilize a hospital MRI suite
Research Platform

EM-FG

Ultrasound

Workstation

CRADA NIH-Philips medical
Commercially Viable Platform
MR/Sono Prostate Biopsy
Procedure Time

- 3D US acquisition using 2D sweep (10 – 24 secs)
- Reconstruction of reference 3D US (~15 seconds)
- Manual pre-op. MRI/US registration (1 – 2 mins)
- Specimen acquisition (~ 11 minutes)
- Motion compensation, US/RTUS reg. (~15 seconds)

15 minutes
Cancer Detection Rates of MR/US Fusion Guided Prostate Biopsies Directly Correlate with Suspicion on Multiparametric MRI

Paul H. Chung¹, Ardeshir R. Rastinehad¹, Angelo A. Baccala¹, Jochen Kruecker⁵, Sheng Xu⁵, Baris Turkbey³, Julia K. Locklin², Stacey P. Gates², Joanna Shih⁴, Neil D. Glossop⁵, Peter L. Choyke³, Bradford J. Wood², and Peter A. Pinto¹*

¹ Urologic Oncology Branch,
² Department of Radiology and Imaging Sciences,
³ Molecular Imaging Program,
⁴ Biometric Research Branch,
National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

⁵ Philips Research North America, Briarcliff, NY, USA
Objective

- To determine the cancer detection rates of our MR/US fusion guided biopsy protocol
MR/US Fusion Guided Biopsy Workflow

1) 3T Multiparametric MR Scan
   - T2 weighted
   - Dynamic contract enhanced
   - MR spectroscopy
   - Diffusion weighted imaging

MR/US Fusion Guided Biopsy Workflow

1) 3T Multiparametric MR Scan

2) MRI Lesions are Assigned PCa Suspicion Levels
   - Low $\rightarrow$ 1 or 2 modalities
   - Medium $\rightarrow$ 3 modalities
   - High $\rightarrow$ 4 modalities
1) 3T Multiparametric MR Scan

2) MRI Lesions are Assigned PCa Suspicion Levels

3) Biopsy Protocol
   - 12 Core Standard Biopsy
   - MR/US Fusion Guided Biopsy
MR/US Fusion Guided Biopsy

TRUS

MRI
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. patients</td>
<td>101</td>
</tr>
<tr>
<td>Mean age, yrs (range)</td>
<td>63 (41-82)</td>
</tr>
<tr>
<td>Mean PSA, ng/mL (range)</td>
<td>8.3 (0.2-103)</td>
</tr>
<tr>
<td>Median PSA, ng/mL</td>
<td>5.8</td>
</tr>
<tr>
<td>Biopsy History</td>
<td></td>
</tr>
<tr>
<td>- No Prior</td>
<td>36</td>
</tr>
<tr>
<td>- Negative</td>
<td>29</td>
</tr>
<tr>
<td>- Positive</td>
<td>36</td>
</tr>
<tr>
<td>Mean No. lesions suspicious for cancer on MRI (range)</td>
<td>2.6 (1-7)</td>
</tr>
<tr>
<td>Median No. lesions suspicious for cancer on MRI</td>
<td>3</td>
</tr>
<tr>
<td>Mean No. cores per lesion (range)</td>
<td>2.2 (1-8)</td>
</tr>
<tr>
<td>Median No. cores per lesion</td>
<td>2</td>
</tr>
</tbody>
</table>
Cancer Detection Rates

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>588</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lesion</td>
<td>264</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patient</td>
<td>101</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Conclusions

- Degree of suspicion on MR imaging directly correlates with incidence of cancer detected on biopsy
- 55% overall cancer detection rate
- 90% of patients with high suspicion on MR imaging were diagnosed with cancer
- This platform may have a future role in active surveillance and image guided focal therapy
68 yo with rising PSA, annual bx x 7 including saturation bx

Right mid anterior central gland lesion

T2 +

DWI +

DCE +

MRS +

High suspicious
Summary

• Multiparametric MR prostate imaging may be the platform for image guided biopsies
• Continued research is necessary to determine its role in the care of our patients with prostate cancer, especially for image guided focal therapy
Era of Image Guided Focal Therapy for Prostate Cancer
PSA Screening Effects on Prostate Cancer

- Shift toward localized disease
- Shift toward lower volume disease
- Shift toward moderately differentiated disease

YET...

- Treatment remains directed at whole gland
Methods of Treating Localized Prostate Cancer

• Surgery
  – Retropubic Prostatectomy
  – Perineal Prostatectomy
  – Laparoscopic Prostatectomy
  – Robotic Assisted Prostatectomy
• Radiation Therapy
  – External Beam
  – Interstitial Seed Implantation
• Active Surveillance
• Ablation
What is best for our patients?

- High incidence of significant morbidity associated with whole gland therapy.
  - Impotence
  - Incontinence
- Patients and physicians are seeking less morbid treatment modalities
  - Image guided focal therapy
Summary

• Localized prostate cancer is the new challenge of the PSA era
• Requires rethinking of our diagnostic and treatment strategies
• MRI is a promising diagnostic tool.
• Further research in this field is required.
Acknowledgements

- Molecular Imaging
  - Peter Choyke, M.D.
  - Baris Turkbey, M.D.
  - Marcelino Bernado, Ph.D.
  - Vijay Shah, Ph.D.
  - Tom Pohida, Ph.D.

- Interventional Radiology
  - Bradford Wood, M.D.
  - Jochen Krueker, Ph.D.
  - Sam Kadoury, Ph.D.
  - Sheng Xu, Ph.D.
  - Julia Locklin, R.N.
  - Stacey Gates, R.N.
  - Carey Buckner, R.N.

- Pathology
  - Maria Merino, M.D.
  - Haresh Mani, M.D.
  - Vladimir Valera, M.D.