MRI –US Fusion Prostate biopsy

• Increasing detection of clinically significant cancer

Preston C. Sprenkle, MD
Assistant Professor
Department of Urology

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Disclosures

• Boston Scientific, Inc. – Consultant
• Janssen Biotech, Inc. – Clinical Trial Site Principal Investigator
Overview

• Defining Clinically Significant

• Prostate MRI

• Improved Identification of CS cancer with Fusion biopsy
# Prostate cancer now common

## Estimated new cases, 2018

By cancer type, both sexes combined

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New Cases 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>268,670</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>234,030</td>
</tr>
<tr>
<td>Prostate</td>
<td>164,690</td>
</tr>
<tr>
<td>Colorectum</td>
<td>140,250</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>91,270</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>81,190</td>
</tr>
</tbody>
</table>

## Estimated deaths, 2018

By cancer type, both sexes combined

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Deaths 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>154,050</td>
</tr>
<tr>
<td>Colorectum</td>
<td>50,630</td>
</tr>
<tr>
<td>Pancreas</td>
<td>44,330</td>
</tr>
<tr>
<td>Breast</td>
<td>41,400</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>30,200</td>
</tr>
<tr>
<td>Prostate</td>
<td>29,430</td>
</tr>
</tbody>
</table>

American Cancer Society, 2018
Clinically significant vs. insignificant

- Historically all detected prostate cancer was treated

  The current state of prostate cancer may not be good medicine but it sure is good business. There are more people making a living from prostate cancer than there are dying from it.

  Is cure possible? Is cure necessary? Is cure possible only when it is not necessary?
Morbidity of Prostate Cancer Treatment

- **Surgery**
  - Incontinence
  - Impotence
  - Risks associated with surgery
- **Radiation**
  - Impotence
  - Cystitis
  - Proctitis
Screen to Treat
Screen to Detect
Active Surveillance is Safe

- For appropriate patients...

Patient Selection is KEY
Adverse pathology present in patients considered candidates for active surveillance (Pre MRI era)

- **Clinical definitions**
  - LR disease (GG1 and cT2a or less, and PSA less than 10 ng/ml)
  - IR disease (GG2 or less, cT2b or less, or PSA less than 20 ng/ml exclusive of patients who met all LR criteria).
  - Adverse pathology was defined as radical prostatectomy with the finding of GG3 or greater, seminal vesicle invasion (pT3b) or lymph node.
MRI
“The discovery that would have the greatest impact on our field would be the development of accurate imaging of tumor within the prostate”

Patrick C. Walsh
Whitmore Lecture
Urol Oncol 2009
Looking inside the Prostate - Multiparametric MRI

- Combines anatomical and functional studies
  - T2 and T1 weighting
  - DWI (Diffusion Weighted Imaging)
    - ADC (Average Density Coefficient)
  - DCE (Dynamic Contrast Enhancement)
Fusing MRI and Ultrasound - targeted biopsy

1. SEGMENTATION

2. RIGID ALIGNMENT

3. SURFACE REGISTRATION

4. ELASTIC INTERPOLATION

TRUS REGISTERED TO MRI

COMPUTED TRUS ON MRI FRAME OF REFERENCE
Targeted Biopsy of prostate cancer
MRI can identify Lesions missed by standard biopsy
Lesion suspicion level correlates with cancer detection
Better risk stratification
Targeted biopsy misses less significant cancer

<table>
<thead>
<tr>
<th>Targeted</th>
<th>No Cancer</th>
<th>3+3</th>
<th>≥ 3+4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cancer</td>
<td>300</td>
<td>83</td>
<td>20</td>
</tr>
<tr>
<td>3+3</td>
<td>57</td>
<td>169</td>
<td>48</td>
</tr>
<tr>
<td>≥ 3+4</td>
<td>44</td>
<td>108</td>
<td>324</td>
</tr>
</tbody>
</table>

68/544 (12.5%) CS (GS≥7) cancers missed by Targeted Bx

152/544 (28%) CS cancers missed by TRUS Bx

Yale 2013-2018 data
Targeted Biopsy (alone) Outcomes

Biopsy Outcomes Stratified by Suspicion Score and Biopsy History (N=1434)

- **ACTIVE SURVEILLANCE**
  - Negative MRI: 62%, 9% Benign, 7% Gleason Score ≥7, 28% Gleason Score = 6
  - PIRADS 2 AS: 64%, 7% Benign, 16% Gleason Score ≥7, 30% Gleason Score = 6
  - PIRADS 3 AS: 50%, 16% Benign, 34% Gleason Score ≥7, 34% Gleason Score = 6
  - PIRADS 4 AS: 22%, 43% Benign, 35% Gleason Score ≥7, 43% Gleason Score = 6
  - PIRADS 5 AS: 15%, 55% Benign, 55% Gleason Score ≥7, 55% Gleason Score = 6

- **PRIOR NEGATIVE**
  - PIRADS 2 PN: 84%, 8% Benign, 14% Gleason Score ≥7, 19% Gleason Score = 6
  - PIRADS 3 PN: 76%, 14% Benign, 10% Gleason Score ≥7, 19% Gleason Score = 6
  - PIRADS 4 PN: 46%, 36% Benign, 36% Gleason Score ≥7, 36% Gleason Score = 6
  - PIRADS 5 PN: 14%, 67% Benign, 67% Gleason Score ≥7, 67% Gleason Score = 6

- **BIOPSY NAÏVE**
  - PIRADS 2 BN: 28%, 12% Benign, 14% Gleason Score ≥7, 24% Gleason Score = 6
  - PIRADS 3 BN: 28%, 18% Benign, 14% Gleason Score ≥7, 24% Gleason Score = 6
  - PIRADS 4 BN: 28%, 28% Benign, 14% Gleason Score ≥7, 28% Gleason Score = 6
  - PIRADS 5 BN: 11%, 83% Benign, 83% Gleason Score ≥7, 83% Gleason Score = 6

- **Legend**
  - Blue: Benign
  - Red: Gleason Score ≥7
  - Green: Gleason Score = 6
Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashim U Ahmed*, Ahmed El-Shater Bosaily*, Louise C Brown*, Rhian Gabe, Richard Kaplan, Mahesh K Parmar, Yolanda Collaco-Moraes, Katie Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Parker, Mark Emberton, and the PROMIS study group†

www.thelancet.com  Published online January 19, 2017  http://dx.doi.org/10.1016/S0140-6736(16)32401-1
Materials and Methods: CPB Procedure

- **Perfomed TPM-biopsy and TRUS together**
  - Patients and physicians blinded to mpMRI results
  - Decreased dropout between studies
  - TRUS performed second to minimize risk of infection

- **Samples**
  - TPM-biopsy = reference standard
  - TRUS biopsy = standard test
  - 10-12 core biopsies
  - Reported by uropathologists at each site

- **Definition of Clinically Significant Prostate Cancer**
  - **Gleason 4+3 or higher, max core > 6 mm**

- **Stats**
  - Assume prevalence of CS disease of 15%
  - Target sample size of 714 men
Increase in significant cancer with higher MRI score

Figure S2 – Proportion of men with no cancer, insignificant cancer and significant cancer (primary definition) based upon TPM biopsy within each MRI score
Results: MP-MRI vs. TPM

205 lesions identified on MRI that are not CS
Majority are equivocal designation

PPV=50%
Sensitivity= 93%
False positive rate= 49%

17 cancers not identified on MRI
NPV= 89%
False negative rate=11%

Figure 2: Diagnostic accuracy for detection of clinically significant cancer (primary definition) between MP-MRI and TPM-biopsy
Results: Sensitivity of MP-MRI

MP-MRI is more accurate than TRUS
- Sensitivity = 93%
- NPV = 89%
- False positive rate = 49%

TRUS is more specific
- Sensitivity = 48%
- PPV = 90%
- Specificity = 96%

<table>
<thead>
<tr>
<th>Comparison</th>
<th>MP-MRI, % (95% CI)</th>
<th>TRUS-biopsy, % (95% CI)</th>
<th>Test ratio* (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary definition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gleason score ≥4+3 or cancer core length ≥6 mm), prevalence of clinically significant cancer 230 (40%, 36–44%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity test</td>
<td>93 (88–96)</td>
<td>48 (42–55)</td>
<td>0.52 (0.45–0.60)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Specificity test</td>
<td>41 (36–46)</td>
<td>96 (94–98)</td>
<td>2.34 (2.08–2.68)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>PPV</td>
<td>51 (46–56)</td>
<td>90 (83–94)</td>
<td>8.2 (4.7–14.3)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>NPV</td>
<td>89 (83–94)</td>
<td>74 (69–78)</td>
<td>0.34 (0.21–0.55)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Secondary definition (Gleason score ≥3+4 or cancer core length ≥1 mm), prevalence of clinically
Discussion: Take home

- Provide level 1 b evidence of diagnostic accuracy of MP-MRI
- If MP-MRI used as a triage test ¼ of men could safely avoid TRUS
- High NPV (89%) of MP-MRI
  - Negative MP MRI implies high probability of no CS cancer in gland
- Low specificity (41%) and low PPV (50%) of MPMRI
  - need to biopsy all MRI3/4/5 lesions

- **TRUS is a poor diagnostic test for clinically significant cancer**
  - Sensitivity= 48%
  - PPV=90%, NPV= 74%
  - Specificity= 96%
PRECISION Trial

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus,
PRECISION population

Mean age 64y; median PSA 6.7; 15% abnormal DRE; 19% family history

Control arm

Informed decision making

Gleason $\geq 3+4=7$ (GG 2) = 26%
Gleason 6 (GG 1) = 22%

PRECISION paradigm

Informed decision making

mpMRI

Abnormal

Targeted Biopsy

Routine follow-up

Gleason $\geq 3+4=7$ (GG 2) = 38%
Gleason 6 (GG 1) = 9%
High precision
• 46% more detection of significant cancer
• 56% less detection of insignificant cancer
• 3 times less biopsy cores (less complications & side effects?)
• 28% of patients avoid biopsy
The NEW ENGLAND JOURNAL of MEDICINE

PRECISION Trial

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus,
Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study

*Olivier Rouvière, Philippe Puech, Raphaèle Renard-Penna, Michel Claudon, Catherine Roy, Florence Mège-Lechevallier, Myriam Decaussin-Petrucci, Lancet Oncol 2019; 20: 100–09*

### Table 3: Detection of clinically significant prostate cancer, according to biopsy strategy

<table>
<thead>
<tr>
<th>Biopsy Strategy</th>
<th>ISUP grade group ≥2 (csPCA-A)</th>
<th>ISUP grade group ≥2 or ISUP grade group 1 with MCCL ≥6 mm (csPCA-B)</th>
<th>ISUP grade group ≥3 (csPCA-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic biopsy</td>
<td>29.9% (24.3–36.0)</td>
<td>32.7% (26.9–38.9)</td>
<td>15.1% (10.9–20.2)</td>
</tr>
<tr>
<td>Targeted biopsy</td>
<td>32.3% (26.5–38.4)</td>
<td>35.9% (29.9–42.1)</td>
<td>19.9% (15.2–25.4)</td>
</tr>
<tr>
<td>Systematic biopsy and targeted biopsy</td>
<td>37.5% (31.4–43.8)</td>
<td>41.8% (35.7–48.2)</td>
<td>21.1% (16.2–26.7)</td>
</tr>
<tr>
<td>Added value of systematic biopsy*</td>
<td>5.2% (2.8–8.7)</td>
<td>6.0% (3.4–9.7)</td>
<td>1.2% (0.2–3.5)</td>
</tr>
<tr>
<td>Added value of targeted biopsy†</td>
<td>7.6% (4.6–11.6)</td>
<td>9.2% (5.9–13.4)</td>
<td>6.0% (3.4–9.7)</td>
</tr>
<tr>
<td>p value‡</td>
<td>0.38</td>
<td>0.26</td>
<td>0.0095</td>
</tr>
</tbody>
</table>

Results are % (95% CI) of 251 patients, or p value. ISUP=International Society of Urological Pathology. csPCA=clinically significant prostate cancer. MCCL=maximal cancer core length. *Difference between the detection rate obtained by combined systematic biopsy and targeted biopsy, and by targeted biopsy alone. †Difference between the detection rate obtained by combined systematic biopsy and targeted biopsy, and by systematic biopsy alone. ‡From the comparison of detection rates obtained by systematic biopsy and targeted biopsy.

Targeted biopsy alone was no better, but combined biopsy detected most cancer.
Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis

EUROPEAN UROLOGY XXX (2019)

Frank-Jan H. Drost\textsuperscript{a,b}, Daniel Osses\textsuperscript{a,b}, Daan Nieboer\textsuperscript{b,c}, Chris H. Bangma\textsuperscript{b}, Ewout W. Steyerberg\textsuperscript{c}, Monique J. Roobol\textsuperscript{b}, Ivo G. Schoots\textsuperscript{a,*}
Fig. 2 – Study flowchart. csPCa = clinically significant prostate cancer; MRI = magnetic resonance imaging; MRI pathway = magnetic resonance imaging with subsequent magnetic resonance imaging-targeted biopsy; PCA = prostate cancer.
Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis

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Frank-Jan H. Drost a,b, Daniel Osse a,b, Daan Nieboer b,c, Chris H. Bangma b, Ewout W. Steyerberg c, Monique J. Roobol b, Ivo G. Schoots a,*

a) Hypothetical cohort

MRI result

- With an assumed prevalence of 30% grade 2 or higher prostate cancer
- 1000 men with a suspected prostate cancer, tested with the MRI pathway

Implications

- Appropriate diagnosis
- Although the reference standard did not detect clinically significant prostate cancer the diagnosis is still appropriate
- Potential unnecessarily induced patient burden, complications and overdiagnosis as there is no clinically significant prostate cancer
- Missed diagnosis which may delay curative treatment and worsen prognosis
- No MRI-targeted biopsy (appropriate)
- Missed diagnosis which may delay curative treatment and may worsen prognosis
MR-US Fusion biopsy detected more clinically significant cancer than systematic biopsy

In Biopsy Naïve patients there was no statistically significant difference

Authors argue all should have MRI prior to biopsy and include combined targeted and systematic
MRI Fusion biopsy detects more CS cancer

- Definition of clinically significant has changed over time
  - Currently GG2 or higher

- MRI and MRI-US fusion biopsy increases detection of Clinically significant prostate cancer

- Clear indication for MR-US fusion biopsy in prior negative biopsy cohort.
  - Mixed evidence in biopsy naïve population
Thank You