Relevant Disclosures

• Profound Medical
Outline

• MR screening
• MR prior to initial biopsy
• MR prior to repeat biopsy
• MR for active surveillance
• MR staging and operative planning
• MR-guided ablation
Landscape of Prostate Cancer Screening and Treatment
PSA and Prostate Cancer in 2016: The Good, The Bad, and The Ugly

• The Good
  – Decreasing Cancer-Specific Mortality
  – Novel tools/tests/drugs

• The Bad
  – Overdiagnosis/Overtreatment
  – Insufficient treatment for advanced disease

• The Ugly
  – Screening and Treatment Patterns
  – US Preventive Services Task Force
  – $$$
Prostate Cancer Mortality: 50% Decrease

Need to minimize overdetection and overtreatment
Minimizing Overdetection and Overtreatment

- Screen smartly (age, health, risk profile, patient desire)
- Minimize unnecessary biopsies
- Know when to stop screening
- Novel serum/urine/tissue biomarkers
- MRI to guide management decisions
- Appropriate use of active surveillance
- Focal therapy (?!?)
Basics of MRI #1

- Wait minimum 6 weeks after biopsy
- Basic technique matters
  - Magnet: 1.5 vs 3T
  - Coil: Phase array +/- endorectal
- Sequences matter
  - DWI (ADC map)
  - T2
  - DCE
Basics of MRI #2

- **Size matters**
  - more likely to see larger cancer

- **Location matters**
  - transition
  - central
  - anterior fibromuscular
  - peripheral

- **Radiologist matters**
  - experience
  - expertise

- **Typically underestimates tumor volume**
• Depending on your institution, MRI prostate is ‘good’ or ‘great’ but far from ‘perfect’

• PIRADS system is helpful, although others exist

• Data from your radiologist/biopsies are invaluable
MRI for Screening
Screening MRI
How Reliable is a ‘Negative’ MRI?

- UCLA: 217 men with MRI fusion biopsy (prior negative biopsy)
  - 9% with Gleason ≥ 7

- NYU: 75 men with MRI fusion biopsy (mixed cohort)
  - 1.3% with Gleason ≥ 7 on biopsy

- Italian: 107 men with standard biopsy (elevated PSA)
  - 3.8% with Gleason ≥ 7 on biopsy

- U of Chicago: 180 men with MRI fusion biopsy (mixed cohort)
  - 6% rate of Gleason 7 or higher

Reference: Filson, Cancer, 2016; Wysock, BJU, 2016; Porpiglia, Eur Urol, 2017; Rodriguez (in preparation)
How Reliable is a ‘Positive’ MRI?

- New York University
- 70 men
- 3T MRI w/o ER coil
- Radical prostatectomy
- Endpoint ‘any cancer’

<table>
<thead>
<tr>
<th>Score</th>
<th>PPV</th>
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<tbody>
<tr>
<td>1</td>
<td>5-8%</td>
</tr>
<tr>
<td>2</td>
<td>15-30%</td>
</tr>
<tr>
<td>3</td>
<td>60-70%</td>
</tr>
<tr>
<td>4</td>
<td>83-93%</td>
</tr>
<tr>
<td>5</td>
<td>94-98%</td>
</tr>
</tbody>
</table>

- United Kingdom
- 540 men, 11 centers
- 1.5T MRI w/o ER coil
- Transperineal fusion biopsy
- Endpoint ‘any cancer’

<table>
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<th>Score</th>
<th>PPV</th>
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<td>1</td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td>45%</td>
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<tr>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>96%</td>
</tr>
</tbody>
</table>

Biopsy-naïve men with elevated PSA randomized to:
– MR-targeted biopsy (if ‘negative’, no biopsy)
– TRUS-biopsy

Primary endpoint: Gleason ≥ 7

Secondary endpoints:
– Rates of Gleason 6
– Tumor volume
– Proportion who avoid biopsy

Accrual: As of Jan 2017, 260 of 460 (ahead of schedule)
Randomized Trial of MRI-Guided vs TRUS Biopsy

Visit 1: Randomisation (n=470)

Arm 1 (n=235)

Visit 2: Multi-parametric MRI

MRI score - 1,2

No biopsy

Visit 4 - Results given Treatment Decision Questionnaire

MRI score 3,4,5

Visit 3: MRI-targeted biopsy of the prostate

Visit 4 – Results given Treatment Decision Questionnaire

Arm 2 (n=235)

Visit 3: 10-12 core trans-rectal biopsy of the prostate

Visit 4 – Results given Treatment Decision Questionnaire

Man with no prior biopsy referred with clinical suspicion of prostate cancer!

MRI score 1,2

No biopsy

Visit 4 - Results given Treatment Decision Questionnaire

MRI score 3,4,5

Visit 3: MRI-targeted biopsy of the prostate

Visit 4 – Results given Treatment Decision Questionnaire

Visit 4 – Results given Treatment Decision Questionnaire
MRI Prior to First Biopsy
MRI Prior to Initial Biopsy

- Done routinely at select centers
- I do not routinely do
- National Comprehensive Cancer Network Guidelines: “MRI is not recommended routinely prior to initial prostate biopsy”
"MRI is not recommended routinely prior to initial prostate biopsy but emerging data suggests targeting using MRI/ultrasound fusion may increase the detection of clinically significant, higher-risk (Gleason grade ≥ 4+3=7) disease while lowering the detection of lower-risk (Gleason sum 6 or lower-volume Gleason grade 3+4=7) disease"
• 1003 men at NIH/NCI undergoing biopsy

• MRI-targeted and systematic biopsies

• MRI-targeted compared to systematic biopsies
  – 30% more high-risk cancers (Gleason ≥ 7)
  – 17% fewer low-risk cancers (Gleason 6)

• Similar findings whether initial (19%) or repeat (81%) biopsy

Reference: Siddiqui et al, JAMA, 2014
• 212 men with PSA < 15 ng/ml and normal DRE

• Randomized to:
  – Arm A: pre-biopsy MRI (n=107) with 1.5T + endorectal coil
    • If lesions, targeted biopsy with 3-6 cores per lesion
    • If no lesions, 12 core systematic biopsy

  – Arm B: 12 core systematic biopsy (n=105)

Reference: Porpiglia et al, Eur Urol, in press
No Previous Biopsy: Randomized Trial MRI-targeted vs 12-core biopsy

MRI-targeted biopsies outperform 12-core TRUS biopsy

‘Negative’ MRI: 3.8% (1 of 26) with Gleason ≥ 7 on 12-core TRUS

Reference: Porpiglia et al, Eur Urol, in press
PROMIS Trial: MRI-Fusion vs TRUS-Guided Biopsies

- 576 men at 11 UK Centers (academic and community)
- Inclusion: PSA < 15 ng/ml and normal DRE
- All had:
  - 1.5T MRI (no endorectal coil)
  - 12 core TRUS
  - Transperineal mapping (reference standard)
- Primary endpoint:
  - Gleason ≥ 4+3 and/or maximum cancer core length ≥6mm

Reference: Ahmed, Lancet Oncology, 2017
MP-MRI scores and disease severity

% by status of disease

MP-MRI score

1
N=23

2
N=135

3
N=163

4
N=120

5
N=135

Significant cancer
Insignificant cancer
No cancer
### MP-MRI compared to TRUS-biopsy

<table>
<thead>
<tr>
<th>Test attribute</th>
<th>TRUS-biopsy</th>
<th>MP-MRI</th>
<th>Odds ratio* [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>48%</td>
<td>93%</td>
<td>0.06 [0.02-0.12]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>96%</td>
<td>41%</td>
<td>0.02 [0.003-0.05]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>PPV</td>
<td>90%</td>
<td>51%</td>
<td>8.2 [4.7-14.3]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>NPV</td>
<td>74%</td>
<td>89%</td>
<td>0.34 [0.21-0.55]</td>
<td>p&lt;0.0001</td>
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</table>
Clinically significant cancers missed by TRUS-biopsy and MP-MRI

<table>
<thead>
<tr>
<th>Number and cancer core length (mm)</th>
<th>TRUS-biopsy Total = 119</th>
<th>MP-MRI Total = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason 3+3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>(6-11mm)</td>
<td>(8mm)</td>
<td></td>
</tr>
<tr>
<td>Gleason 3+4</td>
<td>99</td>
<td>16</td>
</tr>
<tr>
<td>(6-14mm)</td>
<td>(6-12mm)</td>
<td></td>
</tr>
<tr>
<td>Gleason &gt;/=4+3</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>(3-16mm)</td>
<td></td>
<td></td>
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</table>
PROMIS Trial

- ‘Negative’ MRI as a triage test would avoid a biopsy in 27% men with 2% fewer cases of clinically significant cancer detected.

- ‘Positive’ MRI with only targeted biopsies would detect 3% more clinically significant cancers compared to TRUS-biopsy.
Previously Negative Biopsy
National Comprehensive Cancer Network Guidelines: Previous Negative Biopsy (2016)

Follow-up:
- PSA and DRE at 6-24 month interval and
- Consider percent free PSA, 4Kscore, PHI, PCA3, or ConfirmMDx and/or Multiparametric MRI and/or refined prostate biopsy techniques

Repeat prostate biopsy, based on risk
MRI for Men with Previously Negative Biopsy

- Society of Abdominal Radiology and AUA Consensus Statement
- PI-RADS 3-5: repeat biopsy with image-guided targeting
- Many biopsy options:
  - MRI-informed, U/S guided ‘fusion’
  - In-bore MRI targeting
  - Cognitive (visual) targeting
  - At least 2 cores from each MRI target
- Targeted biopsy alone only considered once quality assurance efforts have validated the performance of MRI

• All men with previous negative biopsy and PSA > 4 ng/ml

• If suspicious MR lesion, randomized after 3T MRI with body coil:
  – Arm A (n=106): In-bore biopsy with 2 cores/lesion (up to 6)
  – Arm B (n=104): Fusion (2 cores/lesion) + plus systematic (12 core)

• Study halted at interim analysis

Previously Negative Biopsy: InBore MR-Bx vs Fusion + Systematic TRUS-Bx

- Total cancer detection rate: 37% vs 39% (p=0.7)
- Total Gleason ≥ 7: 29% vs 32% (p=0.7)
- Mean # of cores: 5.6 (in-bore) vs 17 (fusion + systematic) (p<0.001)

**SUGGESTS:** if previously negative biopsy, MR-targeted biopsies alone may be sufficient

MRI for Active Surveillance
MRI for Restaging Biopsy Prior to Surveillance

- 60 patients at U Toronto with low-risk prostate cancer
- MRI and re-biopsy with extra cores from MRI lesion
- Upgrading: Gleason 7, > 3 cores, or >50% single core

<table>
<thead>
<tr>
<th></th>
<th>Normal MRI</th>
<th>Lesion &lt; 1 cm</th>
<th>Lesion &gt; 1 cm</th>
</tr>
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<tbody>
<tr>
<td>Upgrading</td>
<td>9%</td>
<td>25%</td>
<td>77%</td>
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</tbody>
</table>

How I Do Surveillance

• MRI fusion re-staging biopsy, typically within 6 months
• PSA/DRE every 6 months (no need for 3 months)
• Surveillance biopsy every 1–3 years (risk-stratify)
• No convincing data (yet?) for routine surveillance MRI
• Remember to repeat rising PSA values
• Document initial discussion well
Serial MRI on Active Surveillance

• 206 men at MSKCC undergoing fusion biopsy while on AS

• MRI either:
  – 1.5T with endorectal coil
  – 3T without

• 35% with Gleason upgrading

• Gray (random)
• Black (targeted)

Reference: Recabal, J Urol, 2015
Serial MRI on Active Surveillance

• 166 men at NCI with low/intermediate-risk PrCa on AS
• Serial MRI (3T with endorectal)
• Mean follow-up 25 months
• 30% upgraded

• Definition of MRI progression:
  – increase in suspicion score
  – an increase in lesion diameter
  – appearance of any new lesion regardless of suspicion score

Reference: Frye, J Urol, 2017
Serial MRI on Active Surveillance

MRI independently predicted pathologic progression

Reference: Frye, J Urol, 2017
Upgrading During Active Surveillance

- 259 men at UCLA on active surveillance
  - 76% Gleason 6
  - 24% Gleason 3+4

- At baseline, all had 3T MRI with body coil

- At last follow-up, 33 (13%) had upgrading to primary Gleason pattern 4 or higher

- 32 of 33 occurred within MRI region of interest

Reference: Nassiri et al, J Urol, 2017
MRI for Staging and Operative Planning
How Well Does MR Identify Cancers

122 men with 3T MRI prior to radical prostatectomy (whole-mount)

Predicting ECE at Surgery

- 183 men at Nijmegen undergoing RP and 50% had ECE
- 3T MRI with endorectal coil
  - Sensitivity: 58%
  - Specificity: 89%
  - PPV: 84%
  - NPV: 68%
- In high-risk patients, PPV was 89%
- In low-risk patients, NPV was 88%

MRI to Plan Nerve-Sparing at Prostatectomy

• 104 patients undergoing radical prostatectomy with pre-operative 1.5T MRI at UCLA

• Single surgeon documented nerve-sparing plan prior and after reviewing MRI findings

• Surgical plan changed in 28 (27%) patients
  – Changed to nerve-sparing in 17 (16%)
  – Changed to nerve-resection in 11 (11%)

• When changed to nerve-sparing, no positive margins on that side

Randomized Controlled Trial: 
Robotic Prostatectomy +/- Pre-Op MRI

- 438 men undergoing robotic prostatectomy

- Randomized pre-op to no MRI (n=216) vs 1.5 T MRI (n=222)
  - No MRI: rate of positive margin = 23%
  - MRI: rate of positive margin = 19%
  - Not significant (p=0.4)

- Among clinical stage T1c patients (55% of cohort)
  - No MRI: rate of positive margin = 27%
  - MRI: rate of positive margin = 16%
  - Significant (p=0.035)

MRI to Predict Continence Following Surgery

- 600 men with MRI prior to radical prostatectomy at MSK
- Measured 11 separate variables
- Two predictors of continence at 6 and 12 months:
  - urethral width (#6)
  - urethral volume: urethral length (#9) x Pi x [urethral width (#6)/2]^2

MRI to Predict Continence Following Surgery

4 studies: 1738 men

For each millimeter of membranous urethral length, continence improves (OR=1.09)

Reference: Mungovan, Eur Urol, 2017
MR-Guided Treatment
MRI-Guided Therapy

- Laser interstitial thermotherapy (LITT)
- Cryotherapy
- HIFU
- Transurethral ultrasound ablation
MRI-Guided Focal Laser Ablation

- Phase II study funded by National Cancer Institute
- 27 men with low or intermediate-risk prostate cancer
- MRI-guided focal laser ablation

MRI-Guided Focal Laser Ablation

• **Technique**
  – Conscious sedation and local anesthesia
  – **Lesion targeting:** Transperineal, 1.5 T
  – Ablation monitored by real time MR thermometry
  – Temperature limits:
    • 90° C within ablation zone to prevent charring/vaporization
    • 50° C near urethra/rectum
  – Same day discharge

• **Follow-up**
  – 3 month: PSA, MR-guided biopsy, and QOL
  – 12 month: PSA, MRI, biopsy, and QOL
MRI-Guided Focal Laser Ablation

- 15-Watt, 980-nm diode laser, delivered through 12 m long silica fiberoptic
- 1 cm light diffusing tip in a 1.6mm diameter coaxial cooling catheter
MRI-Guided Focal Laser Ablation

GS 4+3 in Right Mid

Ablation

12-month MRI
MRI-Guided Focal Laser Ablation

- **Primary endpoint (3 month MR-biopsy of ablation zone)**
  - 26 (96%) without cancer
  - 1 (4%) with necrosis and < 1 mm of Gleason 6

- **Secondary endpoint (12 month systematic biopsy)**
  - 3 (11%) with in-zone cancer
    - 2 with 1 mm of Gleason 6
    - 1 with 3 mm of Gleason 3+4
  - 8 (30%) with out-zone cancer (**same % as at diagnosis**)  
    - 7 with Gleason 6
    - 1 with Gleason 3+4
  - 1 (3%) with both in-zone and out-zone

MRI-Guided Focal Laser Ablation

18 men with intermediate or high-risk prostate cancer

Median treatment time: 85 minutes

13 with QOL follow-up data
  – IIEF unchanged (p=0.24)
  – IPSS unchanged (p=0.12)

Median PSA:
  – Pre: 9.5 ng/ml
  – Post: 1.8 ng/ml

NO FOLLOW-UP BIOPSIES

MR-Guided Transurethral Ultrasound Ablation: Phase 1

• 30 men (80% low-risk, 20% intermediate-risk)

• General anesthesia with suprapubic tube

• In-bore MR-guided whole-gland ablation with 3 mm peripheral safety margin

• Median time of treatment: 36 minutes

• Toxicity:
  – 33% UTI
  – 17% prolonged catheterization (> 2 weeks)
  – 3% urethral stricture requiring treatment

## MR-Guided Transurethral Ultrasound Ablation: Phase 1

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>Baseline</th>
<th>3 mo</th>
<th>12 mo</th>
</tr>
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<tbody>
<tr>
<td>IPSS</td>
<td>8 (5–13)</td>
<td>6 (4–10)</td>
<td>5 (4–7)</td>
</tr>
<tr>
<td>UCLA-PCI-SF-BH</td>
<td>100 (90–100)</td>
<td>100 (89–100)</td>
<td>100 (100–100)</td>
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<tr>
<td>ECOG status, n (%)</td>
<td>Baseline</td>
<td>3 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>Grade 0</td>
<td>30/30 (100)</td>
<td>28/28 (100)</td>
<td>29/29 (100)</td>
</tr>
</tbody>
</table>

![Graph showing patient proportion over time](image)

• Baseline median (IQR) PSA: 5.8 ng/ml (3.8 – 8.0)
  – 3 month: 0.9 (0.4 – 1.7)
  – 12 month: 0.8 (0.6 – 1.1)

• Biopsy outcomes
  – any cancer: 55%
  – ‘clinically significant’: 31%

Conclusions

• MRI is a valuable imaging tool for screening and targeting.

• MRI has significant limitations
  – incomplete accuracy
  – suboptimal staging
  – cost

• Sensibly integrating MRI can lead to:
  – fewer men undergoing biopsies
  – improved quality of care
Cubs: World Series Champions