Multi-parametric MRI in prostate cancer practice made easy

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London
Outline

- To briefly illustrate the expanded role of functional MRI techniques in clinical practice
  - Diffusion weighted MRI (DW-MRI)
  - MR spectroscopic imaging (1H-MRSI)
  - Dynamic contrast enhanced MRI (DCE-MRI)
- To demonstrate in practice how structured reporting using scoring schema can aid in communicating imaging findings back to surgeons / oncologists

- Padhani AR. Integrating multiparametric prostate MRI into clinical practice. *Cancer Imaging* 2011 - in press
Introduction

- High field 3T MRI presents new exciting opportunities for promoting men's prostatic health
- Advanced MRI tools enable us to tackle new indications in the prostate cancer patients journey
  - Raised PSA/PCa3 with negative TRUS biopsies
  - Active surveillance patients – enables appropriate patient selection
- Move into new areas of established disease
  - To identify poor prognosis tumours and guide focal therapies to dominant intraprostatic lesions
- Improved ability to tackle transition zone tumors
- Integration/ relative weighting/ communication of complex biological information is a major bioinformatics challenge
# Prostate cancer patient journey & contribution of MRI to care

<table>
<thead>
<tr>
<th>Clinical Journey begins here</th>
<th>→ Suspect cancer</th>
<th>→ Stage known cancer</th>
<th>→ Treatment of initial disease</th>
<th>→ Monitoring effectiveness of therapy</th>
<th>→ Surveillance of treated disease</th>
<th>→ Suspect relapse</th>
<th>→ Treatment of relapsed disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial observation (active surveillance)</td>
<td>Curative intent</td>
<td>Palliative</td>
<td></td>
<td>Local salvage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery</td>
<td>Ablative therapies (HIFU, PDT, cryotherapy brachytherapy)</td>
<td>External beam radiotherapy to prostate ± pelvic nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical scenario</td>
<td>Raised PSA with negative TRUS biopsy or biopsies</td>
<td>Cancer presence confirmed by biopsy</td>
<td>Small volume Low aggressiveness</td>
<td>Organ confinement No tumour at prostatic apex No metastases</td>
<td>Organ confined disease No metastases</td>
<td>Usually includes neoadjuvant hormonal therapy</td>
<td>Usually after focal therapies</td>
</tr>
<tr>
<td>Clinical (C) or Research (R) requirements</td>
<td>Define tumour location and size for targeted biopsy (C)</td>
<td>TNM stage (C) Define dominant lesion (C) Define lesion aggressiveness (C/R) Therapy planning (C)</td>
<td>Confirm organ confinement (C) Document size and location (C) Detect adverse features (C) Target pelvic nodal dissection (C)</td>
<td>Define dominant lesion location and size (C/R) Detect adverse features (C)</td>
<td>Define dominant lesion location and size (C/R) Detect adverse features (C) Target pelvic nodal dissection (C)</td>
<td>Define extent of nodal &amp; distant metastases (C) Requirement s for local palliation (C)</td>
<td>Treatment verification (R) Define volume and extent of residual disease (R)</td>
</tr>
<tr>
<td>Contribution made by MRI techniques¹</td>
<td>Morphology</td>
<td>MRI biopsy</td>
<td>MRSI</td>
<td>DW-MRI</td>
<td>DCE-MRI</td>
<td></td>
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<td>0</td>
<td>+++</td>
</tr>
</tbody>
</table>

¹ Define tumour location and size for targeted biopsy (C)

## Clinical scenario

- **Disease is not localised and salvage is impossible**
- **Disease is localised and salvage is possible**
- **Significant rise in serum PSA**
- **Rare to use imaging in this role (Serum PSA surveillance)**
- **Organ confined disease No metastases**
- **Small volume Low aggressiveness**
- **Cancer presence confirmed by biopsy**
- **Define tumour location and size for targeted biopsy (C)**
- **TNM stage (C) Define dominant lesion (C) Define lesion aggressiveness (C/R) Therapy planning (C)**
- **Confirm organ confinement (C) Document size and location (C) Detect adverse features (C) Target pelvic nodal dissection (C)**
- **Define dominant lesion location and size (C/R) Detect adverse features (C) Target pelvic nodal dissection (C)**
- **Define extent of nodal & distant metastases (C) Requirement s for local palliation (C) Treatment verification (R) Define volume and extent of residual disease (R)**
- **Detect active disease in absence of significant PSA rise (R) Identify site and volume of recurrence (C) Define extent of local disease and absence of metastases (C) Define extent of relapsed disease and complication s (C) Requirement s for local palliation (C)**
Advanced MRI tools available for clinical practice - 2010

<table>
<thead>
<tr>
<th>Tool (abbreviation)</th>
<th>Biological property depicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion MRI (DWI, DW-MRI)</td>
<td>Extent of gland formation, cellular density, necrosis and perfusion</td>
</tr>
<tr>
<td>Spectroscopy (MRSI)</td>
<td>Cell membrane turnover/energetics and replacement of normal glandular tissues</td>
</tr>
<tr>
<td>Dynamic contrast enhanced (DCE-MRI)</td>
<td>Blood flow and vascular permeability</td>
</tr>
</tbody>
</table>

![MRI images and annotations](image_url)
Prostate cancer localisation with dynamic MRI and spectroscopy


MPKS = DCE-MRI score

Peripheral zone

Central Gland
The multiparametric MRI challenge

<table>
<thead>
<tr>
<th>T2W</th>
<th>b800</th>
<th>ADC</th>
<th>DCE-Sub</th>
<th>Tum-MRSI</th>
<th>PZ-MRSI</th>
<th>Mean curve</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Pre Rx" /></td>
<td><img src="image2.png" alt="b800 Pre Rx" /></td>
<td><img src="image3.png" alt="ADC Pre Rx" /></td>
<td><img src="image4.png" alt="DCE-Sub Pre Rx" /></td>
<td><img src="image5.png" alt="Tum-MRSI Pre Rx" /></td>
<td><img src="image6.png" alt="PZ-MRSI Pre Rx" /></td>
<td><img src="image7.png" alt="Mean curve Pre Rx" /></td>
</tr>
<tr>
<td><img src="image8.png" alt="Post antibiotics" /></td>
<td><img src="image9.png" alt="b800 Post antibiotics" /></td>
<td><img src="image10.png" alt="ADC Post antibiotics" /></td>
<td><img src="image11.png" alt="DCE-Sub Post antibiotics" /></td>
<td><img src="image12.png" alt="Tum-MRSI Post antibiotics" /></td>
<td><img src="image13.png" alt="PZ-MRSI Post antibiotics" /></td>
<td><img src="image14.png" alt="Mean curve Post antibiotics" /></td>
</tr>
<tr>
<td><img src="image15.png" alt="Post LH-RHa" /></td>
<td><img src="image16.png" alt="b800 Post LH-RHa" /></td>
<td><img src="image17.png" alt="ADC Post LH-RHa" /></td>
<td><img src="image18.png" alt="DCE-Sub Post LH-RHa" /></td>
<td><img src="image19.png" alt="Tum-MRSI Post LH-RHa" /></td>
<td><img src="image20.png" alt="PZ-MRSI Post LH-RHa" /></td>
<td><img src="image21.png" alt="Mean curve Post LH-RHa" /></td>
</tr>
<tr>
<td><img src="image22.png" alt="Post HIFU" /></td>
<td><img src="image23.png" alt="b800 Post HIFU" /></td>
<td><img src="image24.png" alt="ADC Post HIFU" /></td>
<td><img src="image25.png" alt="DCE-Sub Post HIFU" /></td>
<td><img src="image26.png" alt="Tum-MRSI Post HIFU" /></td>
<td><img src="image27.png" alt="PZ-MRSI Post HIFU" /></td>
<td><img src="image28.png" alt="Mean curve Post HIFU" /></td>
</tr>
</tbody>
</table>
Essential communication elements

- **Scoring systems that indicate likelihood of a “significant cancer” being present**
  - Likert-like 5-grade scoring systems*
    » Score 1: clinically significant disease is **highly unlikely** to be present
    » Score 2: clinically significant cancer is **unlikely** to be present
    » Score 3: the presence of clinically significant cancer is **equivocal**
    » Score 4: clinically significant cancer is **likely** to be present
    » Score 5: clinically significant disease is **highly likely** to be present

- **Structured reporting using a graphical interface**
  - Matches prostate anatomy

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What is clinically significant cancer?

- A tumor that poses a significant risk to the health of an individual. Depends on
  - Aggressiveness of the tumor
  - Life expectancy (period of risk)
- No universally accepted pathologic criteria
- Definition often used*
  - Tumor volume > 0.5 ml and/or
  - Gleason pattern 4 or 5 and/or
  - Extracapsular disease


From M Karavitakis et al. Prostate Cancer and Prostatic Diseases (2011) 14, 46–52
T2-weighted MRI

- Excellent at depicting internal prostatic anatomy
- Best for more advanced disease presentations
- Signal intensity of tumors appears to correlate with grade*
- Better at depicting dense cellular (dense) cancers than sparse infiltrating disease**

<table>
<thead>
<tr>
<th>Score*</th>
<th>Peripheral zone appearances</th>
<th>illustrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - clinically significant disease is highly unlikely</td>
<td>Normal PZ with uniform high signal intensity</td>
<td><img src="image1" alt="Illustration" /></td>
</tr>
<tr>
<td>2 – clinically significant disease is unlikely</td>
<td>Linear, wedge shaped or geographic non-focal areas of low SI, usually not well demarcated</td>
<td><img src="image2" alt="Illustration" /></td>
</tr>
<tr>
<td>3 - indeterminate</td>
<td>Appearances not in categories 1/2 or 4/5</td>
<td><img src="image3" alt="Illustration" /></td>
</tr>
<tr>
<td>4 – clinically significant disease is likely</td>
<td>Low signal (dark gray-black) intensity focus/mass, well defined lesion confined to prostate</td>
<td><img src="image4" alt="Illustration" /></td>
</tr>
<tr>
<td>5 – clinically significant disease is highly likely</td>
<td>Low signal intensity mass, with invasive features including extracapular or seminal vesicle invasion, mass effect on capsule including bulging</td>
<td><img src="image5" alt="Illustration" /></td>
</tr>
</tbody>
</table>

* Subtract 1 if significant haemorrhage in area of abnormality
<table>
<thead>
<tr>
<th>Score*</th>
<th>Transition zone appearances</th>
<th>illustrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - clinically significant disease is highly unlikely</td>
<td>TZ containing stromal &amp; glandular hyperplasia/adenoma with well defined margins. No low SI nodules or lenticular lesions</td>
<td><img src="image1" alt="Illustration" /> <img src="image2" alt="Illustration" /></td>
</tr>
<tr>
<td>2 – clinically significant disease is unlikely</td>
<td>Round shaped low SI lesions with a smooth margins. Lenticular shaped, band like low SI in midline or around central adenoma</td>
<td><img src="image3" alt="Illustration" /> <img src="image4" alt="Illustration" /></td>
</tr>
<tr>
<td>3 - indeterminate</td>
<td>Appearances not in categories 1/2 or 4/5</td>
<td><img src="image5" alt="Illustration" /></td>
</tr>
<tr>
<td>4 – clinically significant disease is likely</td>
<td>Lenticular shaped anterior low SI lesion without capsule invasion. “charcoal” sign: homogeneous low SI lesion with loss of internal structure and un-sharp margins</td>
<td><img src="image6" alt="Illustration" /> <img src="image7" alt="Illustration" /></td>
</tr>
<tr>
<td>5 – clinically significant disease is highly likely</td>
<td>Lenticular or round mass with bulge / irregularity / retraction of the anterior prostate capsule. Irregular, infiltrating mass destroying TZ architecture, invading adjacent PZ/SV/bladder</td>
<td><img src="image8" alt="Illustration" /> <img src="image9" alt="Illustration" /></td>
</tr>
</tbody>
</table>

* Subtract 1 if significant haemorrhage in area of abnormality
Limitations of T2-weighted MRI

- Tumour volume is underestimated and locations are not well depicted
  - Not all tumours are visible
  - Transition zone tumours not well seen (30% of cancers)
  - False positives: scars, BPH, prostatitis, hemorrhage & treatment effects

- Restricted ability to distinguish localized (T2) from early T3 (advanced) disease
  \[\rightarrow\] great staging variability (37-96%)

- Important biologically characteristics are not well depicted
  - Tumour volume, location, histological grade, vascularisation, hypoxia, proliferation rate, perineural invasion
DW-MRI pathological correlations

Qualitative assessment – hyperintensity in high b-value images

Quantitative assessment – ADC value

Park BK et al. Investigative Radiology 2007; 24:842-847
ADCs for tumors with different Gleason scores in the whole prostate

ADCs for tumors with different D’Amico clinical risk scores in the whole prostate

Turkbey B et al. Radiology 2011;258:488-495

©2011 by Radiological Society of North America
Distinguishing tumour from T2-shine through
(look for hyperintensity on **very** high b-value images)

For some moderate grade tumours it is necessary to have very high b-values
### Scoring system for DW-MRI (PZ)

**TZ criteria to be decided**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>b1000</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - clinically significant disease is highly unlikely</td>
<td>No reduction in ADC compared to normal glandular tissue / no increase in signal on high b-value images (≥b1000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 – clinically significant disease is unlikely</td>
<td>Diffuse, hyperintensity on ≥b1000 image with low ADC; No focal features - linear, triangular or geographical features allowed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - indeterminate</td>
<td><strong>Diffuse</strong> unilateral hyperintensity on ≥b1000 image with diffuse low ADC (no focal features)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 – clinically significant disease is likely</td>
<td><strong>Focal</strong> area(s) of reduced ADC but isointense SI on high b-value images (≥b1000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 – clinically significant disease is highly likely</td>
<td><strong>Focal</strong> area/mass of hyperintensity on the high b-value images (≥b1000) with reduced ADC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Validating DCE-MRI for prostate cancer localisation and staging

ROC curves show Az values for DCE-MRI (MPKS) and MRS for localization of prostate tumors with volumes of >0.5 cm³


N = 32


<table>
<thead>
<tr>
<th>Staging</th>
<th>T2-weighted MR Images</th>
<th>Dynamic MR Images</th>
<th>Combined Data Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct</td>
<td>72 (n = 23)</td>
<td>84 (n = 27)</td>
<td>91 (n = 29)</td>
</tr>
<tr>
<td>Understaging</td>
<td>19 (n = 6)</td>
<td>3 (n = 1)</td>
<td>3 (n = 1)</td>
</tr>
<tr>
<td>Overstaging</td>
<td>9 (n = 3)</td>
<td>12 (n = 4)</td>
<td>6 (n = 2)</td>
</tr>
<tr>
<td>AUC*</td>
<td>84 (75, 94)</td>
<td>92 (84, 100)</td>
<td>95 (88, 100)</td>
</tr>
</tbody>
</table>
Scoring scheme for DCE-MRI curves

Symmetry and focalness are assessed on the basis of corresponding normal tissue (PZ/TZ).
Subtract 1 from TZ lesions – because normal BPH is hypervascular.

<table>
<thead>
<tr>
<th>Curve score</th>
<th>Symmetry &amp; focalness score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>Definite benign (1)</td>
</tr>
<tr>
<td>2</td>
<td>Asymmetry or focal (+1)</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Asymmetry &amp; focal (+2)</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Asymmetry or focal (+1)</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Asymmetry &amp; focal (+2)</td>
<td>Definite malignant (5)</td>
</tr>
</tbody>
</table>
Rising PSA – negative biopsy x 2

- 56 yo raised serum PSA level and 2 negative TRUS

- ADC map does not depict all intraprostatic lesions – misses the small, Gleason 6 tumour foci
Threshold metabolite approach vs classifier systems


TABLE 1. Choline + Creatine/Citrate Ratios for the Different Tissues in the Prostate on a 5-Point Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Peripheral Zone</th>
<th>Central Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Definitely benign tissue</td>
<td>≤0.44</td>
<td>≤0.52</td>
</tr>
<tr>
<td>2. Probably benign tissue</td>
<td>0.44–0.58</td>
<td>0.52–0.66</td>
</tr>
<tr>
<td>3. Possible malignant tissue</td>
<td>0.58–0.72</td>
<td>0.66–0.80</td>
</tr>
<tr>
<td>4. Probably malignant tissue</td>
<td>0.72–0.86</td>
<td>0.80–0.94</td>
</tr>
<tr>
<td>5. Definitely malignant tissue</td>
<td>&gt;0.86</td>
<td>&gt;0.94</td>
</tr>
</tbody>
</table>
CC/C ratio marker for cancer?

87 patients

(Cho+Cr)/Ci

PZ peripheral zone
CG central gland
Ur (peri-)urethral area

Tumor is represented by the highest CC/C ratio within 5 mm of the classified voxel.

<table>
<thead>
<tr>
<th></th>
<th>Normal tissue</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.29</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>0.32±0.15</td>
<td>0.38±0.15</td>
</tr>
<tr>
<td>Mean</td>
<td>0.35</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>0.38±0.15</td>
<td>0.47±0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>0.93±0.59</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Arend Herrshap - Nimegen
Integration, reporting and communication

- Structured reporting method via graphical interface to match prostate anatomy
  - Anterior-posterior border 1.7cm from the rectal wall (average length of core biopsy needle)
- Use scoring system that indicates the likelihood of a “significant cancer” being present
- Assign scores per prostate/sector/lesion (max 5 lesions)
  - Dominant cancer focus makes up to 90% of the cancer volume and 80% of small foci have tumour volumes < 0.5 ml
- Give a putative TNM stage
- Take account of patient history and symptoms, serum PSA, DRE findings, concomitant medications (particularly anti-androgens) and time since TRUS biopsy
Active surveillance – baseline (Dec 2008)

PSA 5.3ng/ml; TRUS - small foci of Gleason 3+3 plus prostatitis in PZ; TRUS missed anterior gland tumor (ADC 835 µm²/s)
TRUS biopsy only = Gleason 3+3 on left side with prostatitis

PZ:
T2W =3/5; DWI =2/5
DCE = 3/5; MRSI =1/5

Ant TZ
T2W =2/5; DWI =4/5
DCE =5/5; MRSI =1/5
Active surveillance – post antibiotics (Dec 2009)

PSA 5.8ng/ml; enlarging anterior gland tumor (ADC 835 → 583 μm²/s) with decreased flow in PZ.

PZ: T2W = 3/5; DWI = 2/5; DCE = 2/5; MRSI = 1/5

Ant TZ: T2W = 4/5; DWI = 4/5; DCE = 5/5; MRSI = 1/5
NAME: Fred Bloggs
DOB: 
PSSC No: 
PSA: 5.9 ng/mL
EXAMINATION DATE: 29/12/09
T2W \ Check DW-MRI \ Check MRSI \ Check DCE-MRI
GLAND SIZE: 5.2 x 3.5 x 4.8 cm
1.5T

Detection \ Staging \ Localisation \ Surveillance \ Response/Relapse

NA=Not available | ND=Non diagnostic

Diffuse change
T2W 3/5
DWI 2/5
DCE 5/5
MRSI 5/5

10 mm 4.3 cm
T2W 4/5
DWI 4/5
MRSI 1/5
DCE 5/5

Cancer Imaging Index
Definitely benign (1) -- probably benign (2) -- indeterminate -- probably malignant (4) -- definitely malignant (5)
Diffusion MRI (DW-MRI)(5/5) -- reflects cellularity and extent of gland formation | Dynamic MRI (DCE-MRI) -- vascular perfusion | Spectroscopy (MRSI) -- cell membrane turnover (mostly synthesis). Only DW-MRI and MRSI correlate with Gleason score.

Other Findings
Mild BPH

Radiology Consultant: 
DATE: 29/12/09

Template Mapping Biopsies

University College London Hospital NHS

Modified Barzell Zones

1. Left Parasagittal Anterior Apex
2. Left Parasagittal Anterior Base
3. Right Parasagittal Anterior Apex
4. Right Parasagittal Anterior Base
5. Midline Apex
6. Midline Base
7. Left Medial Anterior Apex
8. Left Medial Anterior Base
9. Right Medial Anterior Apex
10. Right Medial Anterior Base
11. Left Lateral
12. Right Lateral
13. Left Parastomal Posterior Apex
14. Left Parastomal Posterior Base
15. Right Parastomal Posterior Apex
16. Right Parastomal Posterior Base
17. Left Medial Posterior Apex
18. Left Medial Posterior Base
19. Right Medial Posterior Apex
20. Right Medial Posterior Base

Clinically insignificant disease
Gleason = 3+4 AND/OR Max Cancer length 4-5mm
Gleason > = 4+3 AND/OR Max cancer length > = 6mm
Post-androgens, pre-HIFU (Oct 2010)

Smaller anterior gland tumor (ADC 1355 µm²/s) with decreased flow & marked metabolic atrophy
Challenges

- Ability to display, co-register, segment, fuse, and analyse every tool in an integrated single workspace would be ideal.
- Methods for dealing with missing functional datasets (not obtained, corruption, artefacts) are needed.
- Relative weighting of individual tests requires further research.
  - Localization: $\text{DW-MRI} > \text{T2W} = \text{DCE-MRI} > \text{MRSI}$
  - Aggressiveness: $\text{DW-MRI} = \text{MRSI} > \text{T2W} > \text{DCE-MRI}$