Prostate cancer – what do we see and how do we see it?

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Senior Clinical Researcher, Division of Surgical & Interventional Science, UCL
Overview

- The prostate
- Assessing the prostate for cancer
  - Digital rectal examination
  - Prostate specific antigen
  - Sampling the prostate
  - Imaging the prostate
  - Image guided sampling
- Image guided management of the prostate
  - Active surveillance
  - Focal therapy
The prostate
The prostate
Assessing the prostate: Digital rectal examination
Digital rectal examination

One important way doctors check for prostate abnormalities is by inserting a rubber-gloved finger into the rectum, where the prostate can be explored by touch. The exam is performed with the patient in a bent-over position.
Clinical staging of prostate cancer

**T1 prostate cancer**
The cancer cannot be felt and can only be seen under a microscope – **localised prostate cancer**.

**T2 prostate cancer**
The cancer can be felt or seen but it is contained within the prostate gland – **localised prostate cancer**.

**T3 prostate cancer**
The cancer can be felt or seen breaking through the capsule of the prostate gland – **locally advanced prostate cancer**.

**T4 prostate cancer**
The tumour has spread to nearby organs, such as the bladder neck, back passage or pelvic wall – **locally advanced prostate cancer**.
Prostate cancer in the UK
Prostate cancer in the UK

- 6% of men in the UK have a PSA test\(^1\)
- 10% of these are raised & prompt a referral for further investigation\(^2\)
- 60-90 000 prostate biopsies done in the UK each year\(^2\)
- Around 25% of these are positive for cancer\(^3\)
- 34 000 men diagnosed with prostate cancer each year

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Men with a diagnosis of prostate cancer

- Disease contained within the prostate (localised) in 86%²
- 45% diagnosed with localised prostate cancer are <70 yrs³
- 14,000 men in the UK could opt for radical treatments each year⁴
- Many of these choose active surveillance

Risk stratification – NICE

<table>
<thead>
<tr>
<th>Risk stratification criteria for men with localised prostate cancer</th>
<th>PSA (ng/ml)</th>
<th>Gleason score</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt; 10</td>
<td>≤ 6</td>
<td>and T1–T2a</td>
</tr>
<tr>
<td>Intermediate risk risk</td>
<td>10–20</td>
<td>7</td>
<td>or T2b–T2c</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20</td>
<td>8–10</td>
<td>or T3–T4</td>
</tr>
</tbody>
</table>
Stage migration in UK

FIG. 1. Temporal trends in clinical T stage within the low-risk category.
NICE guidance (CG 58): Localised prostate cancer: treatment options

<table>
<thead>
<tr>
<th>Radical treatments</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Active surveillance</td>
<td>✔</td>
<td>●</td>
<td>✗</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>●</td>
<td>✔</td>
<td>✔*</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>●</td>
<td>●</td>
<td>✗</td>
</tr>
<tr>
<td>Conformal radiotherapy†</td>
<td>●</td>
<td>✔</td>
<td>✔*</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>✗‡</td>
<td>✗‡</td>
<td>✗‡</td>
</tr>
<tr>
<td>High-intensity focused ultrasound</td>
<td>✗‡</td>
<td>✗‡</td>
<td>✗‡</td>
</tr>
</tbody>
</table>

* Offer if there is a realistic prospect of long-term disease control
† Conformal radiotherapy should be given at a minimum dose of 74 Gy (at a maximum of 2 Gy per fraction)
‡ Unless as part of a clinical trial comparing use with established interventions

**Key:**
- ✔ preferred treatment
- ● treatment option
- ✗ not recommended
Initial management of low-risk localized prostate cancer in the UK: analysis of the British Association of Urological Surgeons Cancer Registry

Gerard P. McVey, Sean McPhail*, Sarah Fowler†, Gregor McIntosh‡, David Gillatt§ and Chris C. Parker

**FIG. 2.** Temporal trends in initial treatment within the low-risk category; Brachy, brachytherapy; WW, watchful waiting.
Assessing the prostate: Prostate specific antigen
Prostate specific antigen (PSA)

- Protein measured in the blood
- Raised in men with
  - A large prostate
  - Prostate cancer
  - Urinary tract infection
- Can measure over 1000 ng/dl in men with metastatic prostate cancer
- In the low ranges (below 15) it is more likely to be due to a large prostate than prostate cancer
- PSA can fluctuate so repeat readings are needed in monitoring cancer
Assessing the prostate: Sampling the prostate
Prostate biopsy
Gleason score

- Pathological grading system for samples seen under the microscope
- Dr Jameson to discuss further

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 + 3</td>
<td>All of the cancer cells found in the biopsy look likely to grow slowly.</td>
</tr>
<tr>
<td>3 + 4</td>
<td>Most of the cancer cells found in the biopsy look likely to grow slowly. There were some cancer cells that look more likely to grow at a more moderate rate.</td>
</tr>
<tr>
<td>4 + 3</td>
<td>Most of the cancer cells found in the biopsy look likely to grow at a moderate rate. There were some cancer cells that look likely to grow slowly.</td>
</tr>
<tr>
<td>4 + 4</td>
<td>All of the cancer cells found in the biopsy look likely to grow at a moderately quick rate.</td>
</tr>
<tr>
<td>4 + 5</td>
<td>Most of the cancer cells found in the biopsy look likely to grow at a moderately quick rate. There were some cancer cells that are likely to grow more quickly.</td>
</tr>
<tr>
<td>5 + 4</td>
<td>Most of the cancer cells found in the biopsy look likely to grow quickly.</td>
</tr>
<tr>
<td>5 + 5</td>
<td>All of the cancer cells found in the biopsy look likely to grow quickly.</td>
</tr>
</tbody>
</table>
Figure 2: Random deployment of the needle leads to detection of small clinically insignificant tumours

Figure 3a: Random deployment of the needle leads to a clinically significant tumour being missed in the PZ

Figure 4: Random deployment of the needle leads to a clinically significant tumour being under-sampled and categorised as low volume

Figure 3b: Random deployment of the needle leads to a clinically significant tumour being missed in the anterior PZ horn
How representative is a core?

$15 \times 1 \times 1 \text{mm}$ vs $50 \times 40 \times 50 \text{mm}$

1 core $= 0.018 / 65\text{cc} = 0.02\%$ of prostate volume

With thanks to Dr Pedro Olivier, Lisbon
Transperineal Template Guided Prostate Biopsies

Barzelli and Melamed, 2007
NICE Guidance on template guided biopsy (IPG 364)

For men with negative results from other biopsy methods (normal governance arrangements)

For active surveillance or focal therapy (special arrangements for clinical governance, consent & research)

NICE encourages research into template mapping biopsy, particularly the comparison with radical prostatectomy
Assessing the prostate: MR imaging
T2 weighted PZ

T2 weighted TZ

Tumorsize dependent detection rate of endorectal MRI of prostate cancer—A histopathologic correlation with whole-mount sections in 70 patients with prostate cancer

Matthias C. Roethke, Matthias P. Lichy, Leo Jurgsch, Jörg Hennenlotter, Ulrich Vogel, David Schilling, Arnulf Stenzl, Claus D. Claussen, Heinz-Peter Schlemmer

- Departments of Diagnostic and Interventional Radiology, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
- Departments of Urology, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
- Departments of Pathology, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
Addition of 1 functional sequence

Dynamic contrast enhancement

<table>
<thead>
<tr>
<th>Tumour vol.</th>
<th>0.2cc</th>
<th>0.5cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>77%</td>
<td>90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>PPV</td>
<td>86%</td>
<td>77%</td>
</tr>
<tr>
<td>NPV</td>
<td>85%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Villers et al., 2006; J Urol. 176(6 Pt 1): 2432-7
Dynamic Contrast Enhanced, Pelvic Phased Array Magnetic Resonance Imaging of Localized Prostate Cancer for Predicting Tumor Volume: Correlation With Radical Prostatectomy Findings

Arnault Villers, Philippe Paeuch, Damien Mouton, Xavier Leroy, Charles Ballereau
and Laurent Lemaitre

From the Departments of Urology (AM, BM, CL) and Pathology (EU), Centre Hospitalier Universitaire de Lille, Lille, France

Purpose: We assessed the value of pelvic phased array dynamic contrast enhanced magnetic resonance imaging for predicting the intraprostatic location and volume of clinically localized prostate cancer.

Materials and Methods: Suspicious areas on pre-biopsy magnetic resonance imaging in 24 patients were assigned a magnetic resonance imaging malignancy score and located with respect to anatomical features of the peripheral and transition and peripheral zone boundaries. The largest surface area and volume were measured. These magnetic resonance imaging findings were compared with radical prostatectomy specimen histopathology findings.

Results: Histopathology maps detected 26 separate cancer foci. The largest tumor focus was located in the peripheral zone in 14 patients and in the transition zone in 10. T1-weighted dynamic contrast enhanced magnetic resonance imaging identified 30 of the 39 tumor foci greater than 0.2 cc and 27 of the 30 greater than 0.5 cc. T2-weighted T1-weighted images were suspicious in 28 of 30 foci greater than 0.2 cc that were identified by histological examination and magnetic resonance imaging sequences. Sensitivity, specificity, and positive and negative predictive values were determined by magnetic resonance imaging were 77%, 91%, 86% and 95% for foci greater than 0.2 cc, and 90%, 88%, 85% and 99% for foci greater than 0.5 cc, respectively. Median tumor volume was 0.87 cc (range 0.003 to 4.32) for foci greater than 0.2 cc and 0.30 cc (range 0.003 to 1.34) for those not detected by magnetic resonance imaging. The peripheral zone and 0.53 cc (range 0.037 to 1.34) for those not detected by magnetic resonance imaging (p < 0.005). Corresponding median volumes for transition zone tumor foci were 0.54 (range 0.75 to 10.97) and 0.435 (range 0.28 to 0.58).

Conclusions: Pre-biopsy pelvic phased array dynamic contrast enhanced magnetic resonance imaging is an accurate technique for detecting and quantifying intraprostatic transition or peripheral zone tumor foci greater than 0.2 cc. It has promising implications for cancer detection, prognosis and treatment.

Key Words: prostate, prostate neoplasms, magnetic resonance imaging, biopsy, prostatectomy

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<th>Tumour vol</th>
<th>0.2cc</th>
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<td>Sensitivity</td>
<td>77%</td>
<td>90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>PPV</td>
<td>97%</td>
<td>86%</td>
</tr>
<tr>
<td>NPV</td>
<td>85%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Diffusion weighted imaging

Diffusion weighted

- Random movement of water in interstitial space
- Cancer restricts movement due to high cell densities and abundance of cell membranes (high signal)
- Compare apparent diffusion coefficients of different acquisition sequences (b values) (low signal)
- Short acquisition times
- High contrast resolution
Assessing the prostate: Targeted sampling
Assessing the prostate: using MRI to decide who to biopsy and where to biopsy
Platinum Priority – Review – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

Image-Guided Prostate Biopsy Using Magnetic Resonance Imaging–Derived Targets: A Systematic Review

Caroline M. Moore a,b,*, Nicola L. Robertson a,c, Nasr Arsanious b, Thomas Middleton b, Arnauld Villers d, Laurence Klotz e, Samir S. Taneja f, Mark Emberton a,c

a Division of Surgical and Interventional Science, University College London, London, UK; b Department of Urology, Croydon University Hospital, London, UK; c Department of Urology, University College London Hospitals Trust, London, UK; d Department of Urology, CHU Lille, Université Lille Nord de France, Lille, France; e Department of Urology, Sunnybrook Health Centre, Toronto, Canada; f Division of Urologic Oncology, New York University Langone Medical Centre, New York, NY, USA
Research Question

In men with a clinical suspicion of prostate cancer, does an MRI guided biopsy strategy result in equivalent detection of clinically significant cancer and a lower detection rate of clinically insignificant cancer compared to standard transrectal ultrasound guided biopsies?
4222 records identified
(EMBASE 2106, Pubmed 2052, DARE 4, Cochrane Trials 57, Cochrane Economic evaluations 3)

908 Duplicate records

3314 unique records

3093 not relevant to research question

222 records for full review

70 review articles

60 technical reports

14 relevant abstracts without full reports

10 reports of targeted cores only

18 reports combining standard plus targeted cores

50 reports comparing targeted versus standard cores
(16 discrete studies: 3 case reports, 2 RCTs, 1 historical case control)
<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>MRI</th>
<th>Mean no. of lesions (range; max allowed)</th>
<th>Sequence used to define target</th>
<th>ER coil</th>
<th>Navigational system for biopsy</th>
<th>Analgesia</th>
<th>Standard cores taken blind to location of lesions</th>
<th>Targeted cores per lesion (mean per patient)</th>
<th>Total cores taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haffner, 2010</td>
<td>555</td>
<td>1.5T Phillips Gyroscan Intera</td>
<td>1.9 (NR; NR)</td>
<td>T2/DCE</td>
<td>No</td>
<td>US (cognitive)</td>
<td>LA</td>
<td>No</td>
<td>2 (3.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Park, 2011</td>
<td>855</td>
<td>3T Phillips Achieva</td>
<td>NR</td>
<td>T2/DCE/DWI</td>
<td>No</td>
<td>US (cognitive)</td>
<td>NR</td>
<td>No</td>
<td>0-3 per patient</td>
<td>10-12 standard + up to 3 targeted</td>
</tr>
<tr>
<td>Sciarra, 2010</td>
<td>101</td>
<td>3T Phillips Achieva</td>
<td>2.6 (1-7; any)</td>
<td>Any 3 positive</td>
<td>Yes</td>
<td>US (EM tracking device)</td>
<td>GA</td>
<td>Yes</td>
<td>Mean 2.2 (range 1-8) (5.8)</td>
<td>17.8 (mean)</td>
</tr>
<tr>
<td>Labanaris, 2010</td>
<td>85</td>
<td>1.5T Phillips Intera Pulsa</td>
<td>1.15 (1-2; NR)</td>
<td>T2</td>
<td>No</td>
<td>US (software)</td>
<td>Spinal anaesthesia</td>
<td>No</td>
<td>1-2 (2.3)</td>
<td>Total 12 cores</td>
</tr>
<tr>
<td>Prando, 2005</td>
<td>71</td>
<td>3T TrioTim</td>
<td>Median 1 (1-3; 3)</td>
<td>T2,DWI, DCE</td>
<td>ER coil or pelvic coil</td>
<td>MRI</td>
<td>NR</td>
<td>No</td>
<td>2 (median 4, range 2-7)</td>
<td>Targeted only</td>
</tr>
<tr>
<td>Lee, 2011</td>
<td>180</td>
<td>1.5T Siemens Avanto</td>
<td>NR</td>
<td>DCE or MRS</td>
<td>Yes</td>
<td>US (cognitive)</td>
<td>LA</td>
<td>No</td>
<td>NR (2.17)</td>
<td>Mean 12.7 in group B (range 10-16), 10 in group A</td>
</tr>
<tr>
<td>Hambrock, 2010</td>
<td>42</td>
<td>1.5T Signa GE</td>
<td>NR</td>
<td>MRS</td>
<td>Yes</td>
<td>US (software)</td>
<td>LA</td>
<td>No</td>
<td>2-3 (NR)</td>
<td>NR</td>
</tr>
<tr>
<td>Singh, 2008</td>
<td>87</td>
<td>3.0T Phillips Achieva</td>
<td>NR</td>
<td>T2/DWI</td>
<td>No</td>
<td>US (MRI images also displayed on US screen)</td>
<td>GA</td>
<td>No</td>
<td>NR (median 9, up to 14)</td>
<td>Up to 26</td>
</tr>
<tr>
<td>Miyagawa, 2010</td>
<td>260</td>
<td>1.0T Siemens Harmony</td>
<td>3</td>
<td>All</td>
<td>Yes</td>
<td>US (cognitive)</td>
<td>LA</td>
<td>NR</td>
<td>3 (NR)</td>
<td>Group A 21; group B 18</td>
</tr>
<tr>
<td>Hadaschik, 2011</td>
<td>13</td>
<td>3T Phillips Intera</td>
<td>NR (NR; max 2 sextants)</td>
<td>T2/DCE</td>
<td>Yes</td>
<td>MRI</td>
<td>Sedation</td>
<td>No</td>
<td>2 per abnormal sextant (4)</td>
<td>Max 10 cores: 2 for tissue bank, 8 cores for analysis</td>
</tr>
<tr>
<td>Rastinehad, 2010</td>
<td>106</td>
<td>3T Magnetom Trio</td>
<td>UK</td>
<td>T2</td>
<td>No</td>
<td>US (BiopSee software)</td>
<td>GA</td>
<td>No</td>
<td>2-6 (2-6)</td>
<td>Mean 23.2</td>
</tr>
<tr>
<td>Natarajan, 2011</td>
<td>47</td>
<td>3T Siemens TrioTim/So matom 3T</td>
<td>1.4 (NR; NR)</td>
<td>NR</td>
<td>No</td>
<td>US (Artemis software with tracking device)</td>
<td>LA</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Park, 2008</td>
<td>43</td>
<td>3T Phillips Achieva</td>
<td>1 (1; 1)</td>
<td>DWI</td>
<td>No</td>
<td>US (cognitive)</td>
<td>NR</td>
<td>No</td>
<td>At least 2 (at least 2)</td>
<td>NR</td>
</tr>
<tr>
<td>Reference</td>
<td>No.</td>
<td>Overall cancer detection (TB and SB)</td>
<td>Cancer detection per lesion</td>
<td>Cancer detection per core (TB)</td>
<td>Cancer detection per core (SB)</td>
<td>Targeted cores demonstrate superiority to standard cores?</td>
<td>Missed cancers with each technique</td>
<td></td>
<td></td>
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<tr>
<td>Haffner, 2010</td>
<td>555</td>
<td>302/555 (54%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes: Greater representation of disease burden and Gleason grade</td>
<td>Standard missed 12 cancers (12 significant); targeted missed 66 cancers, (13 significant)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park, 2011</td>
<td>85</td>
<td>MRI group 13/44 (30%); no MRI 4/41 (10%)</td>
<td>NR</td>
<td>14/37 (38%) from MR targets; 0/6 from US targets</td>
<td>38/400 (8%) in MRI group; 11/450 (2%) in non MRI group</td>
<td>Yes – increased cancer detection from 10% to 30%</td>
<td>NR but if a target lay within a systematically sampled region, the core was counted as systematic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sciarr, 2010</td>
<td>180</td>
<td>A = 22/90 (24%); B = 44/90 (49%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes: Greater detection accuracy, high detection rate of clinically significant disease from group B to A</td>
<td>NA (comparison between cohorts rather than within patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labanaris, 2010</td>
<td></td>
<td>Group A =</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prando, 2005</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee, 2011</td>
<td>87</td>
<td>46/87 (53%)</td>
<td>19/32 (59%) for anterior lesion; 19/30 (63%) for apical lesions.</td>
<td>149/518 (29%)</td>
<td>32/903 (4%)</td>
<td>No: All cancers found on targeting were also found on systematic biopsy</td>
<td>2 cancers found in men with no lesion on MR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hambrock, 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes: Greater detection accuracy 55/248 (22%), 5 (15%) in TRUS cohort</td>
<td>NA (historical cohort comparison)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh, 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes: Targeted biopsy detected 25% vs standard biopsy 1/2 missed with standard; 1/2 missed with targeted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyagawa, 2010</td>
<td></td>
<td>52/85 (61%)</td>
<td>NR</td>
<td>m 75/833 (9%)</td>
<td>Yes</td>
<td>Standard missed 18/52; targeted missed 7/52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadaschik, 2011</td>
<td>106</td>
<td>63/106 (59%)</td>
<td>63/142 (44%)</td>
<td>101/410 cores (25%)</td>
<td>179/2951 (9%)</td>
<td>Yes: MR-GB detected 25% vs 9% systematic cores</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rastinehad, 2010</td>
<td>101</td>
<td>55/101 (55%)</td>
<td>24/34 (71%) strong suspicion; 29/72 (40%) moderate suspicion; 23/158 (15%) low suspicion.</td>
<td>20.6% overall (54%, 21% and 5% for strong, moderate and low suspicion on MRI)</td>
<td>11% overall (30%, 12% and 4% for strong, moderate and low suspicion on MRI)</td>
<td>Yes: Mean 2.6 cores vs 12 cores required for equal performance</td>
<td>Standard missed 10/55; targeted missed 10/55.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natarajan, 2011</td>
<td>47</td>
<td>30/47 (64%)</td>
<td>23/65 (35%)</td>
<td>19/57 (33%) for highly suspicious lesions</td>
<td>9/124 (7%)</td>
<td>Yes</td>
<td>Modified technique: standard missed 4/12, targeted missed 3/12.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park, 2008</td>
<td>43</td>
<td>17/43 (40%)</td>
<td>NR</td>
<td>30/38 (79%)</td>
<td>35/140 (25%)</td>
<td>Yes</td>
<td>5/17 missed with standard; none missed with targeted.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data synthesis: cancer detection per core: 376/1252 (30%) of targeted cores detected cancer versus 368/5441 (7%) standard cores

Data synthesis: cancer detection per patient: 650/1345 (48%) of men with targeted biopsy versus 526/1442 (36%) men for standard biopsy
What would we miss if men with a negative MRI did not undergo standard biopsy?

• We would miss:
  • 51/555 men with a negative MRI had cancer on standard biopsy (9%)
  • 13/555 (2.3%) had significant cancer (>4mm cancer core length, any pattern 4)

• We would avoid:
  • Biopsy in 1 in 3 men
  • Diagnosis of low volume low grade cancer in 1 in 10 men
Conclusion

MRI-targeted biopsy offers a more efficient sampling strategy than standard TRUS biopsy

- Equal detection of clinically significant disease with fewer cores
- Reduction in the detection of clinically insignificant disease
- Better representation of disease burden (cancer core length, Gleason score)
MRI-targeted biopsy with visual registration and ultrasound guidance

Fig. 2 – Magnetic resonance imaging–targeted biopsy with ultrasound guidance and visual registration. A lesion (white arrow) that is highly likely to be clinically significant cancer is seen in the left anterior horn on (a) T2-weighted, (b) diffusion-weighted, and (c) dynamic contrast-enhanced images and depicted in red by a radiologist on a diagrammatic colour coded report. The urologist uses this report to visually register the location of the lesion during the biopsy procedure with transrectal ultrasound guidance. (d) The biopsy needle is seen within the lesion on the ultrasound image.
MRI-targeted biopsy with software registration and ultrasound guidance

**Fig. 3** – Magnetic resonance (MR) imaging-targeted biopsy with ultrasound guidance and software registration. Series showing (from left to right): T2-weighted image showing a low-intensity lesion in the left peripheral zone, delineation of the target volume on the T2-weighted image, a three-dimensional model of prostate volume and target volume, registration of MR volume to ultrasound image, and the biopsy needle within the target volume on the ultrasound image.
MRI-targeted biopsy using an inbore biopsy device

Fig. 4 – Magnetic resonance imaging–targeted biopsy using a direct in-bore technique. These images show a right peripheral zone lesion identified on the apparent diffusion coefficient map and diffusion-weighted images, and then the needle in the target in axial and sagittal T2-weighted images.
HEALTH INNOVATION CHALLENGE FUND

2. Project deliverables

There are many innovative technologies available either today or in development that have surgical applications. The HIC Fund is looking for the following outputs:

- New devices or instruments (including integrated software as appropriate) with proven effectiveness and efficacy which will demonstrably reduce or eliminate invasive surgery

- Complete end-to-end solutions which translate new technology into safer and cost-effective practice within the NHS

- Scalable solutions that can be reproduced across surgical units in the UK and which are not dependent upon the unique skills of an individual surgeon.
The SmartTarget Device

- Not reliant on expertise
- Automatic, deformable image registration
- < 3mm error
- Widely compatible
- Diagnosis and therapy
- Low-cost
Prostate and tumour contouring in an MR image
Multi-slice MR contours used to form a finite element model (FEM)
Prostate deformation

Computer modelling of prostate deformation due to endorectal probe/coil pressure

Hu et al., *Medical Image Analysis* (In Press);
Automatic 3D non-rigid registration

Hu et al., *Medical Image Analysis* (In Press);
Tumour targeting using the SmartTarget system.
Using imaging to inform prostate cancer management: Active surveillance
What is Active Surveillance?

To defer or avoid treatment in men with localised prostate cancer.....

With the option of choosing treatment if the disease changes
A balance

Potential benefit of treatment

Potential harm of treatment
Why don’t we treat all prostate cancers straight away?

- Prostate cancer treatments can be very effective but can have serious side effects
  - Problems with urine leakage (1 in 7 men 1 year after surgery)
  - Problems with erections (7 in 10 men 1 year after surgery)
- It is best to offer treatment to those men who are most likely to benefit from them
Why don’t all men with prostate cancer benefit from treatment?

Prostate cancer is very common, but many more men have prostate cancer than would ever notice it or die from it.
40 men out of 100 would have some prostate cancer if we looked very carefully
13 out of 100 men would be found to have cancer using PSA and standard biopsy to screen men aged 55-70.
7 in 100 men would present with symptoms of prostate cancer if there was no PSA testing.
2-3 in 100 men die of prostate cancer
491,348 deaths in 2009

159,779 due to cardiovascular disease (33%)

9,402 due to prostate cancer (2%)
What proportion of men who have localised prostate cancer die from prostate cancer?
Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D.,
William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D.,
Patricia Gilhooly, M.D., B. Mayer Grob, M.D., Imad Nsouli, M.D., Padmini Iyer, M.D., Ruben Cartagena, M.D.,
Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Roohollah Sharifi, M.D., William Blank, M.D.,
Parikshit Pandya, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., and Thomas Wheeler, M.D.,
for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group

A  Death from Any Cause

B  Death from Prostate Cancer

354 (48.4%) men died from any cause

52 (7.1%) men died of prostate cancer
Of the men who died in the study 5 out of 6 died of non prostate cancer causes.

And these men had only had standard biopsy for diagnosis so would have some men with higher risk disease.
A balance

Potential benefit of treatment

Potential harm of treatment
<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Radical Prostatectomy</th>
<th>Observation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence†</td>
<td>49/287 (17.1)</td>
<td>18/284 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erectile dysfunction‡</td>
<td>231/285 (81.1)</td>
<td>124/281 (44.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bowel dysfunction§</td>
<td>35/286 (12.2)</td>
<td>32/282 (11.3)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Table 2. Patient-Reported Urinary, Erectile, and Bowel Dysfunction at 2 Years, According to Study Group.*
How can we tell which men with prostate cancer will be troubled by it?
By assessing:

  How aggressive the cancer is (Gleason grade)

  How large the cancer is (MRI or biopsy measurements)
MRI in active surveillance
Impact of Multiparametric Endorectal Coil Prostate Magnetic Resonance Imaging on Disease Reclassification Among Active Surveillance Candidates: A Prospective Cohort Study

David Margel,* Stanley A. Yap, Nathan Lawrentschuk, Laurence Klotz, Masoom Haider, Karen Hersey, Antonio Finelli, Alexandre Zlotta, John Trachtenberg and Neil Fleshner†

**Figure 1.** Study schematic shows 60 patients who underwent MRI and 3 predefined groups, including 1—normal MRI, 2—cancer characteristics on MRI concordant with initial biopsy (Bx) and 3—lesion on MRI more than 1 cm in any dimension.
Stable on surveillance
65 year old man <5% cancer on TURP. MRI 2009, PSA 0.9. PSA rose to 2.6 in 2011. Increase in size of right PZ lesion, particularly marked on diffusion.
Using imaging to inform prostate cancer management: Focal therapy
What is focal therapy?
Why are we considering focal therapy?

Technological developments

- Imaging
- Biopsy techniques
- Treatment modalities
  - Heat
  - Cold
  - Light activated therapies
  - Radiotherapy
  - New kids – electroporation, nanoparticles, alcohol….
T2-Weighted
Dynamic Contrast Enhanced
Gleason 4+4
CCLmax 4mm
1 of 2 cores +ve
Targeted
(24 cores)
UCL Focal HIFU Trials

Hemi-HIFU Trial

Focal-HIFU Trial

Lesion Control HIFU Trial
Focal Therapy in Men With Localized Prostate Cancer: A Phase I/II Trial

H. U. Ahmed,*,† A. Freeman, A. Kirkham, M. Sahu, R. Scott, C. Allen,‡ J. Van der Meulen and M. Emberton§

“... 89% of men achieved the trifecta status of pad-free, leak-free continence, erections sufficient for intercourse and cancer control at 12 months.”
Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study

Hashim U Ahmed, Richard GHindley, Louise Dickinson, Alex Freeman, Alex P Kirkham, Mahua Sahu, Rebecca Scott, Clare Allen, Jan Van der Meulen, Mark Emberton

Lancet Oncology, April 2012
Focal HIFU results

Proportion, %

Time, months

- Pad-free continence
- Leak-free/Pad-free continence
- Erections sufficient for penetration

- No evidence of disease
- Trifecta (pad-free leak-free AND erectile function satisfactory for penetration AND no evidence of clinically significant disease)

- Any cancer on biopsy
- Clinically significant cancer on biopsy (≥3mm and/or Gleason ≥ 3+3)
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>64 (SD +/-5.8)</td>
</tr>
<tr>
<td>PSA (median)</td>
<td>7.4 (IQR 5.6 - 9.4)</td>
</tr>
<tr>
<td>Initial biopsy</td>
<td></td>
</tr>
<tr>
<td>TRUS biopsy</td>
<td>22 (39%)</td>
</tr>
<tr>
<td>TPM biopsy</td>
<td>34 (61%)</td>
</tr>
<tr>
<td>Disease distribution</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>17 (30%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>39 (70%)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>T2a</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>T2b</td>
<td>18 (32%)</td>
</tr>
<tr>
<td>T2c</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>T3a</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>NCCN Risk Category</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>47 (84%)</td>
</tr>
<tr>
<td>High</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>
Median PSA fell from 7.4 at baseline to nadir of 2.4
## Cancer Outcomes

<table>
<thead>
<tr>
<th>6-Month Protocol Biopsies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of any cancer</td>
<td>30/52</td>
</tr>
<tr>
<td>Absence of clinically significant disease</td>
<td>42/52</td>
</tr>
<tr>
<td>Overall absence of clinically significant disease (12-months)</td>
<td>48/56</td>
</tr>
</tbody>
</table>
Erections sufficient for intercourse preserved in 77% (30/39)

Pad-free continence 92% (48/52)
Leak-free pad-free continence 92% (46/50)
The INDEX Study
PIs: Ahmed/Emberton; Co-ordinator: Dickinson
NCRN-adopted
Industry supported – SonaCare Medical
Available 12-month biopsy data (treated side only)

31 men so far
Absence of any disease = 81% (25/31)
Absence of clinically significant disease = 90% (28/31)

Residual Disease
Clinically significant: <1mm – 3mm Gl 3+4

Re-Treatment Rate = 2/31 patients (6%)
The INDEX Study

140 men with localised PCa

Focal HIFU

1-2 weeks
TWOC, contrast-MRI

6 weeks, 3*, 6 and 9* months:
PSA, questionnaires

12 months:
mp-MRI, TRUS biopsy of treated side

18*, 24, 30* month follow up

36 months
mp-MRI, Template biopsies,

38* months
Trial exit

Tissue Biobank

- Serum, germline
- Kallikreins
- PTEN glycoproteins

Imaging Databank

- Imaging Biomarkers
- MRI CAD
- USS Tissue Characterisation

Histology Biobank

- Histological Biomarkers discovery
- TMA

UCL
The Institute of Cancer Research

University of Oxford
University of Bristol
Imperial College London

Stoke and North Hampshire NHS Foundation Trust
RCT: focal therapy vs active surveillance

Photodynamic therapy vs active surveillance
European multi-centre study – recruitment started
Inclusion criteria limited to low volume Gleason 3+3
Difficulties in establishing an optimal protocol due to advances in clinical practice
VTP Procedure

Sagittal plane

Apex

5mm

Cylindrical Diffuser

5mm

Transverse

5mm

5mm

5mm
1103 day 7 MRI

6 month biopsy negative for cancer
Tookad Soluble Phase III
European Multi-centre
N=400

Eligible patients
- Active surveillance
- TookadSoluble VTP
  - mp-MRI
    - Treatment planning
    - Planned Intervention
      - T1 GAD MRI
        - Verification
        - RETREATMENT

PSA
PROMS
Adverse events
3 MONTHLY

12 Month biopsy
12 core

24 Month biopsy
12 core
### Current Focal Therapy studies

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Treatment</th>
<th>No pts</th>
<th>Gleason grade</th>
<th>Inclusion tests</th>
<th>Primary</th>
<th>Secondary</th>
<th>Follow-up (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cryotherapy</td>
<td>100</td>
<td>≤6</td>
<td>TPM (≥12 cores) + ‘Imaging’ (PZ tumours only included)</td>
<td>Adverse events and oncological - ?F/U biopsies</td>
<td>QoL</td>
<td>74</td>
</tr>
<tr>
<td>I</td>
<td>Laser (Visualase)</td>
<td>20</td>
<td>≤7</td>
<td>TRUS + MRI</td>
<td>Adverse events (6/12)</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>I</td>
<td>Laser</td>
<td>15</td>
<td>?any grade</td>
<td>TRUS</td>
<td>Oncological (12 +2 core TRUS)</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>II</td>
<td>MRgFUS (ExAblate)</td>
<td>80</td>
<td>≤6</td>
<td>TPM +/- MRI</td>
<td>Adverse events (6/12) and oncological (6/12 TPM)</td>
<td>Adverse events (24/12) and oncological (24/12 TPM and PSA)</td>
<td>24</td>
</tr>
<tr>
<td>II</td>
<td>Brachy</td>
<td>80</td>
<td>≤6</td>
<td>TRUS + MRI</td>
<td>Adverse events (6 - 24/12)</td>
<td>Oncological (12/12 and 24/12 TRUS)</td>
<td>24</td>
</tr>
<tr>
<td>II</td>
<td>HIFU</td>
<td>140</td>
<td>≤7</td>
<td>TPM + MRI</td>
<td>Oncological (36/12 TPM)</td>
<td>Functional outcomes and short-term oncological (12/12 TRUS)</td>
<td>38</td>
</tr>
</tbody>
</table>
Thank You

Any questions?
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Mr Hashim Uddin Ahmed (MRC Clinician Scientist)
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