What constitutes clinically significant lesions?

Mark Emberton

Division of Surgery and Interventional Science
UCLH/UCL Comprehensive Biomedical Research Centre
What is clinically significant?
What cancer is clinically significant?

• All cancer
  – cancers are inherently unstable and unpredictable

• None
  – No reduction in mortality seen when ‘all cancer’ is treated versus when it is left alone (PIVOT, AUA 2011)
Towards a more meaningful range

• **Floor**
  – A cancer that would not, if left alone, result in any material harm to a man within his remaining life

• **Ceiling**
  – A cancer that, if left untreated, would progress through local invasion and metastases and result in diminished quality of life and/or reduced life expectancy
Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer

Figure 1. Age distribution of 139 patients undergoing cystoprostatectomy, 55 of whom were found to have prostate cancer.
Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer

Figure 2. Volume distribution of 55 unsuspected largest prostate cancers in 139 cystoprostatectomies.
Limitations of Stamey criteria

- Based on a single series of 139 cases
- Findings would vary with age, ethnicity, family history
- Assumes that cancer significance is directly related to tumour volume.
- To use the same volume/grade criteria regardless of patient life expectancy is an oversimplification
97 cystoprostatectomies, median age 70 yrs
58 (60%) with prostate cancer
31 (32%) ‘significant’ cancers using Stamey criteria
If we specify that 8% of 97 cases were significant, then tumor volume cut-off would be 1.09ml
Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer
Epstein et al. JAMA (1994) 271:368-74

- 157 radical prostatectomies for T1c disease, 1988-92
  - Median age 61yrs
  - Median PSA 8.1
  - Gleason <=6 in 74% of cases
  - Mean of 5 biopsy cores (<=2 cores in 21 cases)

- 26/157 (16%) insignificant (<0.2ml, Gleason < 7, organ confined)

- PSA density >0.15, Gleason grade 4 or 5, >2 +ve cores, and >50% core involvement associated with significant cancer

- 19/26 insignificant cancers correctly identified by this model
Clinical significance in ‘focal therapy’

- Cancers that are unlikely to have metastasized
- Cancers that we are not happy to monitor
- In-lobe recurrence
  - Are there lesions that will recur?
  - Does in-lobe recurrence affect long term prognosis?
- Out of lobe new cancer
  - Does the presence of a ‘significant’ treated cancer result in a higher rate of new cancers in time?
‘Clinical significance’ is only of use if it can be derived prior to a treatment decision

- Current diagnostic pathways are incapable of doing this
TRUS detects clinically insignificant disease

- Clinically insignificant cancers are identified by chance
- Important cancers are incorrectly classified as unimportant
• TRUS biopsies are done in a blinded manner

• They are subject to random and systematic error

• Means that they are ‘wrong’ about half the time
Figure 3c: Random deployment of the needle leads to a clinically significant tumour being missed in the anterior TZ.
Accuracy of TRUS biopsy at detecting clinically important prostate cancer $\geq 0.5\text{cc}$

Lecornet et al. BAUS ONC 2010
Whole prostate analysis

Detection of 0.2cc lesions

ROC curves for detection of significant cancer $\geq 0.2cc$
Accuracy of TRUS biopsy at detecting clinically important prostate cancer $\geq 0.5cc$

Anterior subset

ROC curves for detection of cancer $\geq 0.5cc$ among the 79 anterior lesions
Can Maximum Cancer Core Length Involvement on Template Transperineal Prostate Mapping Biopsies Rule-in and Rule-out Clinically Significant Prostate Cancer?

**Methods:**
- Scanned and digitized with tumours delineated
- 3D reconstruction
- Fixation related shrinkage taken into account
- Computer TPM simulations conducted
Validity of biopsy max CCL against reference

Detection of Lesions $\geq 0.5\text{cc}$ by Template Mapping Biopsies

- **Sensitivity**
- **Specificity**

Accuracy values for $\geq 0.5\text{ cc}$ lesion detection for increasing cancer core length (CCL) thresholds
Validity of biopsy max CCL against reference

Detection of Lesions $\geq 0.2$ cc by Template Mapping Biopsies

Accuracy values for $\geq 0.2$ cc lesion detection for increasing cancer core length (CCL) thresholds
What is the distribution of prostate cancer volume in an unselected group of men

Courtesy of Arnauld VILLERS, Lille France
Distribution of prostate cancer foci
215 lesions / 96(104) prostates / 345 Cystoprostatectomy specimens
Multi-focality / Location

UNIFOCAL 42%

MULTIFOCAL 58%

UNILATERAL 21%

BILATERAL 79%
Distribution of small foci (<0.1cc) 146/215 lesions
The remarkable evolution of breast cancer surgery from the radical mastectomy advocated by William Halsted to cosmetically appealing breast conservation has been championed by women and pioneering surgeons, and the safety and benefits of this approach have ultimately been confirmed through high-level scientific evidence.

Houssami & Hayes CA Cancer J Clin 2009
Multi-focality in breast cancer

- Multi-centric or multi-focal cancer occurs in up to 70% of women
- Radical mastectomy standard of care for 80 years
- RCTs have demonstrated that breast conservation plus RT confers equivalence
- TARGIT RCT suggest that the benefit comes from treating the index lesion (Lancet, 2010)
What might be the way forward?

• Apply a test whose diagnostic accuracy is positively associated with tumor volume
• Use ‘sensible’ thresholds as triggers for confirmation
• Use the information to biopsy the ‘heart’ of the lesion
• Thereby attribute accurate risk stratification of the dominant lesion
Distribution of prostate cancer foci
215 lesions / 96(104) prostates / 345 Cystoprostatectomy specimens

Nerveux, Emberton, Montroni and Villers (2011, in press).
Tumour vol  0.2cc  0.5cc

<table>
<thead>
<tr>
<th></th>
<th>0.2cc</th>
<th>0.5cc</th>
</tr>
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<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>
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</table>

Villers et al. J Urol December 2006
The reference standard

Clinically insignificant disease
Gleason 3+3 and max CCL $\leq$ 3mm

Indeterminate disease
Gleason 3+4 and / or max CCL 4-5mm

Clinically significant disease
Gleason $\geq 4+3$ and/or max CCL $\geq 6$mm

Derived by 5mm template prostate mapping
### The Index test 1.5T MRI (no ERC)

Ability of MRI to detect lesions conforming to 3 definitions of prostate cancer

<table>
<thead>
<tr>
<th>Definition</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Pos LR</th>
<th>Neg LR</th>
<th>ROC AUC</th>
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<tbody>
<tr>
<td><strong>DEFINITION 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any cancer</td>
<td>0.5</td>
<td>0.86</td>
<td>0.79</td>
<td>0.6</td>
<td>3.8</td>
<td>0.6</td>
<td>0.7</td>
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<td><strong>DEFINITION 2</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Gleason $\geq 3+4$ CCL $\geq 4$mm</td>
<td>0.75</td>
<td>0.83</td>
<td>0.55</td>
<td>0.88</td>
<td>4.8</td>
<td>0.3</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>DEFINITION 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason $\geq 4+3$ CCL $\geq 6$mm</td>
<td>0.84</td>
<td>0.77</td>
<td>0.39</td>
<td>0.97</td>
<td>3.7</td>
<td>0.2</td>
<td>0.85</td>
</tr>
</tbody>
</table>
MICROSCOPIC DESCRIPTION
A. Left para ant apex: Benign prostatic core with atrophy.
B. Left para ant base: Benign prostatic core with atrophy.
C. Right para ant apex: Benign prostatic core with atrophy.
D. Right para ant base: Benign prostatic core with atrophy.
E. Mid apex: Benign prostatic core with atrophy.
F. Mid base: Benign prostatic core with atrophy.
G. Left med ant apex: No specimen was received.
H. Left med ant base: No specimen was received.
I. Right med ant apex: No specimen was received.
J. Right med ant base: No specimen was received.
K. Left lateral: Benign prostatic core with atrophy.
L. Right lateral: Prostatic core with focal high grade PIN.
M. Left para post apex: Benign prostatic core with atrophy.
N. Left para post base: Benign prostatic core with atrophy.
O. Right para post apex: Benign prostatic core with atrophy.
P. Right para post base: Benign prostatic core with atrophy.

Q. Targeted anteroseptal: Adenocarcinoma Gleason 3+4 in 2 of 5 cores, 1mm (10%) and 4mm (40%).
HGPIN / atypical acini

Gleason = 3+3, AND CCLmax <4mm

Gleason = 3+4 AND/OR CCLmax 4-5mm

Gleason >/= 4+3 AND/OR CCLmax >/=6mm
Targeting multiple lesions
MICROSCOPIC DESCRIPTION

A. Left para ant apex: Benign prostatic core with atrophy.
B. Left para ant base: Benign prostatic core with atrophy and focal intraluminal polymorphs.
C. Right para ant apex: Adenocarcinoma Gleason 3+3, 2mm (15%).
D. Right para ant base: Adenocarcinoma Gleason 3+3, 3mm (20%).
E. Mid apex: Benign prostatic core with atrophy.
F. Mid base: Benign prostatic core with atrophy.
G. Left med ant apex: Adenocarcinoma Gleason 3+3, 4mm (40%).
H. Left med ant base: Adenocarcinoma Gleason 3+3, 3mm (30%).
I. Right med ant apex: Adenocarcinoma Gleason 3+3, 1mm (<10%).
J. Right med ant base: Benign prostatic core with atrophy.
K. Left lateral: Two prostatic cores with focal high grade PIN.
L. Right lateral: Adenocarcinoma Gleason 3+4 overall in 2 of 2 cores, 1mm (10%) and 5mm (50%).
M. Left para post apex: Benign prostatic core with atrophy.
N. Left para post base: Two benign prostatic cores with atrophy.
O. Right para post apex: Benign prostatic core with atrophy.
P. Right para post base: Benign prostatic core including seminal vesicle / ejaculatory duct epithelium.
Q. Left med post apex: Benign prostatic core with atrophy.
R. Left med post base: Benign prostatic core with atrophy.
S. Right med post apex: Benign prostatic core with atrophy.
T. Right med post base: Benign prostatic core including seminal vesicle / ejaculatory duct epithelium.

U. Targeted left anterior: Adenocarcinoma Gleason 3+3 in 3 of 4 cores, 1mm (10%), 4mm (40%) and 10mm (65%).

V. Targeted right anterior: Adenocarcinoma Gleason 3+4 overall in 3 of 4 cores, 2mm (15%), 2mm (20%) and 4mm (30%).
**HGPIN / atypical acini**

**Gleason = 3+3, AND**
**CCLmax <4mm**

**Gleason = 3+4**
**AND/OR**
**CCLmax 4-5mm**

**Gleason >/= 4+3**
**AND/OR**
**CCLmax >/=6mm**
Monitoring and Targeting a peripheral lesion
Q1 2010 sequences  - low risk by TRUS
Q2 2011 sequences - low risk by TRUS
Q1 2010 sequences - low risk by TRUS
Q2 2011 sequences - low risk by TRUS
Q1 2010 sequences - low risk by TRUS
Q2 2011 sequences - low risk by TRUS
MICROSCOPIC DESCRIPTION

A. Left para ant apex: Adenocarcinoma Gleason 3+3, 2mm (15%).
B. Left para ant base: Benign prostatic core with atrophy.
C. Right para ant apex: Benign prostatic core with atrophy.
D. Right para ant base: Benign prostatic core with atrophy.
E. Mid apex: Benign prostatic core with atrophy.
F. Mid base: Benign prostatic core with atrophy.
G. Left med ant apex: Benign prostatic core with atrophy.
H. Left med ant base: Benign prostatic core with atrophy.
I. Right med ant apex: Benign prostatic core with atrophy.
J. Right med ant base: Prostatic core with focal high grade PIN.
K. Left lateral: Adenocarcinoma Gleason 3+4, 1mm (20%). Perineurial invasion is seen.
L. Right lateral: Adenocarcinoma Gleason 3+3, 1mm (<10%).
M. Left para post apex: Adenocarcinoma Gleason 3+4, 1mm (10%).
N. Left para post base: Adenocarcinoma Gleason 3+4, 4mm (30%).
O. Right para post apex: Benign prostatic core with atrophy.
P. Right para post base: Benign prostatic core with atrophy.
Q. Left med post apex: Adenocarcinoma Gleason 3+4, 4mm (50%).
R. Left med post base: Benign prostatic core with atrophy.
S. Right med post apex: Benign prostatic core with atrophy.
T. Right med post base: Benign prostatic core with atrophy.

U. Targeted left post PZ: Adenocarcinoma Gleason 3+4 overall, 4 foci measuring 1mm, 2mm, 5mm and 6mm, fragmented cores so percentage involvement not assessable.
Perineurial invasion is seen.
Tumour infiltrates fibro-adipose tissue suggesting extension beyond the gland.
HGPIN / atypical acini

Gleason = 3+3, AND
CCLmax <4mm

Gleason = 3+4
AND/OR
CCLmax 4-5mm

Gleason >/= 4+3
AND/OR
CCLmax >/=6mm
<table>
<thead>
<tr>
<th>Authors</th>
<th>Target generation</th>
<th>Sampling</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkbey et al. Cancer Imaging. 2011 Mar</td>
<td>Mp-MRI</td>
<td>TRUS</td>
<td>Sn 0.61, Sp 0.73, AUC 0.67</td>
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<tr>
<td>Haffner BJU Int. 2011 Mar</td>
<td>Mp-MRI</td>
<td>TRUS</td>
<td>Sn 0.95, Sp 1.0, Acc 0.98</td>
</tr>
<tr>
<td>Chen et al J Magn Reson Imaging. 2011 Feb</td>
<td>MRI DIFF</td>
<td>TRUS</td>
<td>Sn 97%, Sp 98%, PPV 92%, NPV 99%, Acc 98%</td>
</tr>
<tr>
<td>Franiel T Radiology. 2011 Apr</td>
<td>Mp-MRI, MRI spec</td>
<td>TRUS</td>
<td>Detection rate 100%, Negative Bx rate 0%</td>
</tr>
<tr>
<td>Testa et al. NMR Biomed. 2010 Nov</td>
<td>Mp-MRI, MRI spec</td>
<td>TRUS</td>
<td>AUC PZ 0.77, AUC TZ 0.82</td>
</tr>
</tbody>
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The reference standard

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Gleason 3+3 and max CCL ≤ 3mm

Indeterminate disease
Gleason 3+4 and / or max CCL 4-5mm

Clinically significant disease
Gleason ≥ 4+3 and/or max CCL ≥ 6mm

Derived by 5mm template prostate mapping
Conclusions

• We do not have a definition of clinically significant disease

• The two key determinants are volume and grade, though both are closely associated.

• Attribution of clinical significance requires a precision, that has hitherto eluded us
Minimally-Invasive Prostate Intervention (MIPI) Group

Division of Surgery and Interventional Science, UCL
- Mr Mark Emberton (Professor and Consultant Urologist)
- Mr Hashim Uddin Ahmed (MRC Research Fellow)
- Miss Caroline Moore (Clinical Lecturer)
- Mr Paul Cathcart (NIHR Academic Clinical Lecturer)
- Mr Paras Singh (NIHR Academic Clinical Fellow)
- Miss Louise Dickinson (NIHR Academic Clinical Fellow)
- Miss Fiona McClean (Research Nurse)
- Miss Lucy Simmons (Research Fellow)
- Mr Adebiyi Damola (Research Fellow)
- Mr Sadat Quoraishi (Research Fellow)

Department of Academic Radiology, UCLH NHS Trust
- Dr Clare Allen (Consultant Radiologist)
- Dr Alex Kirkham (Consultant Radiologist)
- Dr Shonit Punwani (Consultant Radiologist)

National Medical Laser Centre
- Professor Steve Bown
- Dr Sandy Mosse

Department of Histopathology, UCLH NHS Trust
- Dr Alex Freeman (Consultant Histopathologist)

Centre for Medical Imaging Science, UCL
- Professor David Hawkes
- Dr Dean Barratt (Royal Academy Senior Research Fellow)
- Mr Tim Carter (Post-doctoral Research Fellow)
- Mr Yipeng Hu (MSc Student)

Clinical Effectiveness Unit, RCS(England) & LSHTM
- Professor Jan van der Meulen (Director)

Cancer Institute
- Professor Stephan Beck
- Dr Chris Bell (Epigenomics group)

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mark.emberton@uclh.nhs.uk