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Department of UROLOGIC SCIENCES UBC

Fingers & Needles

Biopsy Strategies in Prostate Cancer Detection

Urology Grand Rounds
2 March 2016
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Objectives

- To discuss various biopsy techniques used in the diagnostic pathway of prostate cancer
- To compare detection rates, associated complications and costs of the different techniques
- To discuss future directions and the potential role of investigational imaging techniques

Considerations for Prostate Biopsy

- Patient characteristics
  - Age, PSA, DRE findings, Prostate volume, Biopsy history
- Procedure characteristics
  - Operator, Route, Number of cores, Location of cores
- Other indicators
  - F/T PSA ratio, PCA3, Imaging

PSA Variability & CaP Risk

Does PSA variability predict chance of finding CaP on biopsy?

- Prospective study (ProtecT)
- 2 PSA levels 6 weeks apart
- Decision to biopsy based on 1st PSA result only
- PSA 3 to 19.99 ng/mL

Rosario Eur Urol 2008

Effect of 20% PSA drop on PCa Risk

Age	Initial PSA (ng/mL)	n	'a priori' risk of cancer on biopsy		Revised risk of cancer on biopsy if 20% drop in PSA	
			Any cancer	High-grade cancer	Any cancer	High-grade cancer
≤60 years	3.0 to 3.99	691	23%	4%	2%	0.5%
	4.0 to 5.99	516	32%	6%	4%	0.2%
	6.0 to 19.99	285	42%	15%	11%	2%

Prostate Imaging

- Standard TRUS
- Advanced TRUS- Elastography, Histoscanning
- MRI- Staging, Multiparametric, Spectroscopy

Imaging

- Standard TRUS
- Advanced TRUS- Elastography, Histoscanning
- MRI- Staging, Multiparametric

Biopsy Strategies

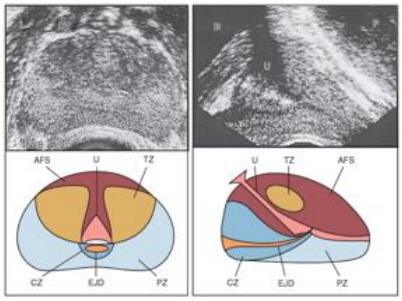
- TRUS Guided- Standard, Histoscan
- MRI- Template, Targeted, Fusion

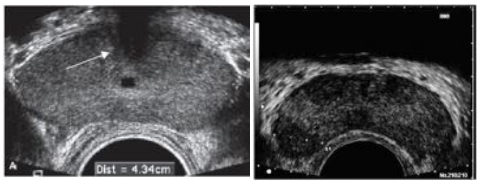
Negative Biopsy

- Extended TRUS, Saturation, TUR, Template

TRUS

- US for prostate imaging 1st reported in 1963 (Takahashi Proc Jap Soc Ultr Med 1963)
- Captures images in transverse and sagittal planes
- Malignant lesions- hypoechoic 60%, isoechoic 39%, hyperechoic 1% (Shonihara J Urol 1989)
- Can detect ECI and SV invasion



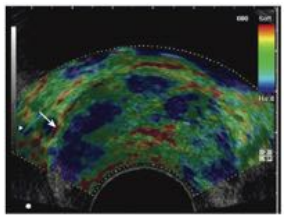


Cystic Lesion

Hypoechoic Lesions

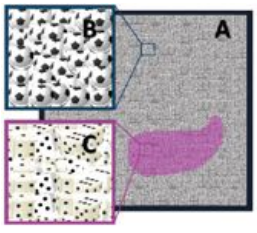
Elastography

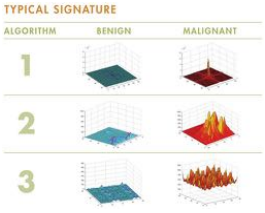
- Malignant tissue more dense, less compressible
- US used to analyse compression characteristics of tissue
- Image taken pre and post compression and shift-diagram generated
- Overall Sens 60.8%, Spec 68.4% for CaP vs RP specimen (Brock J Urol 2013)

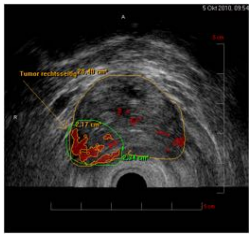


Histoscanning

- 'Tissue characterisation technology developed to differentiate, characterise and visualise prostate tissue based on analysis of backscattered US' –AMD
- Sens 90%, Spec 70% for localising lesions ≥0.2ml within a sextant (Simmons BJUI 2012)







MRI

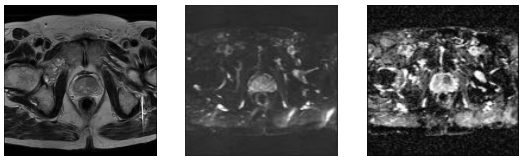
- Staging with T2
- Tumour detection with T2, DW, DCE, Spectroscopy
- PIRADS scoring system 1-5. Dickinson Eur Urol 2011 (v1), Wienreb Eur Urol 2015 (v2)
- Sectors: 27 (v1), 39 (v2)
- T2
  - Time taken for spinning protons to return to phase after exposure to magnetic pulse
  - Tissue with high water content have high signal
  - Malignant prostate tumours have low signal
  - Good anatomical images of prostate, periprostatic tissues and pelvis for nodes

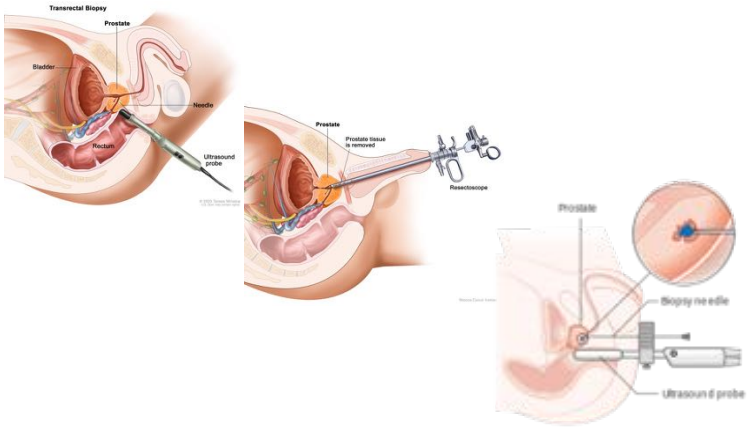
MRI

- Diffusion-Weighted (DW)
  - Measure of movt of water molecules within tissue
  - Tumour cells densely packed so less movt
  - Tumour has low signal
  - Apparent Diffusion Coefficient (ADC) map can be generated
- Dynamic Contrast Enhancement (DCE)
  - Measures 'wash-in' and 'wash-out' of Gadolinum contrast from ROI
  - Tumour more vascular so contrast flux is quicker than benign tissue

MRI

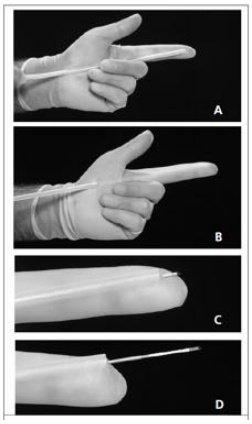
- Spectroscopy
  - Measures relative conc of metabolites in the tissue. Citrate, Choline, Polyamines
  - Normal prostate tissue high in Citrate and Polyamines
  - Tumour is identified by changes in normal peak patterns in ROI
  - Technically demanding and still experimantal





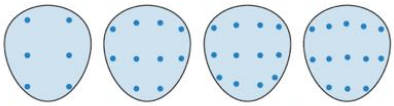
Digitally-Guided Biopsy

- Of 2293 CaP pts,35% had abnormal DRE (Okotie Urology 2007)
- Equivalent yield as TRUS with 8-core systematic biopsy (Abrams Can J Urol 2001)
- Digitally-guided biopsies unsafe. Modified techniques have been described (Ghei Ann R Coll Surg Eng 2005)
- Not recommended!



Standard TRUS Biopsy

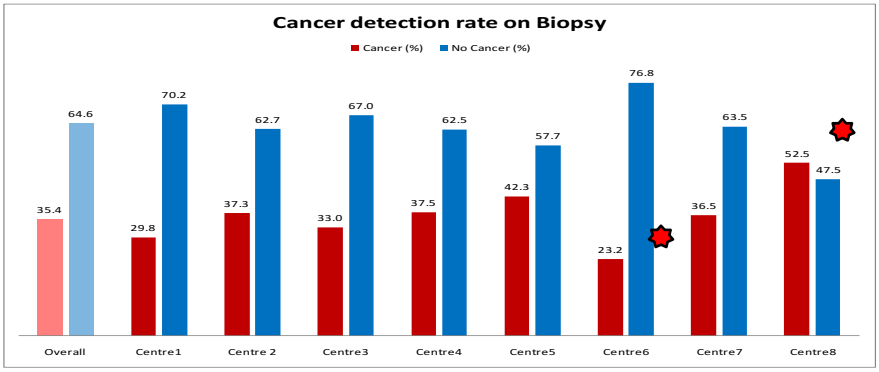
- Various strategies reported, cores ranging from 8-14
- Increasing cores increases yield, but no additional benefit over 12 cores (Eichler J Urol 2006)
- Lateral and apical directed
- Anterior of gland poorly sampled. Potentially 30% of tumours missed



STUDY	NO. OF CORES	CANCER DETECTION RATE
Eskew et al, 1997	6	26.1%
	13	40.3%
Naughton et al, 2000	6	26%
	12	27%
Presti et al, 2000	6	33.5%
	8	39.7%
	10	40.2%
Babaian et al, 2000	6	20%
	11	30%

Operator Effects

- Variability of cancer detection rate and adverse effects using standardised 10-core lateral peripheral zone protocol (Rosario BMJ 2012)

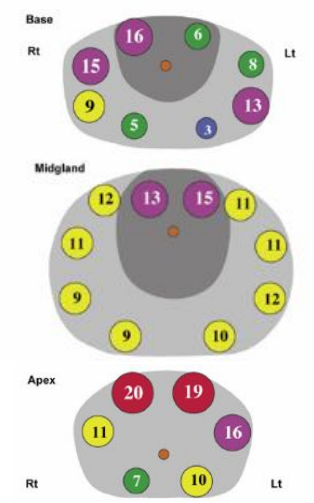


Unpublished Figure

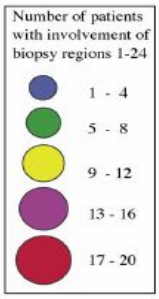
Yield of Repeat TRUS Biopsy

	PCa detection biopsy 1	PCa detection biopsy 2	PCa detection biopsy 3	PCa detection biopsy 4	Inclusion criteria
Djavan 2001	231/1051 (22%)	83/820 (10%)	36/737 (5%)	4/94 (4%)	PSA 4-10 ng/ml
Keetch 1994	391/1136 (34%)	82/427 (19%)	16/203 (5%)	6/91 (4%)	-PSA >4.0ng/ml -Abnormal DRE or TRUS

Location of Cancer on Repeat Biopsy



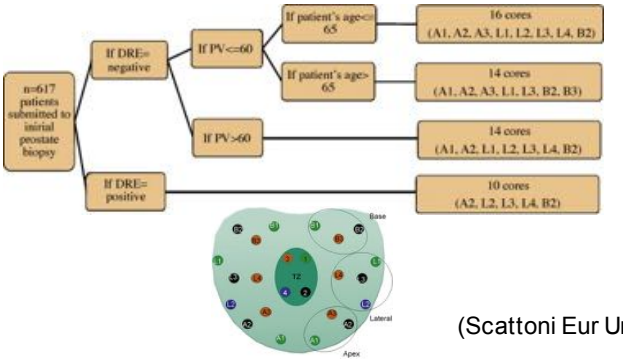
- 102 pts. Transperineal Template Biopsy after negative Standard TRUS
- Median 50 cores



Merrick et al Eur Urol 2007

Extended TRUS Biopsy

- 617 consecutive pts, CaP in 289 (47%), 24-core scheme
- Optimal biopsy scheme to obtain 95% detection rate, using 24-core template as gold standard



(Scattoni Eur Urol 2010)

Saturation Biopsy

- Controversy in defining. Usually >20-core with TZ
- Transrectal or Transperineal route

Study	Patients, n	Previous negative biopsies, n	Median PSA level, ng/ml	Median gland volume, g	Median number of cores	Detection rate
Borboroglu et al. (2000)[16]	57	≥1	9	NR	22	30%
Igel et al. (2001)[17]	88	2	13	48 (positive biopsy group); 73 (negative biopsy group)	17	43%
Stewart et al. (2001)[18]	224	≥1	9	NR	23	34%
Fleshner and Klotz (2002)[19]	37	≥3	22	54	35	14%
Rabets et al. (2004)[20]	116	≥1	9	NR	24	29%
Pinkstaff et al. (2005)[21]	210	≥1	14	NR	21	37%
Bott et al. (2006)[22]	60	≥2	13	54	24	38%
Moran et al. (2006)[23]	180	≥1	8	43	41	38%
Merrick et al. (2007)[24]	102	2	9	78	50	42%

Abbreviation: NR, not reported.

Adverse events of TRUS-Bx

- Pain (mainly in younger men)
- Bleeding
- Sepsis
  - Symptomatic (4.2 to 5.5%)
  - Serious (0.5 to 1%)
- Hospitalisation (0.8 – 1.4 %)
- Death (?)

(Loeb Eur Urol 2012, Rosario BMJ 2011)

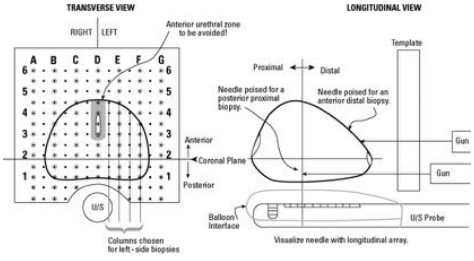
Transurethral Biopsy

Source	n	TUR only CaP	Median PSA	Mean Prev Biopsy	Mean Tissue
Rovner 1997	71	2.8%	16.2	1.85	1.47g
Puppo 2006	21	28.5%	10.7	3.5	21.5g
Lin 2008	410	17.1%	NR	1	NR
Ploussard 2009	113	5.3%	9.8	3	25g
Pepe 2010	75	20%	11.8	2	46g

- High morbidity. Retention 30% vs 17% for SBx, Readmission 26% vs 10% for SBx, Sepsis 0% vs 4% for SBx. 54 pts TURBx, 48 SBx. (Yates Urol Oncol 2013)

Transperineal Template Biopsy

- Brachytherapy grid. 5mm intervals (Onik Urol Oncol 2008)
- Minimum dataset and definitions (Kuru BJUI 2013)
- 54% 1st n=153, 36% rpt n=174, 29% upgraded from GI 3+3 n=307 (Vyas BJUI 2013)
- AUR n=11, Haematuria n=2, Urosepsis n=0
- US/MRI fusion recommended to guide targeting



Comparison of standard biopsy with 3D biopsy in prostate cancer

Pathology findings	Standard biopsy mean (SD)	3D biopsy mean (SD)	*P*-value
Total biopsy core number	9.9 (3.6)	50.2 (23.4)	<0.0001
Positive biopsy core number	1.8 (1.3)	5.4 (5.7)	<0.0001
Mean Gleason score	6.3 (0.9)	6.6 (0.9)	0.02
Stage			
T1	85 (79%)	72 (67%)	0.03
T2	22 (21%)	30 (28%)	
T3	0 (0%)	5 (5%)	

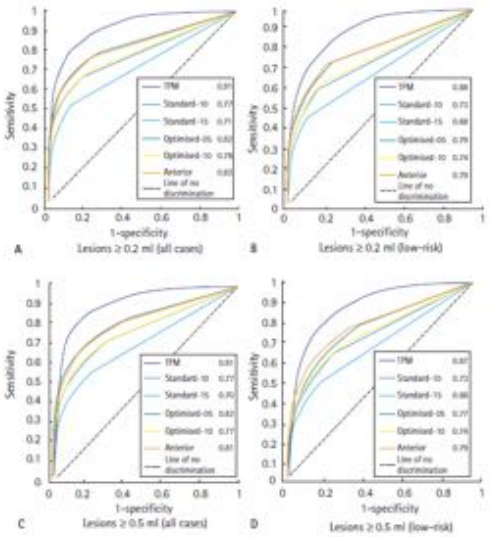
Potential change in management

Bilateral cancer	n = 60 (55%)
Gleason score increased	n = 25 (23%)
Stage increased	n = 15/22 (68%)
Midline biopsy +	n = 19 (17%)
Potential NVB involv.	n = 27 (25%)
At least one of criterion	n = 84 (76%)

- Pts being assessed for Focal Therapy

Onik Urol Oncol 2008

Transperineal Template Biopsy



- 107 RP specimens. Pathology used to create simulated 3D models
- Subjected to TPM and 5 TRUS techniques
- Correction for path processing
- TPM performs better

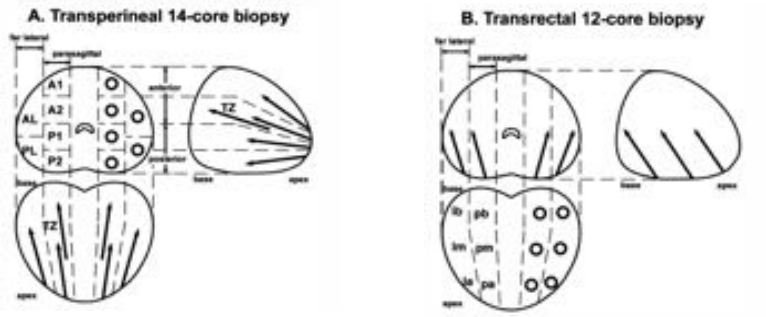
(Hu BJU Int 2012)

TP & TR Combination

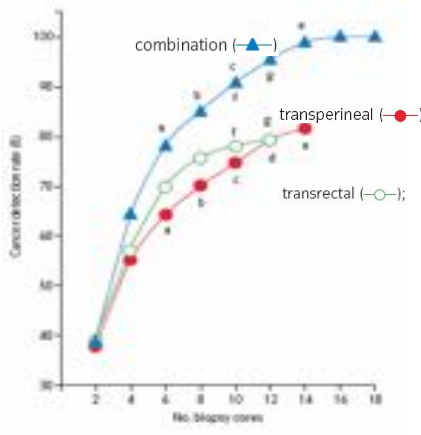
Satoru Kawakami · Nobuhiko Hyochi · Junji Yonese
Masataka Yano · Yasuhisa Fujii · Yukio Kageyama
Iwao Fukui · Kazunori Kihara

Int J Clin Oncol (2006) 11:127–132
DOI 10.1007/s10147-005-0547-0

Three-dimensional combination of transrectal and transperineal biopsies for efficient detection of stage T1c prostate cancer



TP & TR Combination



- 237 pts, previous neg biopsy. 37% cancer detection rate
- Determined the best 26-core combination of TP & TR
- Combination of 14 TP and 12 TR biopsies detected all cancers sampled on 3D26.

Kawakami S Eur Urol 2007

MRI-Guided Prostate Biopsy

- Pros
  - Higher yield of cancer per core (30% vs. 7%)
  - Fewer men biopsied (avoid in 38% biopsy-naïve men)
  - Less 'insignificant cancer' detected
- Cons
  - Missed cancers (23% in biopsy-naïve and 15% if previous negative biopsy. 2.3% clinically significant)
  - No prospective clinical validation

  (Moore Eur Urol 2012)

MRI-Guided Prostate Biopsy

Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study Eur Radiol (2013) 23:2019–2029

Flavie Bratan · Emilie Niaf · Christelle Melodelima · Anne Laure Chesnais · Rémi Souchon · Florence Mège-Lechevallier · Marc Colombel · Olivier Rouvière

Gleason score	Tumour volume (mL)		
	< 0.5	0.5-2	> 2
GS6	21-29%	43-54%	67-75%
GS7	63%	82-88%	97%
GS > 7	80%	93%	100%

MRI-Guided Prostate Biopsy

- 890 with ADC lesions 8-core systematic+4-core targeted, 558 with no ADC lesion 8-core systematic TR route

Detection and Localization of Prostate Cancer With the Targeted Biopsy Strategy Based on ADC Map: A Prospective Large-Scale Cohort Study

Yuji Watanabe, MD, PhD,[1*] Akito Terai, MD, PhD,[2] Tohru Araki, MD,[3] Masako Nagayama, MD,[1] Akira Okumura, MD,[1] Yoshiki Amoh, MD,[1] Takayoshi Ishimori, MD, PhD,[1] Mana Ishibashi, MD, PhD,[1] Satoru Nakashita, MD, PhD,[1] and Yoshihiro Dodo, MD[1]

JOURNAL OF MAGNETIC RESONANCE IMAGING 35:1414–1421 (2012)

Positive Predictive Value and Negative Predictive Value of the MR Findings for the Detection of Prostate Cancer

	MR findings for the cancer detection		
	No.	%	95% CI
PPV	624/890	70.1	67–73
NPV	485/558	86.9	84–90

Cancer Detection Rates for Group A, B and Overall Patients According to the Range of PSA Levels

	Overall patients			Group A			Group B			*P* value	
serum PSA level ng/mL	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	Group A vs Group B	Group A vs total
PSA < 4	20/77	26.0	16–36	17/41	41.5	26–57	3/36	8.3	0–17	<0.001	0.0842
4 <= PSA <= 10	385/928	41.5	38–45	331/501	66.1	62–70	54/427	12.6	9–16	<0.001	<0.001
10 < PSA <= 20	145/264	54.9	49–61	133/185	71.9	65–78	12/79	15.2	7–23	<0.001	<0.001
PSA > 20	147/179	82.1	77–88	143/163	87.7	83–93	4/16	25.0	4–46	<0.001	0.1492
Total	697/1448	48.1	46–51	624/890	70.1	67–73	73/558	13.1	10–16	<0.001	<0.001

Best Re-Biopsy Strategy

Repeat Prostate Biopsy Strategies after Initial Negative Biopsy: Meta-Regression Comparing Cancer Detection of Transperineal, Transrectal Saturation and MRI Guided Biopsy

Adam W. Nelson[1], Rebecca C. Harvey[2], Richard A. Parker[2], Christof Kastner[1], Andrew Doble[1], Vincent J. Gnanapragasam[1,3]*

Table 2. Weighted summary statistics of data extracted from each paper by repeat biopsy strategy.

Strategy (no. studies) [no. patients]	TP-B (14) [1756]	TS-B (12) [1987]	MRI-B (20) [914]	Overall (46) [4,657]
Mean Age (years)	64·9	63·8	64·0	64·3
Mean PSA (ng/L)	11·0	9·0	10·6	10·1
Mean No. previous biopsy episodes[1]	1·5	1·8	1·9	1·7
Mean No. Cores at repeat biopsy	30·4	24·0	9·8	24·8
Cancer Detection Rate (%)	36·8	30·0	37·6	34·0

[1]For the studies that do not report the mean number of biopsies, the median was used instead where possible. (TP-B – Transperineal biopsy, TS – B, Transrectal saturation biopsy, MRI-B – MR guided biopsy).

doi:10.1371/journal.pone.0057480.t002

- No statistical difference in detection rates
- Large variability in data sets led to poor quality analysis

Complications

Complications	Percentage of patients affected
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C	0.8
Epididymitis	0.7
Rectal bleeding > 2 days +/- surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

Pooled data from EAU Guidelines 2015

Costs

Cost-effectiveness of Magnetic Resonance (MR) Imaging and MR-guided Targeted Biopsy Versus Systematic Transrectal Ultrasound–Guided Biopsy in Diagnosing Prostate Cancer: A Modelling Study from a Health Care Perspective

Maarten de Rooij [a,b,], Simone Crienen [a], J. Alfred Witjes [c], Jelle O. Barentsz [b], Maroeska M. Rovers [a,d], Janneke P.C. Grutters [a,d]*

EUROPEAN UROLOGY 66 (2014) 430–436

Description	Unit costs, €
Diagnostic procedure	
TRUSGB	300
mp-MRI	345
MRGB	800
Histopathologic analysis	231
Treatment	
RP	12 800
RT	Insignificant tumour: 2401 Significant tumour: 4035
Watchful waiting/active surveillance	100 (per year)

mp-MRI = multiparametric magnetic resonance imaging; MRGB = magnetic resonance–guided biopsy; RP = radical prostatectomy; RT = radiation therapy; TRUSGB = transrectal ultrasound–guided biopsy.

Strategy	Mean cost per strategy in € (95% CI)	Incremental costs in € (95% CI)	Effectiveness in QALY (95% CI)	Incremental QALYs (95% CI)	ICER (cost/QALY)
TRUSGB	2392 (2227–2563)	–	6.90 (3.84–8.22)	–	–
MRI	2423 (2219–2637)	31 (−95 to 162)	7.00 (3.72–8.32)	0.10 (−0.18 to 0.34)	323

CI = confidence interval; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; TRUSGB = transrectal ultrasound–guided biopsy; MRI = magnetic resonance imaging.

- UK: TRUS biopsy £500, TP biopsy £2000 MRI scan £500 (approx)

MRI/US Fusion

MRI/ultrasound fusion devices approved by US Food and Drug Administration

Manufacturer/ trade name	US image acquisition	Biopsy route	Tracking mechanism	Year of FDA approval	Comments
Philips/PercuNav	Manual US sweep from base to apex	Transrectal	External magnetic field generator	2005	Prospective targeting, integrated with existing ultrasound device, freehand manipulation
Eigen/Artemis	Manual rotation along fixed axis	Transrectal	Mechanical arm with encoders	2008	Prospective targeting, stabilized TRUS probe
Koelis/Urostation	Automatic US probe rotation, three different volumes elastically registered	Transrectal	Real-time TRUS-TRUS registration	2010	Retrospective targeting, real-time elastic registration
Hitachi HI-RVS (real-time virtual sonography)	Real-time biplanar TRUS	Transrectal or transperineal	External magnetic field generator	2010	Prospective targeting, integrated with existing ultrasound device
BioJet/Jetsoft GeoScan	Manual US sweep in sagittal	Transrectal or transperineal	Mechanical arm with encoders; uses stepper	2012	Prospective targeting, rigid registration

FDA, US Food and Drug Administration; US, ultrasound.

Marks et al. Curr Opin Urol (Jan 2013)

MRI/US Fusion Devices

Artemis (Eigen/Siemens)

Uronav (Phillips)

Urostation (Koelis)

VGH experience

Hologic system

Rigid fusion, GPS-like navigation

(have also had experience with Artemis and Urostation)

VGH experience

Hologic system

Rigid fusion, GPS-like navigation

(have also had experience with Artemis and Urostation)

TIPS/TRICKS

Lesions not uncommonly visible on ultrasound (esp peripheral zone)

Accurate segmentation = more accurate fusion

Patient movement can offset registration, may need to manually correct

Internal fiducials (utricle cysts, bph nodules, calcification, urethra)

Patient positioning, tray table, ergonomics

Our experience

>350 Patients since 2012
Increasing each year

Most common indications

1. Rising PSA despite negative systematic biopsy
2. Suspicious lesion detected on active surveillance

In a cohort of 95 consecutive patients

Fusion vs Systematic

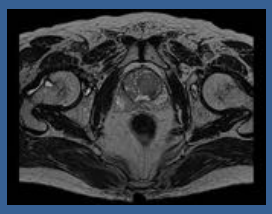
Percentage of positive cores: **16.5%** vs **10.5%**

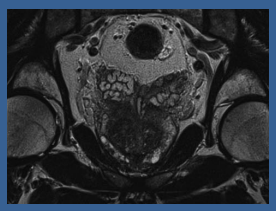
Of positive cores how many showed significant PCa: **66%** vs **53%**

When MRIs retrospectively reclassified with PIRADS v2, 77 lesions would not have been biopsied, potentially improving this to ~26%

Mean age of patients **65**

Issues to consider with this technology





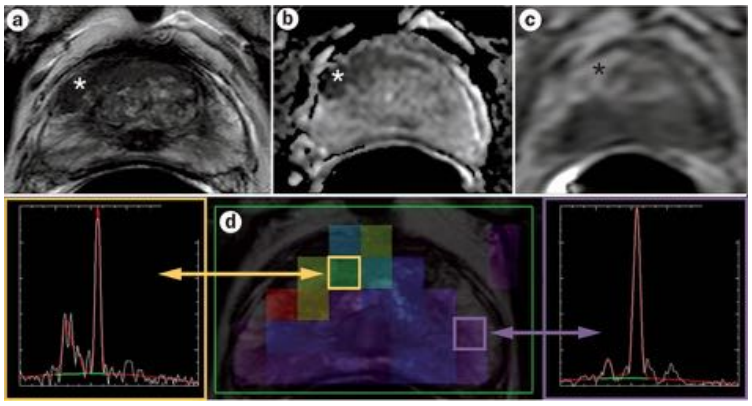
EXTREMELY dependent on quality of MRI acquisition and interpretation

- Performance of fusion technique only as good as the MRI study that it draws the targeting data from
- Prostate MRI is still evolving - protocol optimization, radiologist education and standardization of reporting (ie. PIRADS) is key
- Whole mount prostatectomy specimens as gold standard for research

Future Directions

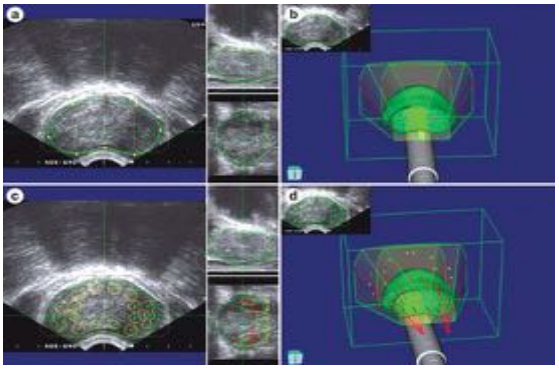
- The e-Finger. An approach is proposed to the in vivo assessment of soft tissue quality using multi-scale mechanical measurements
- Assesses stiffness of prostate tissue to help determine need for biopsy
- Team at Herriott-Watt University, Edinburgh

Future Directions



Incorporation of MRI Spectroscopy

Future Directions



BioXbot for robotic TP biopsy
(Ho Urology 2011)

Clinical Trials

- PROMIS
  - Role of MRI in biopsy naïve men with suspected CaP
- PICTURE
  - Comparison btw MRI and Transperineal Template biopsy for detecting CaP

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