Optimizing CaP detection and characterization with improved TRUS biopsy, MRI and PET Scans

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Disclosures

- Clinical Investigator:
  - Medivation, Progenics, Blue Earth Diagnostics
- Consultant/Advisor:
  - Augmenix, Tolmar Pharm., 3D Biopsy
- Research Support:
  - National Cancer Institute
  - NIH-NIDDK
  - Prostate Cancer Foundation
  - Peter Michael Foundation
  - St. Louis Men's Group Against Cancer
  - Barnes-Jewish Hospital Foundation

Digitally Guided Transperineal Biopsy

- Reported by Barringer (SGO 34:168, 1922)
- Used a screw-tip needle guided into the prostate
  - Retreived prostate tissue in 16/38 pts.
- Ferguson (American J Surg 9:507, 1930)
  used aspiration and angulation of an 18 g.
  cutting needle
    Prostate tissue in ~80% of the 280 pts.

Digitally Guided Transrectal Biopsy

- Astraldi (Urol Cut Rev 41:421, 1937)
  - 300 cases using Franzen guide and a 23-25 g. needle
  - Combined aspiration and cutting.
  - Up to 6 passes per nodule
  - “satisfactory in 80%”
- Peirson used Silverman needle (NEJM 228: 675-678, 1943)
  - 86% satisfactory

Open Perineal Biopsy

- Transverse incision between ischial tuberosities
- Divide central perineal tendon
- Grasp firm area w Allis clamp
- Excise lesion; do frozen section
- Required general anesthesia and 1 week hospital stay
- Popularized by Young in 1926

Rad Px. if DRE Suspicious

- Colby et al: J Urol 69:797, 1953
- Cancer in prostate of 58% patients who had palpable abnormality but no pre-op biopsy
- “…seems unwise to embark on radical surgery without histologic evidence of prostatic carcinoma.”

Open Transrectal Biopsy

- Grabstald (1954) published a series w excellent accuracy but made later radical prostatectomy very difficult, so he abandoned that approach.

Digitally Guided Transperineal Biopsy

- Tissue core of 5 mm. length
- Local anesthesia
- Concern for tract seeding
- ~80% accurate
- Kauffman recommended open biopsy if needle bx. negative (California Medicine 81; 5: 308-313, 1954)

Digitally Guided Transrectal Biopsy

- Aspiration initially
- Most recommended a histologic biopsy if aspirate was negative.
- Refinements included use of a sound to stabilize the prostate and position it closer to the rectal wall. Barnes (Calif Med. 1959: 91(2): 57-61)

Digitally Guided Transrectal Biopsy

- Silverman needle became preferred by Parry (J Urol. 1960; 84: 643–648)
- Multiple agents instilled into rectum to reduce infection
  - Vioform (iodochlorhydroxyquin U.S.P)
  - 3% Betadine (providone-iodine
  - Triophyll (tri-iodophynol).

Transurethral Biopsy

- 300 cases reported by Denton (J Urol 97:127, 1967) comparing TUR and perineal needle biopsy
  - Favored needle
  - OK if large tumor

Cutting Needles

- One-hand operated “Tru-Cut” needles in 1978
- Initially not better than Silverman

Ultrasound Guidance

- Started in mid-1960's
- Takahashi (Proc Jpn Soc Ultrasound Med. 1963; 3: 7)
  - used 3.5 MHz transducer
- McNeal (Am J Clin Pathol. 1968; 49: 347)
  - described the distinct zones of the prostate
  - Watanabe (J Clin Ultrasound. 1974; 2: 91-98) visualized them w 7 MHz transducer.

Modern Era of TRUS Guided Bx

- Wash U PSA screening program used TRUS guided quadrant biopsy (started in 1989)
  - NEJM 324:1154, 1991
- Hodge reported sextant biopsy
  - J Urol. 1989; 142: 71–74

Limitations of Traditional TRUS-Guided Prostate Biopsy

- Operator Dependent
- Cores randomly arrayed
- Often misses significant pathology requiring re-Bx.
  - 2nd and 3rd Bx are pos. 15 to 20%
- Often under- or over-estimates CaP grade and extent on RP

Conventional 2-D TRUS Biopsy

- Accurate assessment of tumor size, grade and location not possible using current conventional biopsy techniques
  - Review of 11 biopsy and RP studies shows “best” biopsy parameters are poor predictors of pathologic findings in screen detected CaP
    - 23-56% Sens to predict Insig. CaP
    - 14-70% Sens to predict Adv. Dx.
    - 27% upgrade and 17% downgrade @ RP

Anast et al : Urol 64:544, 2004

What is Ideal Number of cores?

- No consensus
  - Recommended number of cores has ranged from 4 to 24 over past 20 years
- Most agree core number depends on prostate size (“core density”) and the threshold volume of cancer that merits detection
  - Age and health of patient

Probability (%) CaP Detected

No. Cores	<35 cc	35-50 cc	50-65 cc	>65 cc
6	63	37	33	26
8	95	89	82	81
10	100	100	100	100

Eski JUrol 173: 1536, 2005

Vienna Nomogram

Size (ml)	<50 yrs	50-60 yrs	60-70 yrs	>70 yrs
<30	8	8	8	6
30-40	12	10	8	6
40-50	14	12	10	8
50-60	16	14	12	10
60-70	18	16	14	12
>70	18	18	14	14

Remzi JUrol:174 1256, 2005

Biopsy “Core Density”: Mathematical Models

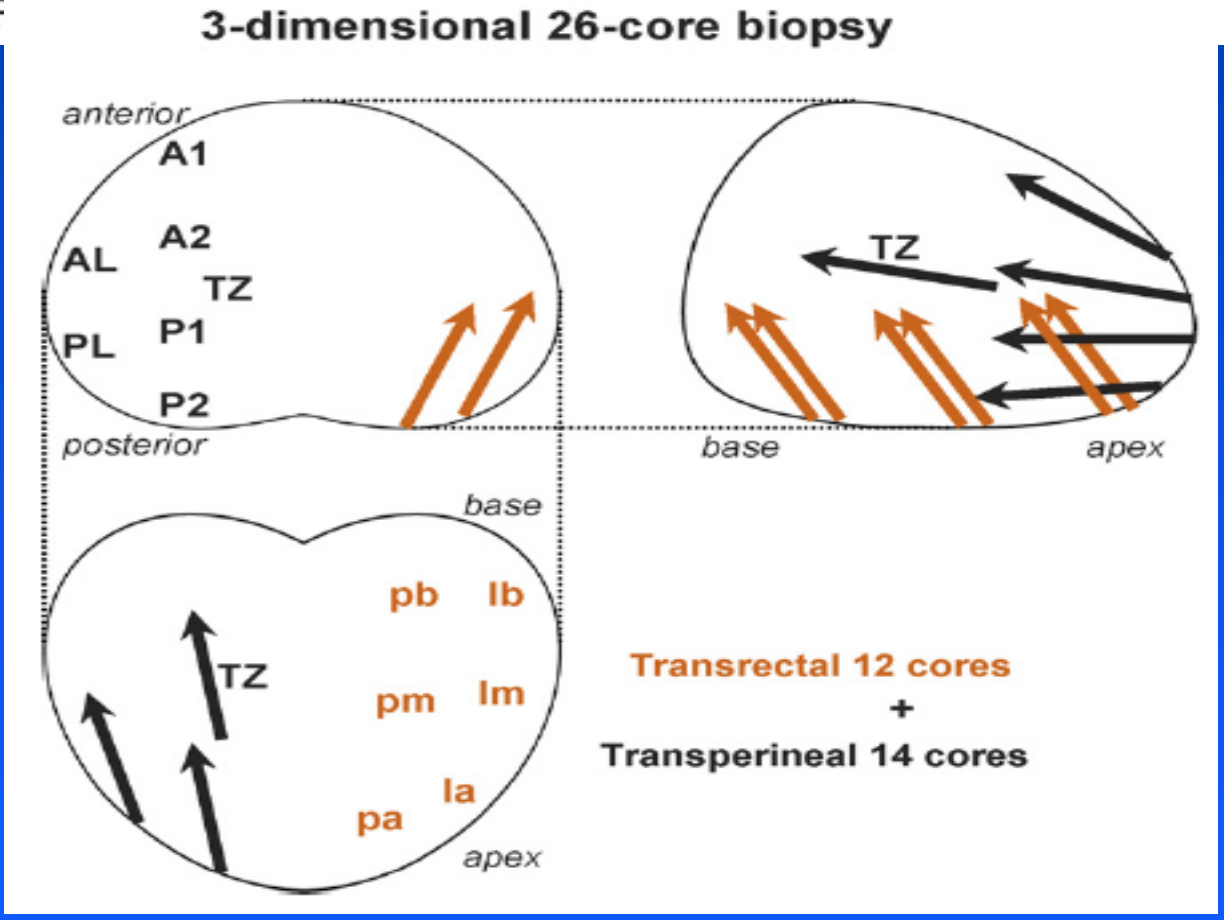
- Considerations
  - Prostate size
  - Tumor size
  - Tumor location within prostate

Number of Cores to detect 1 cc CaP

Prostate Vol	No Cores
20	6
30	8
40	12
50	14
60	16
70	20
80	22

Optimal Sampling Sites for Repeat Prostate Biopsy: A Recursive Partitioning Analysis of Three-Dimensional 26-Core Systematic Biopsy

Satoru Kawakami[a,*], Tetsuo Okuno[a], Junji Yonese[b], Toru Iiari[c], Gaku Arai[a], Yasuhisa F



EUROPEAN UROLOGY 51 (2007) 675–683

Systematic Review of Complications of Prostate Biopsy

Stacy Loeb [a,], Annelies Vellekoop [a], Hashim U. Ahmed [b], James Catto [c], Mark Emberton [b], Robert Nam [d], Derek J. Rosario [c], Vincenzo Scattoni [e], Yair Lotan [f]*

- Infection
  - Nam et al.: 30 d. hosp rate 4.1% in 2005
  - Carignan et al: 4-fold infection increase from 2002 to 2011
  - Loeb et al: ERSPC 4.2% fever; 0.8% serious infection

  Increasing Flouroquinolone resistance

  rectal swab

  formalin needle deconatamination

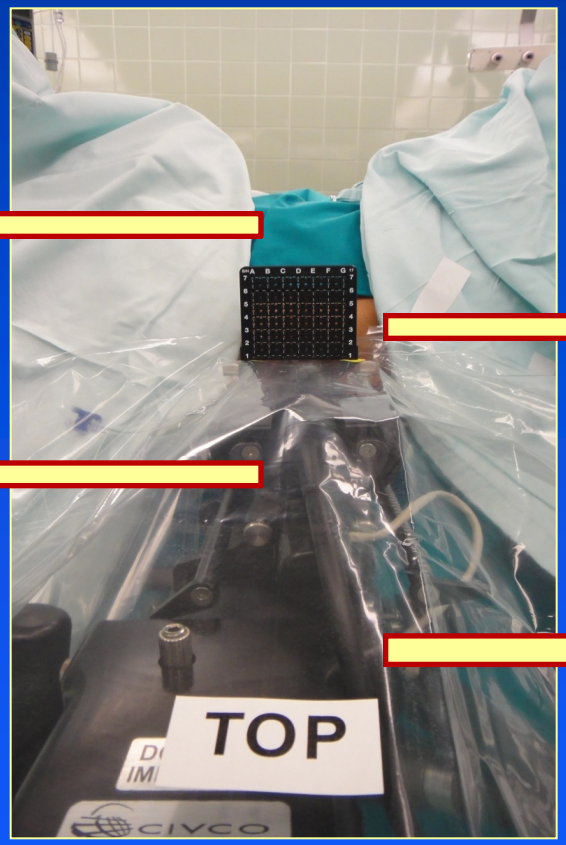
Template Guided 3D-PMB: Potential Advantages

- Reproducible
- Less likely to miss important pathology; may obviate need for re-Bx.
- More likely to accurately characterize Ca P
  - Better guide to treatment decisions

3D-PMB: Transperineal Approach

- Patient in dorsal lithotomy position
- “Stepper” unit stabilizes and advances U/S probe; standard biopsy needle inserted transperineally
- Gnerally performed under anesthesia

Transperineal Mapping Biopsy (TMB)
OR Setting

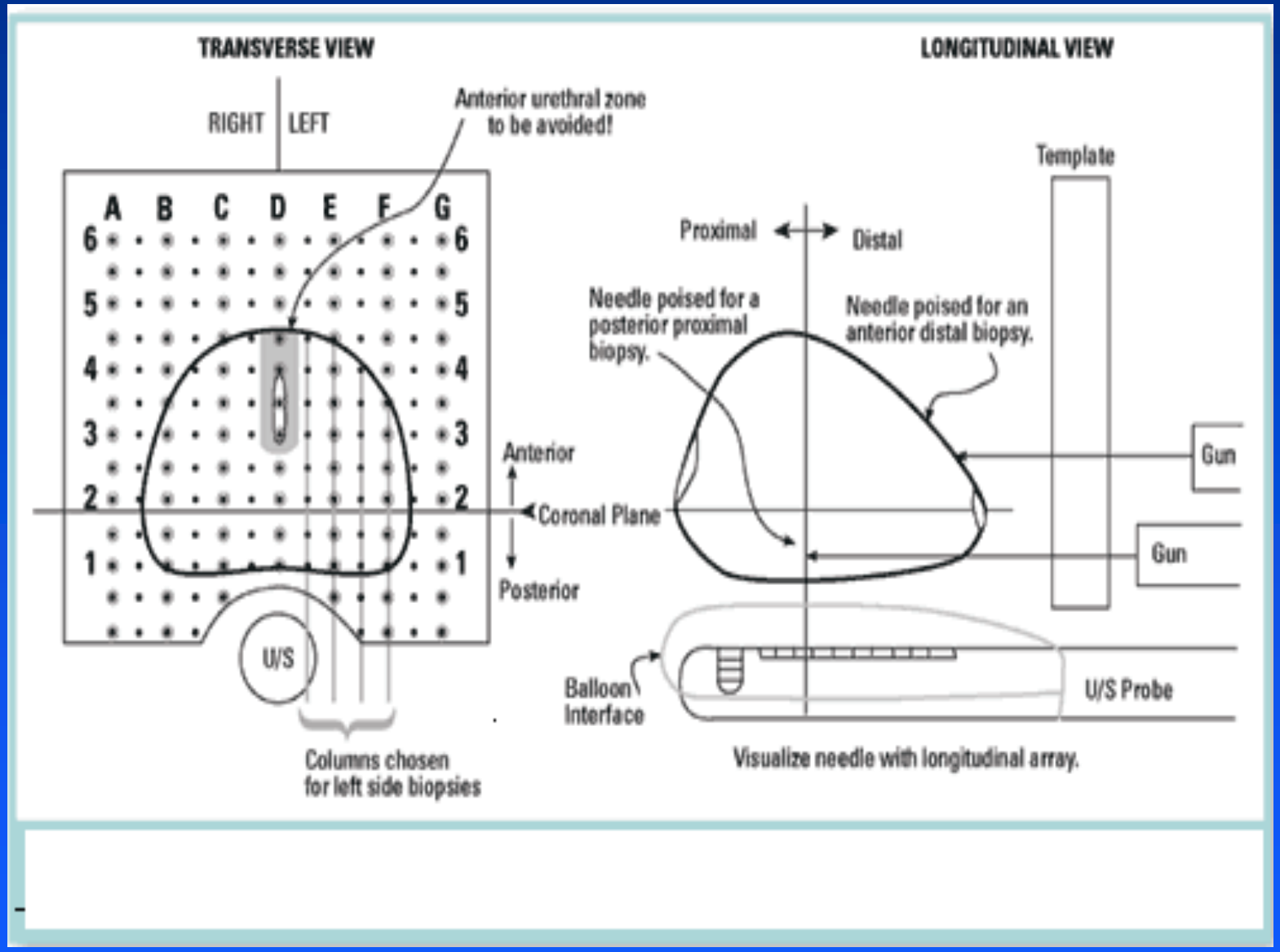


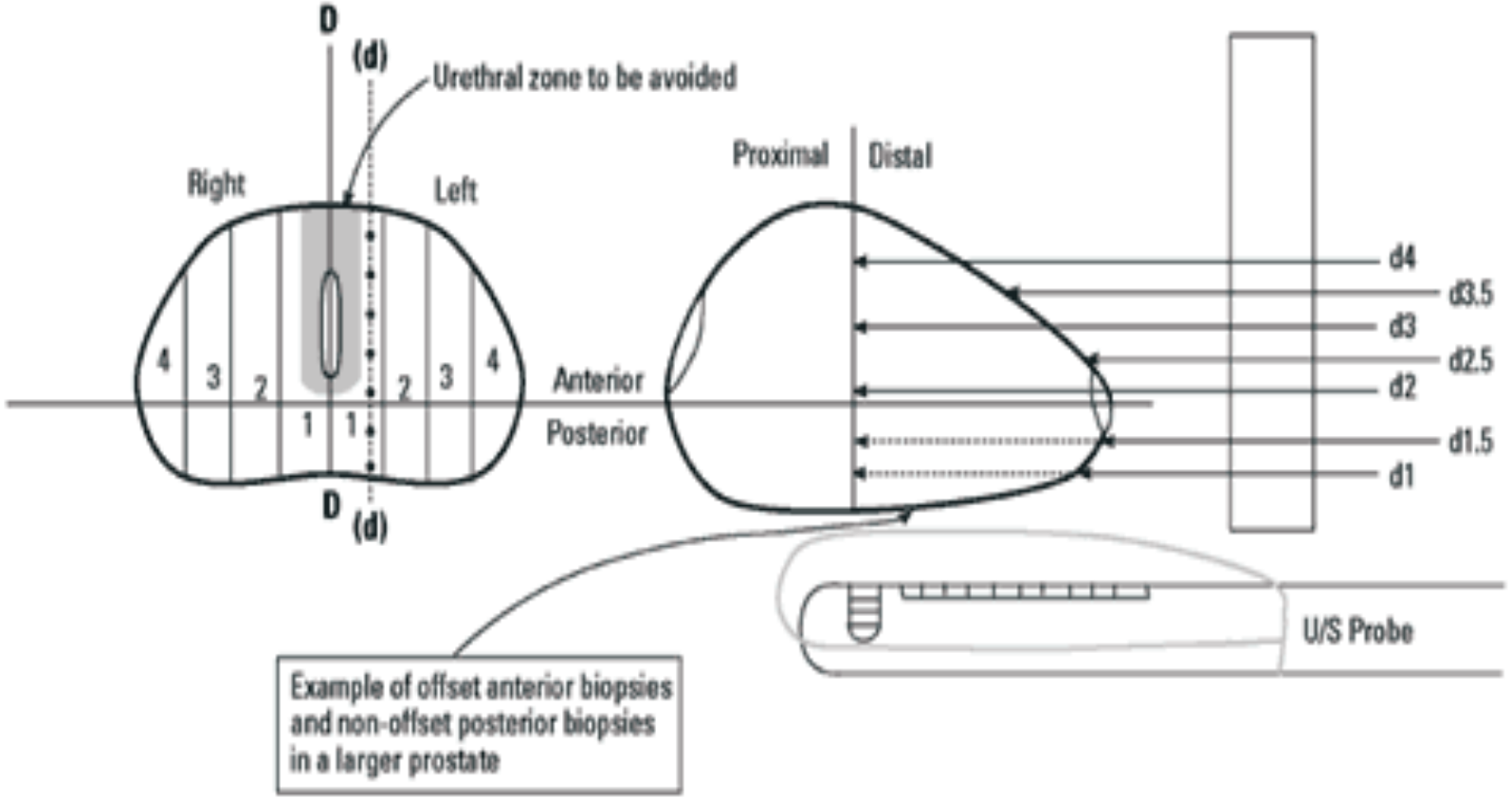
Foley catheter

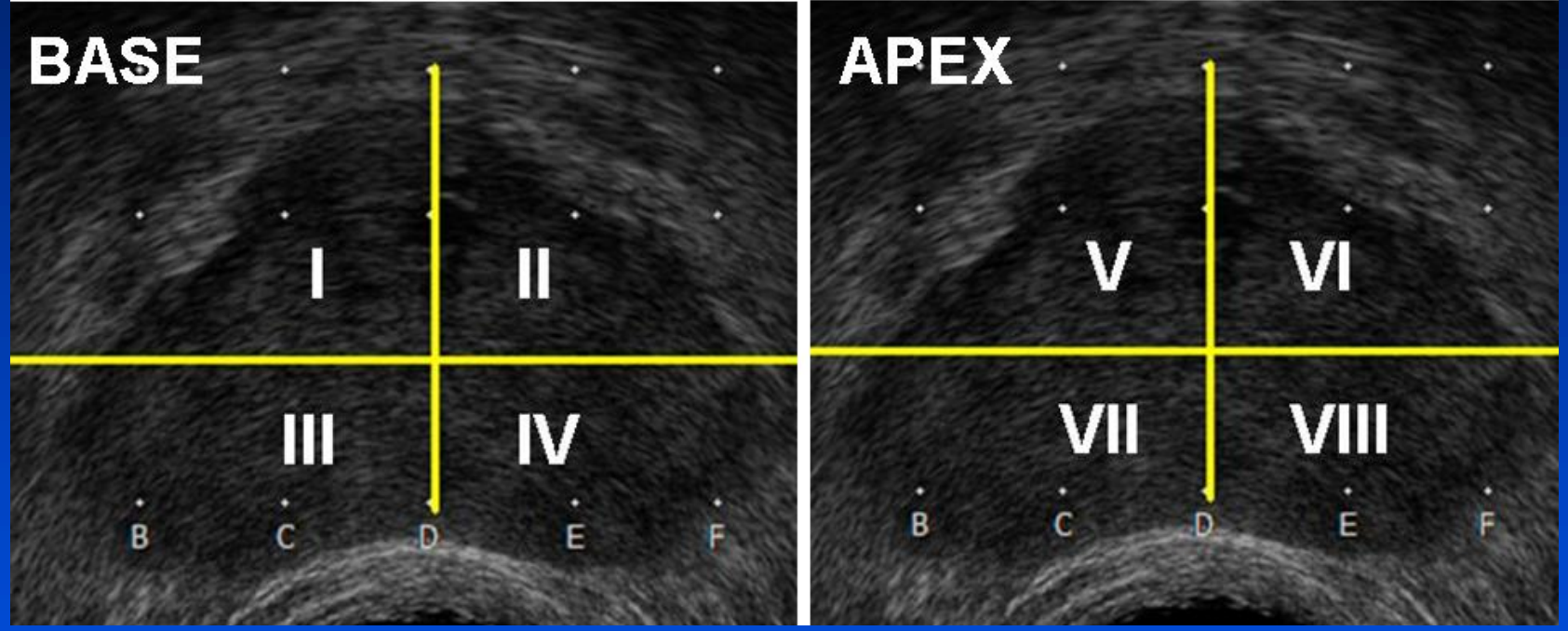
TRUS probe

Template or Grid

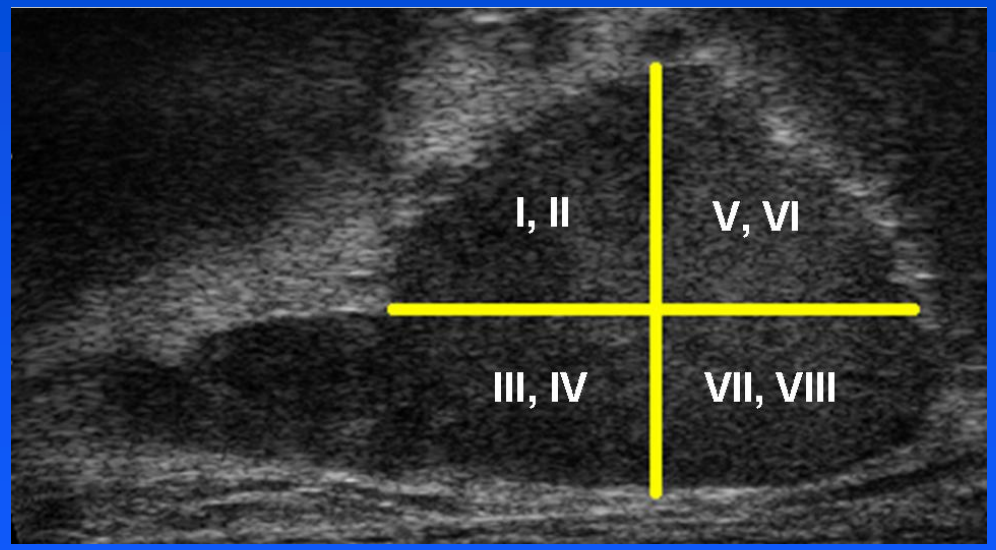
Brachy - stepper

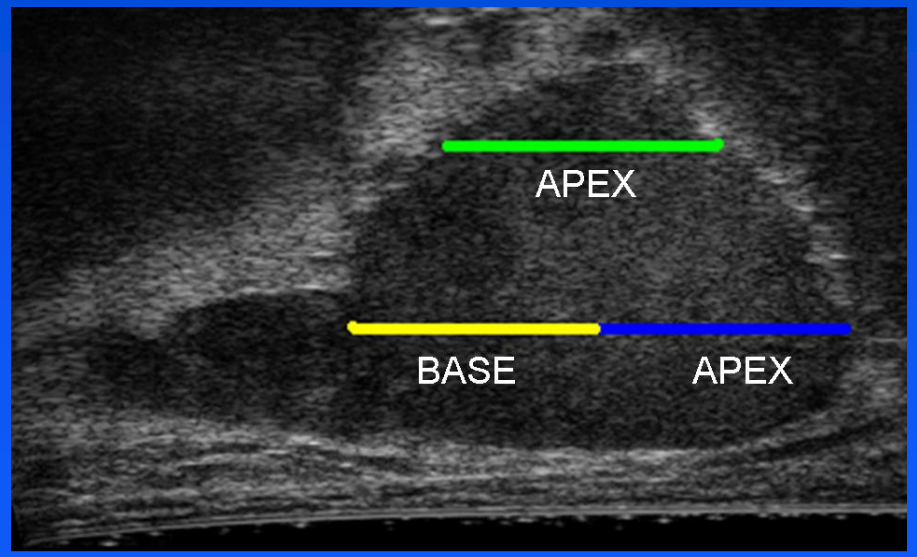

TRANSVERSE VIEW
LONGITUDINAL VIEW
RIGHT
LEFT
Anterior urethral zone to be avoided!
A B C D E F G
6
5
4
3
2
1
Anterior
Coronal Plane
Posterior
U/S
Columns chosen for left side biopsies
Template
Proximal
Distal
Needle poised for a posterior proximal biopsy.
Needle poised for an anterior distal biopsy.
Gun
Gun
Balloon Interface
U/S Probe
Visualize needle with longitudinal array.


D
(d)
Urethral zone to be avoided
Right
Left
4
3
2
1
1
2
3
4
D
(d)
Anterior
Posterior
Proximal
Distal
d4
d3.5
d3
d2.5
d2
d1.5
d1
U/S Probe
Example of offset anterior biopsies and non-offset posterior biopsies in a larger prostate



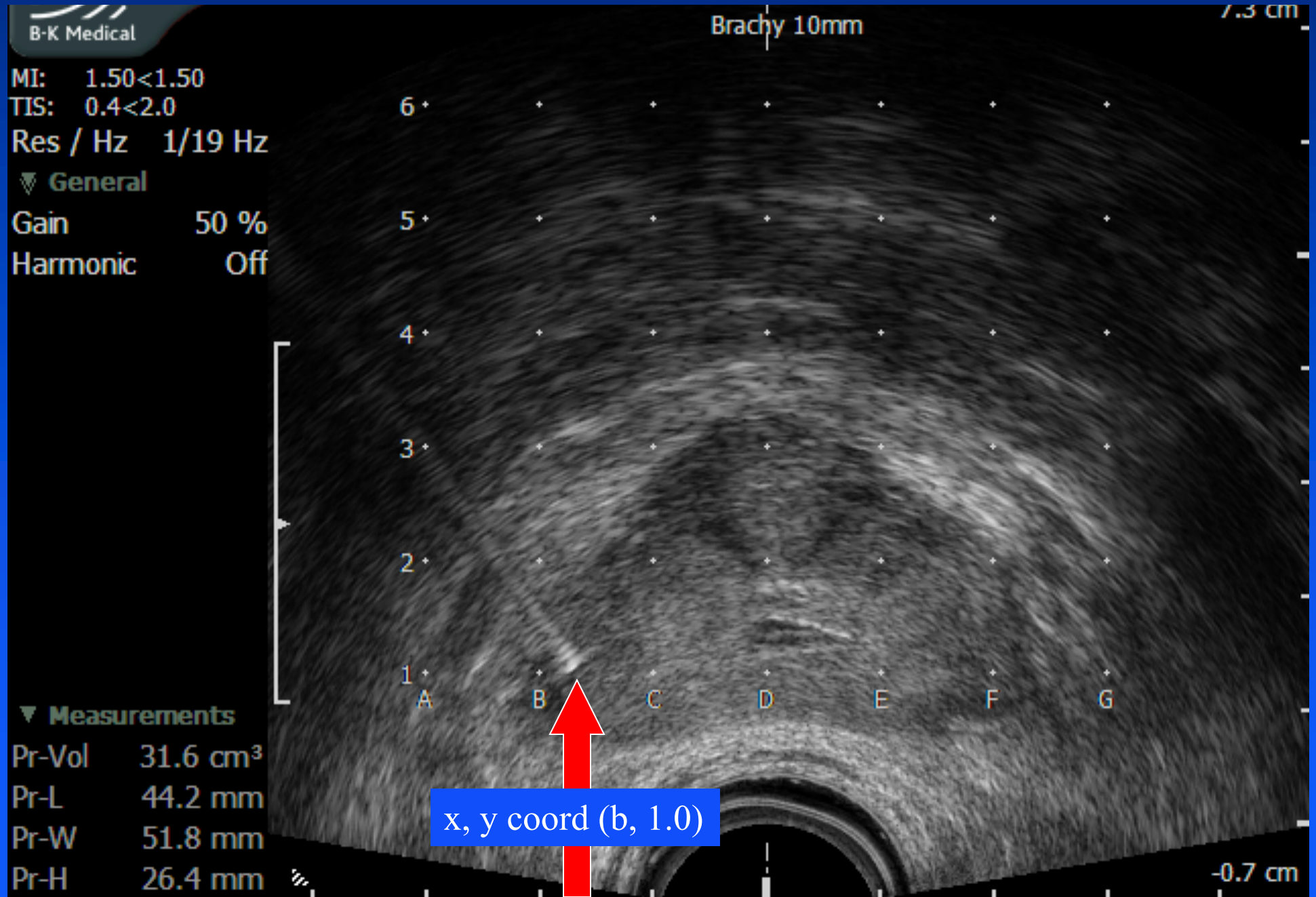
Octant assignments in axial view



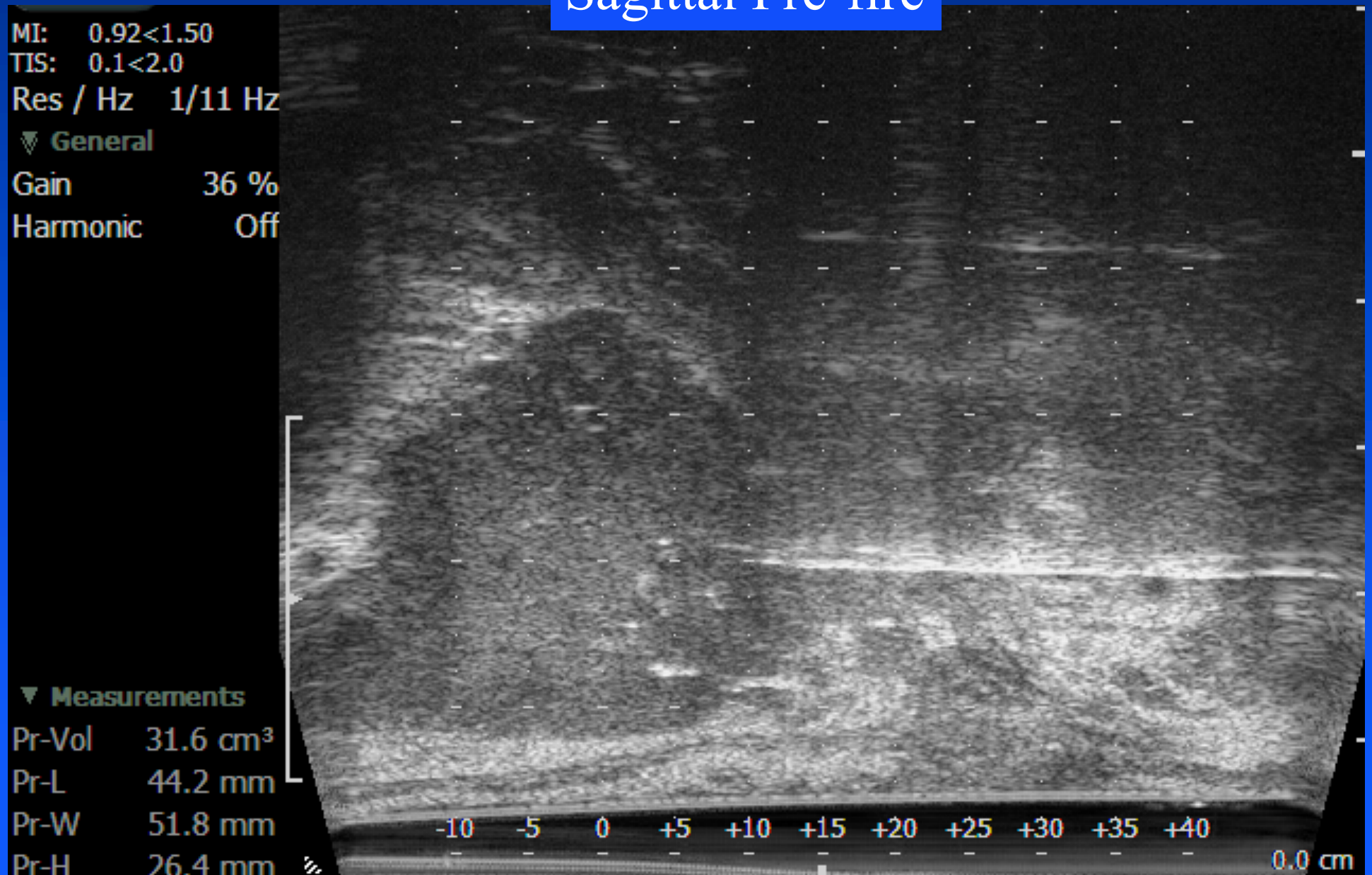


Octant assignments in sagittal view

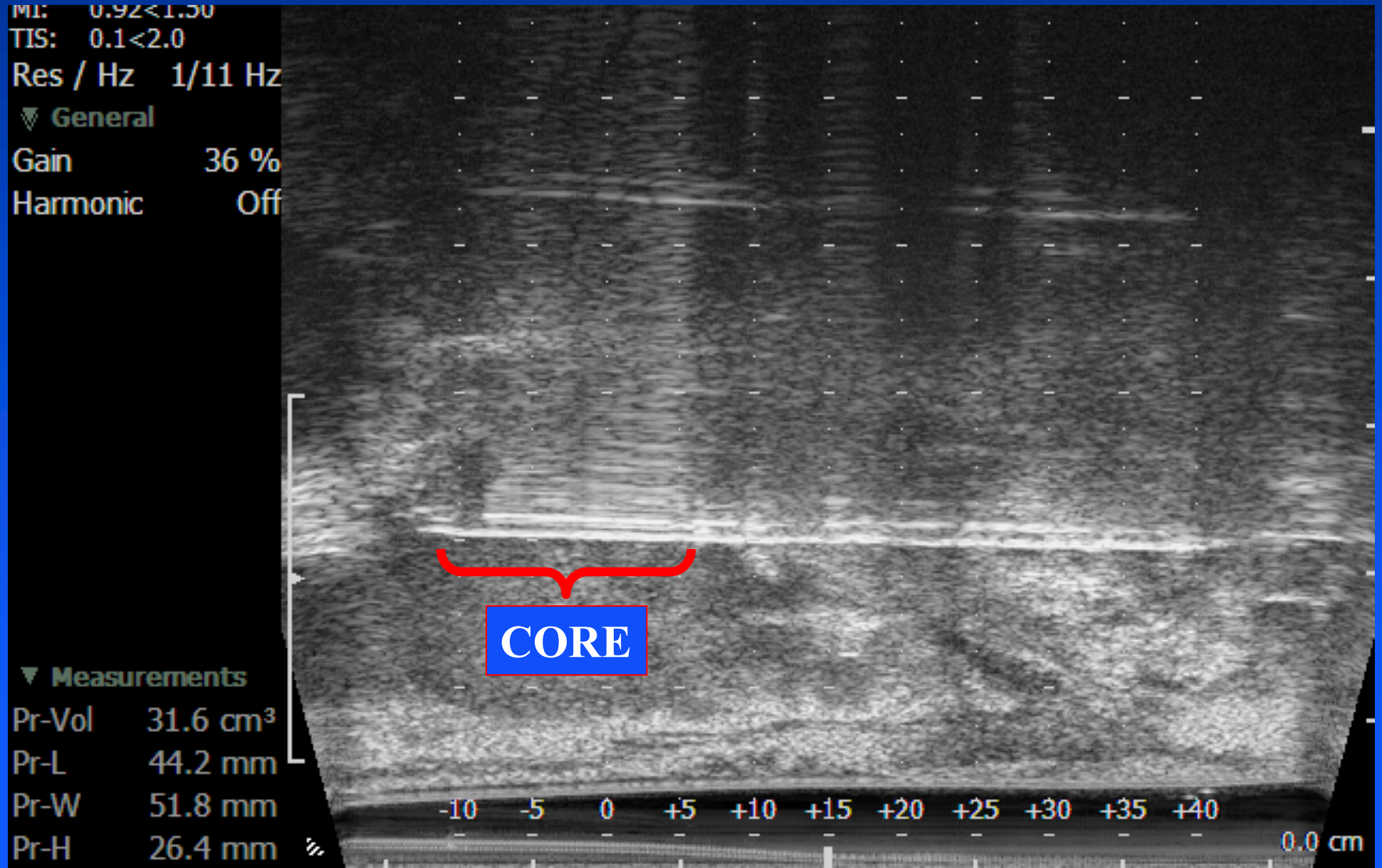
Moran et al.


B-K Medical
Brachy 10mm
MI: 1.50<1.50
TIS: 0.4<2.0
Res / Hz 1/19 Hz
General
Gain 50 %
Harmonic Off
Measurements
Pr-Vol 31.6 cm³
Pr-L 44.2 mm
Pr-W 51.8 mm
Pr-H 26.4 mm
6
5
4
3
2
1
A
B
C
D
E
F
G
x, y coord (b, 1.0)
-0.7 cm

Sagittal Pre-fire

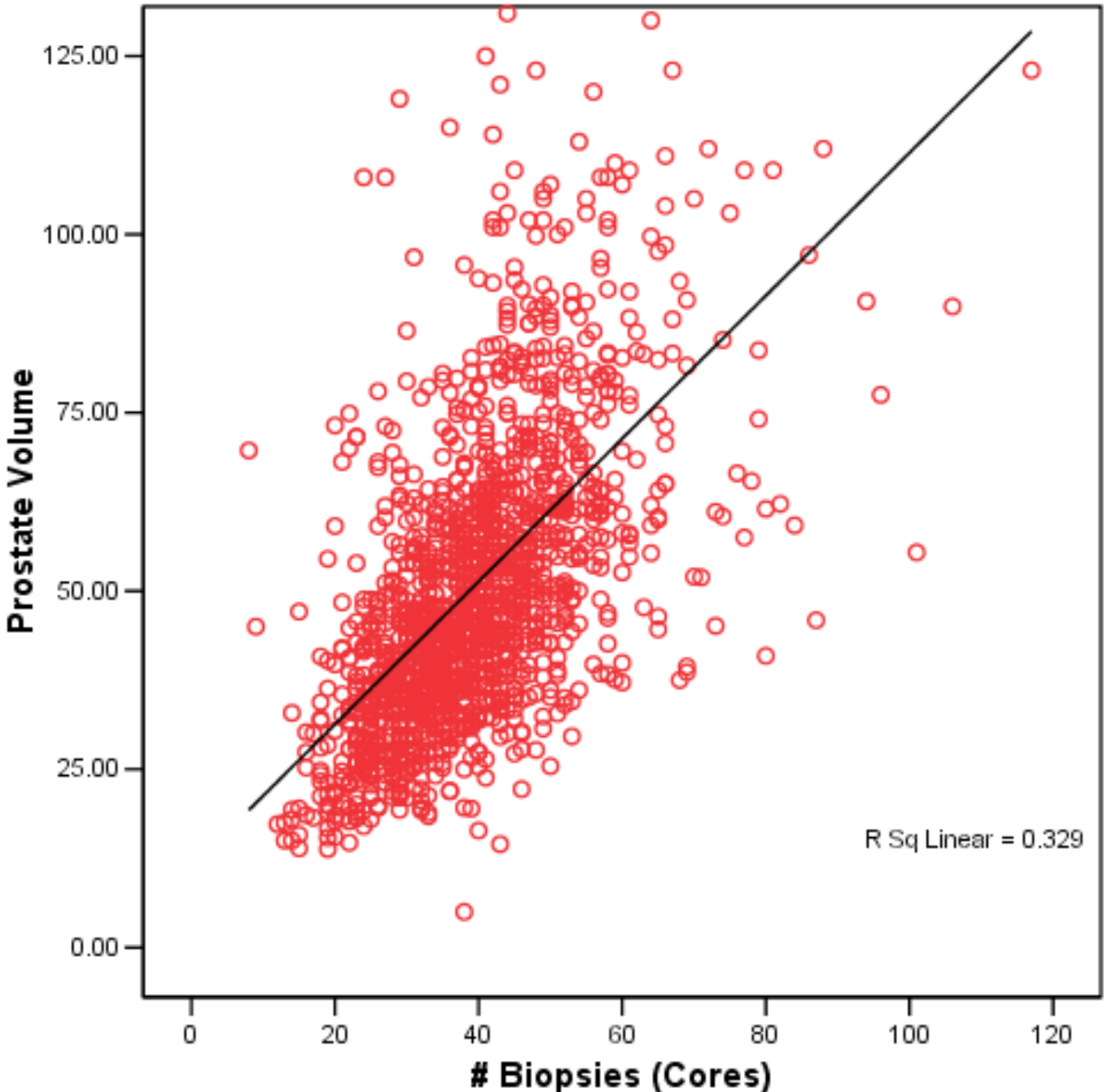


Sagittal Post-fire



3D PMB: Transperineal to diagnose CaP

	No.	PriorBx	Cores	%CaP	%Comp
Moran	1085	1-10	38	39	11.5
Merrick	102	2.1	50	42	---
Bott	60	2-8	24	38	4
Pinkstaff	210	>2	21	37	11
Satoh	128	>1	---	23	---
Furono	113	0-4	18	43	---
Igel	88	2	15	43	2
Andriole	68	2-10	36	42	29



Ratio:
1 core per 1.2cc of prostate

Moran et al.

Transperineal 3D PMB for selecting men for Focal Therapy- Wash U

- 46 pts with Gleason <7 and 1 or 2 contiguous involved cores on conventional biopsy
- Cores arrayed at 5 mm intervals
- 14 (30%) not suitable for focal therapy or Surveillance
  - Usually due to upgrading and/or presence of multiple or anterior tumors
- RP: 72% octants accurately assessed

Transperineal 3D PMB for selecting men for Focal Therapy

- 110 pts with Gleason <7 and 1 or 2 contiguous involved cores on conventional biopsy
- Cores arrayed at 5 mm intervals; 1.6 core/gm tissue
- 57 (52%) not suitable for focal therapy or Surveillance
- Those undergoing RP: “precise location of tumor”

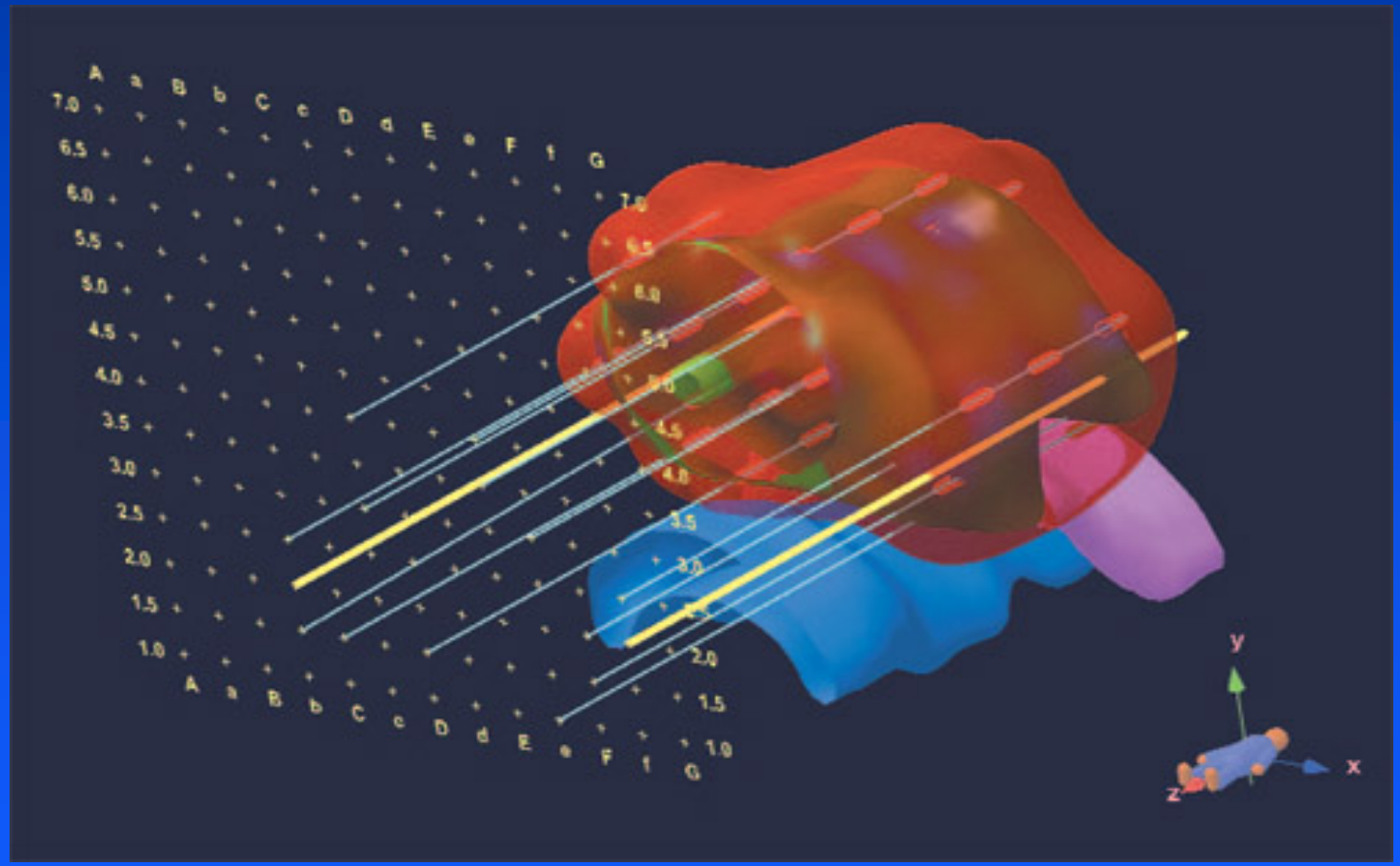
Barzell et al Urology 2007: 70:27

Transperineal Biopsy to Predict RP findings

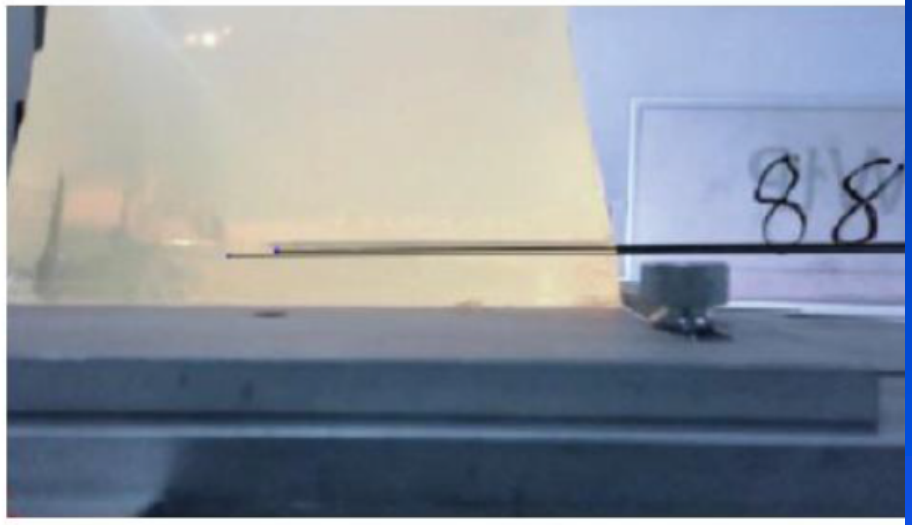
- 62/85 (73%) concordance rate between Gleason score reported on 3D-PMB and final RP specimen.
  - Gleason score increased in 13/85 (15%), downgraded in 10/85 (12%).
- 81/85 (95%), 3D-PMB accurately predicted octant location of tumor .

Moran et al. Urology 2009. 73: 386-388

Transperineal Mapping Prostate Biopsy



Deflection Analysis of Different Needle Designs for Prostate Biopsy and Focal Therapy

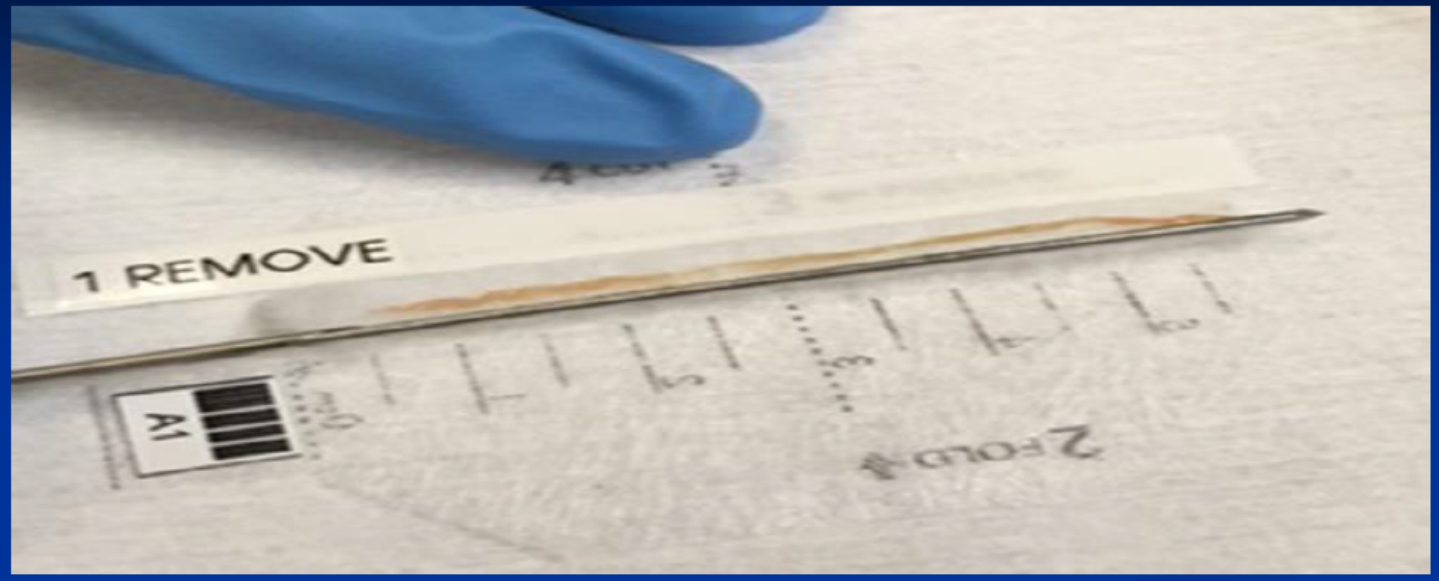


4-point trocar tip deflected 1/9th (0.1mm) of Bard (lancet tip)

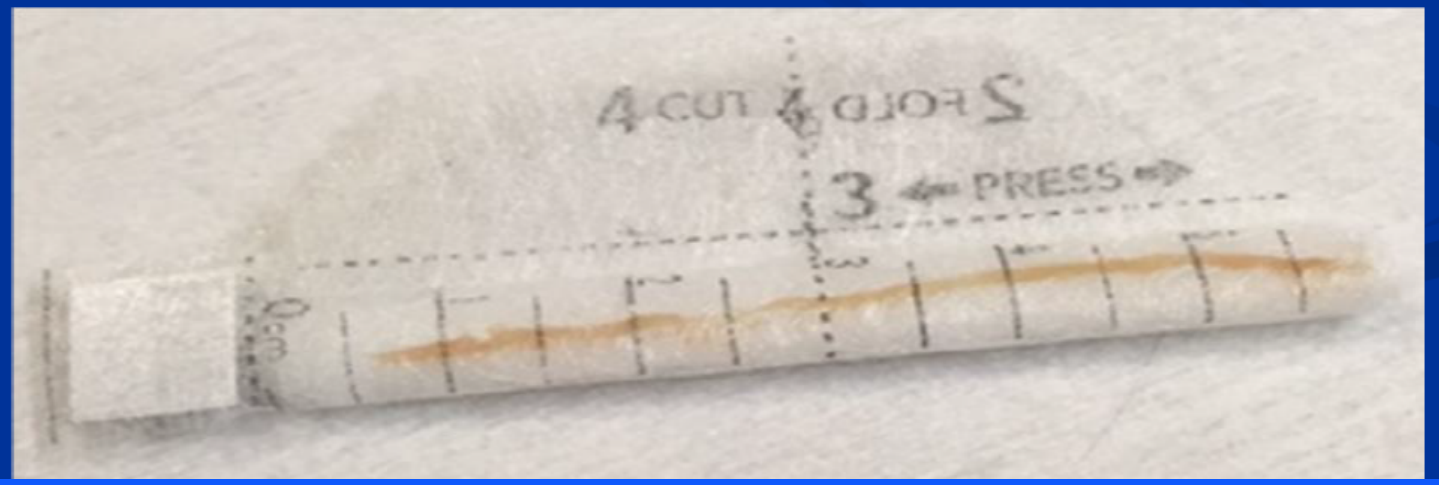
Technology in Cancer Research & Treatment
1–8

Stone et al.

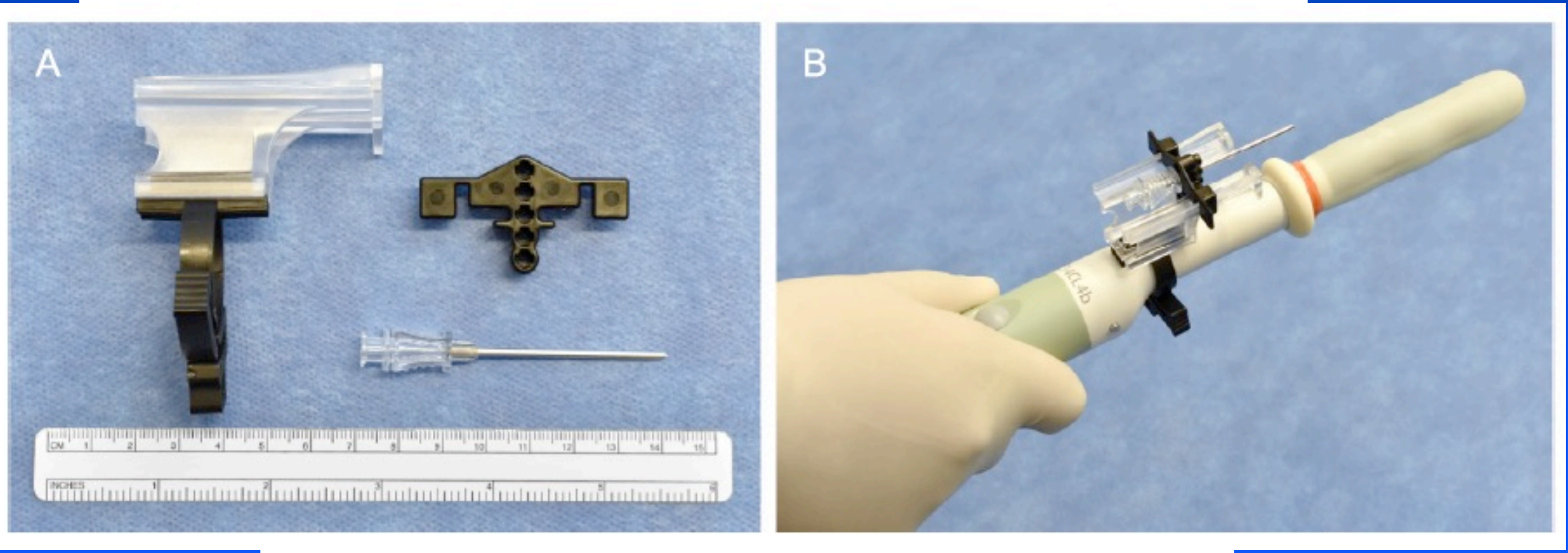
Non-woven material grabs tissue



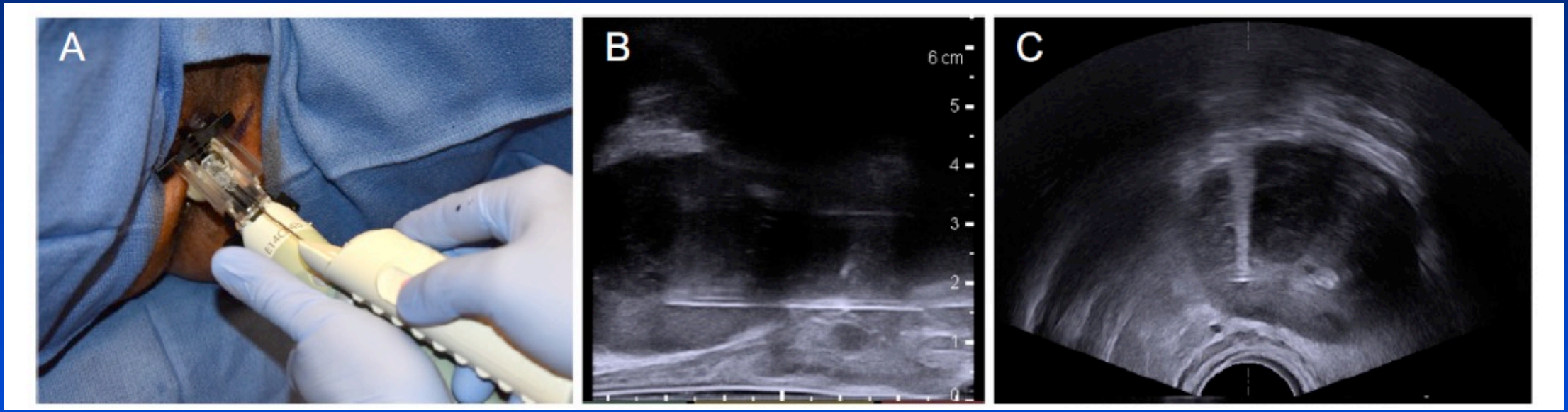
The carrier is able to be processed, embeddable and sliced on microtome

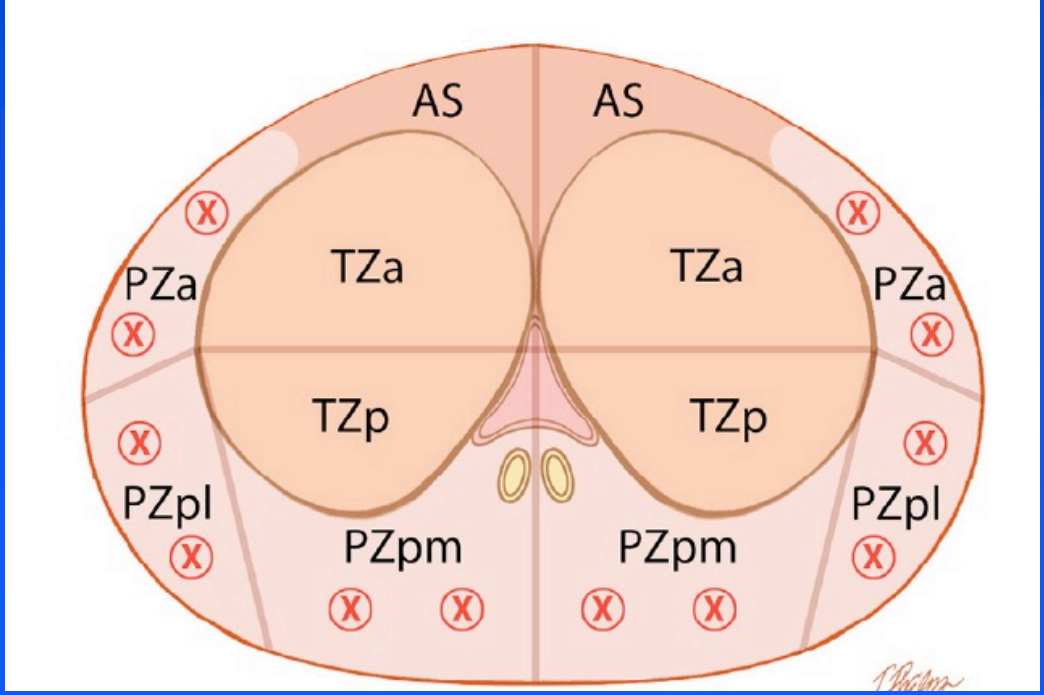


Initial Experience Performing In-office Ultrasound-guided Transperineal Prostate Biopsy Under Local Anesthesia Using the PrecisionPoint Transperineal Access System



https://doi.org/10.1016/j.urology.2018.01.021


A
B
6 cm
5
4
3
2
1
0
C


AS
AS
PZa
TZa
TZa
PZa
TZp
TZp
PZpl
PZpm
PZpm
PZpl

MRI to identify Prostate Cancer

Cognitive biopsy using MRI targeting @ Wash U

- No fusion
- Description of lesion location using length from BN and midline
- 73% PPV for PIRAD 3-5 lesions
  - 59% were Gleason 6
  - Depends on size of MRI lesion
  - Neg MRI misses 7% Gleason 7 on 12 core-template
  - Kim et al: Urol. Onc. 33:109, 2015

A Prospective, Blinded Comparison of Magnetic Resonance (MR) Imaging–Ultrasound Fusion and Visual Estimation in the Performance of MR-targeted Prostate Biopsy: The PROFUS Trial

James S. Wysock[a], *Andrew B. Rosenkrantz*[b], *William C. Huang*[a], *Michael D. Stifelman*[a],

Table 5 – Cancer detection rate by targeted biopsy technique

	MRF-TB			
	Gleason sum ≥7, no. (%)	Gleason 6, no. (%)	No cancer, no. (%)	Total, no. (%)
VE-TB				
Gleason sum ≥7	22 (12.8)	0 (0)	4 (2.3)	26 (15.1)
Gleason 6	7 (4.1)	7 (4.1)	6 (3.5)	20 (11.6)
No cancer	6 (3.5)	13 (7.6)	107 (62.2)	126 (73.3)
Total	35 (20.3)	20 (11.6)	117 (68.0)	172

MRF-TB = magnetic resonance imaging–ultrasound fusion targeted biopsy; VE-TB = visually estimated targeted biopsy.

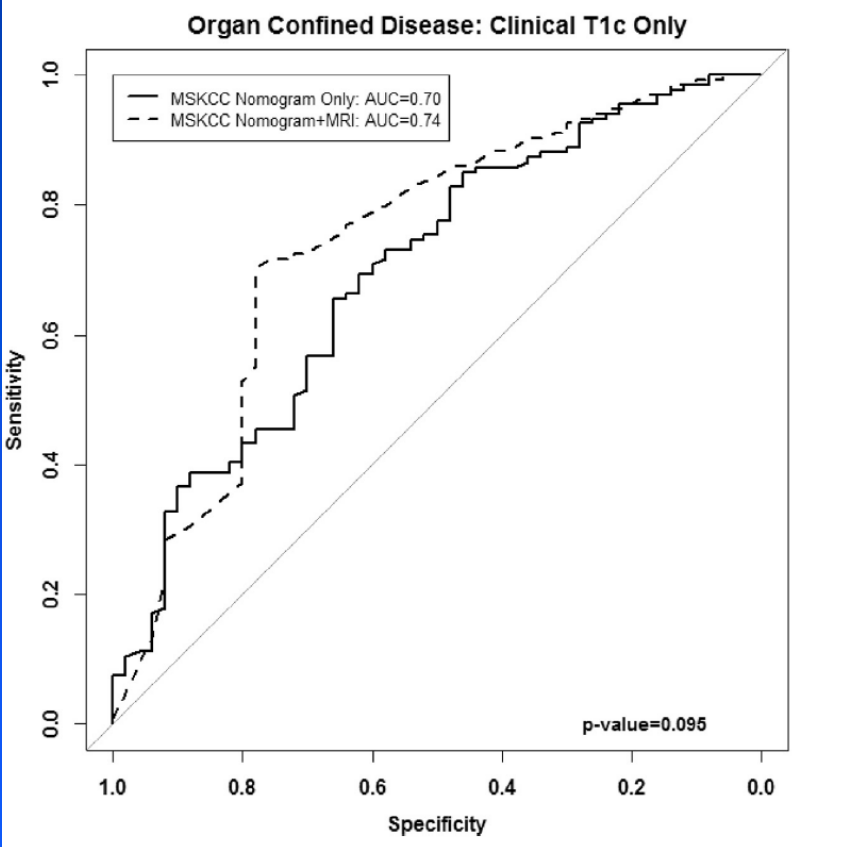
Figure 3. Comparison of Pathology From Standard Extended-Sextant Biopsy and Targeted MR/Ultrasound Fusion Biopsy for Prostate Cancer

Targeted MR/Ultrasound Fusion Biopsy Results		No Cancer	Standard Extended-Sextant Biopsy Results				Totals
			Low-Risk Cancer		Intermediate-Risk Cancer	High-Risk Cancer	
			Gleason 6	Gleason 3+4 Low Volume[a]	Gleason 3+4 High Volume[b]	Gleason ≥4+3	
	No cancer	439	74	12	12	5	542
Low-Risk Cancer	Gleason 6	38	84	12	10	3	147
	Gleason 3+4 Low volume[c]	17	14	9	19	7	66
Intermediate-Risk Cancer	Gleason 3+4 High volume[d]	14	21	7	29	4	75
High-Risk Cancer	Gleason ≥4+3	26	13	12	19	103	173
	Totals	534	206	52	89	122	1003

MRI-Fusion Biopsy @ Wash U: Biopsy Naïve Pts

- 73% PPV (PI-RAD 3-5 lesions)
  - Neg MRI misses 4% Gleason 7 CaP
- Preferred over “random” ultrasound-guided biopsy
  - Less likely to miss cancer
  - More likely to accurately assess cancer grade and size
  - Fewer cores/biopsy session; likely lower complications (bleeding/sepsis)
- Urology 88: 119-124, 2016

MRI improves Kattan Nomogram to predict RP pathology



Author: John K. Weaver, Eric H. Kim, Joel M. Vetter, Anup Shetty, Robert L. Grubb III, Seth A. Strope, Gerald L. Andriole

PII: S0090-4295(17)31247-5
DOI: https://doi.org/10.1016/j.urology.2017.10.051
Reference: URL 20794

Magnetic Resonance Imaging Provides Added Value to the Prostate Cancer Prevention Trial Risk Calculator for Patients With Estimated Risk of High-grade Prostate Cancer Less Than or Equal to 10%

Eric H. Kim, John K. Weaver, Anup S. Shetty, Joel M. Vetter, Gerald L. Andriole, and Seth A. Strope

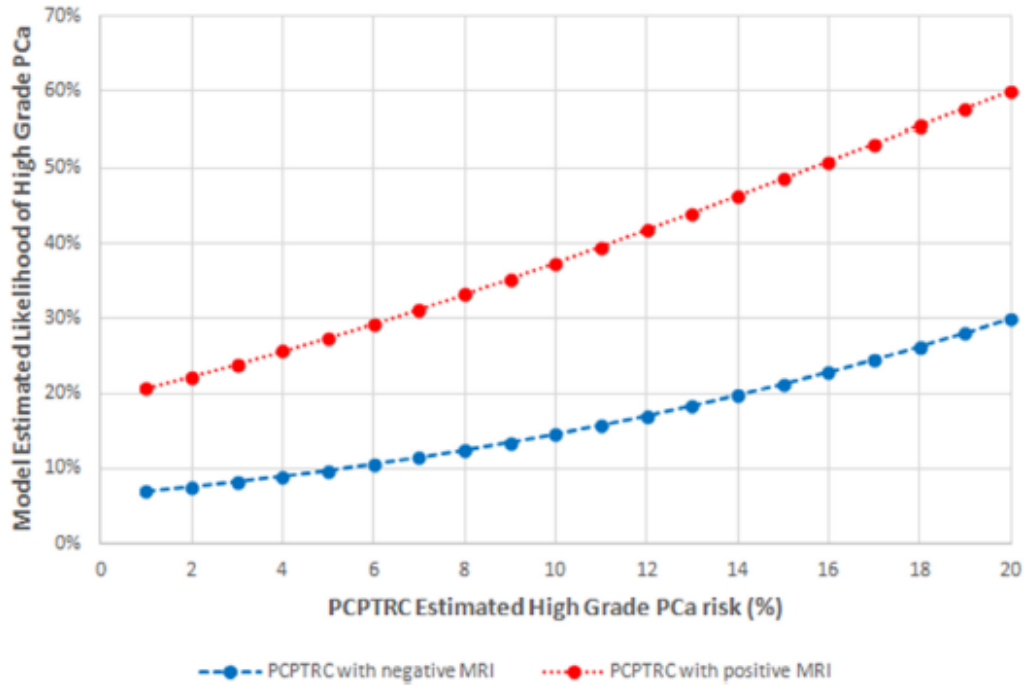


Figure 1. Observed high-grade PCa risk as a function of PCPTRC estimated risk and MRI result. PCa, prostate cancer; PCPT, Prostate Cancer Prevention Trial; PCPTRC, PCPT risk calculator. (Color version available online.)

UROLOGY 102: 183–189, 2017.

Presence of Magnetic Resonance Imaging Suspicious Lesion Predicts Gleason 7 or Greater Prostate Cancer in Biopsy-Naive Patients

John K. Weaver, Eric H. Kim, Joel M. Vetter, Kathryn J. Fowler, Cary L. Siegel, and Gerald L. Andriole

Table 3. Multivariate logistic regression analysis for predictors of Gleason 7 + biopsy result in biopsy-naive patients

Variable	OR	*P* Value
Age (continuous variable)	1.12	.18
Family history of PCa	1.35	.78
Prior 5-ARI use	0.22	.27
Abnormal DRE	15.1	.12
PSA > 10 ng/mL	7.25	.41
PSA density > 0.15 ng/mL^2	1.88	.60
Presence of MSR	40.2	.01

UROLOGY 88: 119–124, 2016.

PROMIS Trial

	TRUS Bx	MRI
No.	576	576
No. Bx.	576	418 (73%)
“Over” Dx. CaP	90 (16%)	62 (11%)
Significant CaP	111 (19%)	213 (37%)

Emberton et al, ASCO 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

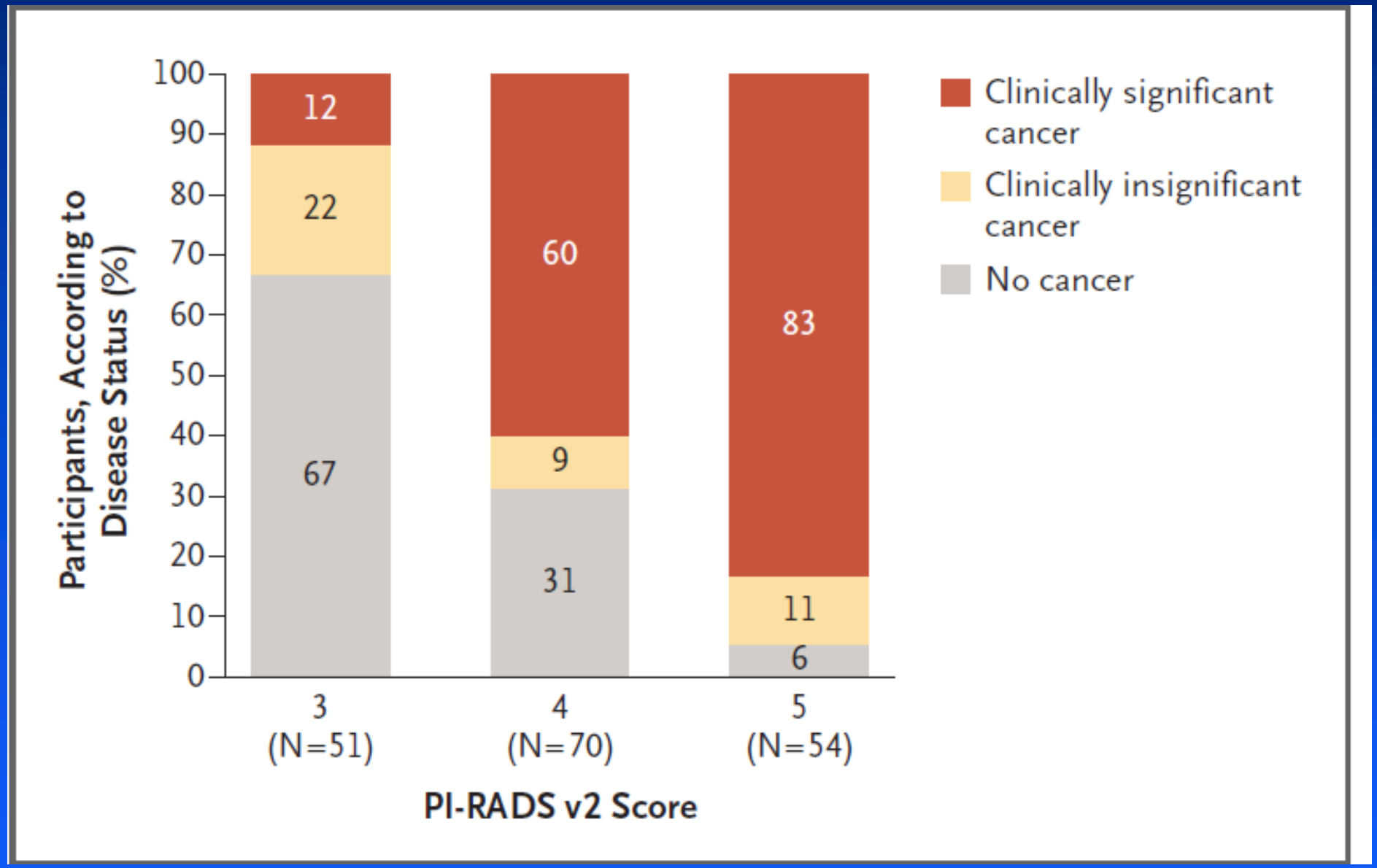
MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus, G. Hellawell, R.G. Hindley, M.J. Roobol, S. Eggener, M. Ghei, A. Villers, F. Bladou, G.M. Villeirs, J. Virdi, S. Boxler, G. Robert, P.B. Singh, W. Venderink, B.A. Hadaschik, A. Ruffion, J.C. Hu, D. Margolis, S. Crouzet, L. Klotz, S.S. Taneja, P. Pinto, I. Gill, C. Allen, F. Giganti, A. Freeman, S. Morris, S. Punwani, N.R. Williams, C. Brew-Graves, J. Deeks, Y. Takwoingi, M. Emberton, and C.M. Moore, for the PRECISION Study Group Collaborators*

This article was published on March 19, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1801993

Outcome	MRI-Targeted Biopsy Group (N = 252)	Standard-Biopsy Group (N = 248)	Difference†	P Value
Clinically significant cancer¶				
Intention-to-treat analysis — no. (%)	95 (38)	64 (26)	12 (4 to 20)	0.005
Modified intention-to-treat analysis — no./total no. (%)	95/245 (39)	64/235 (27)	12 (3 to 20)	0.007
Per-protocol analysis — no./total no. (%)	92/235 (39)	62/227 (27)	12 (3 to 20)	0.007
Clinically insignificant cancer — no. (%)	23 (9)	55 (22)	−13 (−19 to −7)	<0.001
Maximum cancer core length — mm	7.8±4.1	6.5±4.5	1.0 (0.0 to 2.1)	0.053
Core positive for cancer — no./total no. of cores (%)	422/967 (44)	515/2788 (18)	—	—
Men who did not undergo biopsy — no. (%)‖	78 (31)	16 (6)	—	—


Participants, According to Disease Status (%)
100
90
80
70
60
50
40
30
20
10
0
12
22
67
60
9
31
83
11
6
3
(N=51)
4
(N=70)
5
(N=54)
PI-RADS v2 Score
Clinically significant cancer
Clinically insignificant cancer
No cancer

Summary: MRI targeted biopsy results in

- Fewer men needing biopsy
- Fewer biopsy cores per biopsy
- More men with clinically significant cancer detected
- Fewer men with clinically insignificant cancer detected
- More favorable 30-day PRO profile

JAMA Oncology | Original Investigation

A Magnetic Resonance Imaging–Based Prediction Model for Prostate Biopsy Risk Stratification

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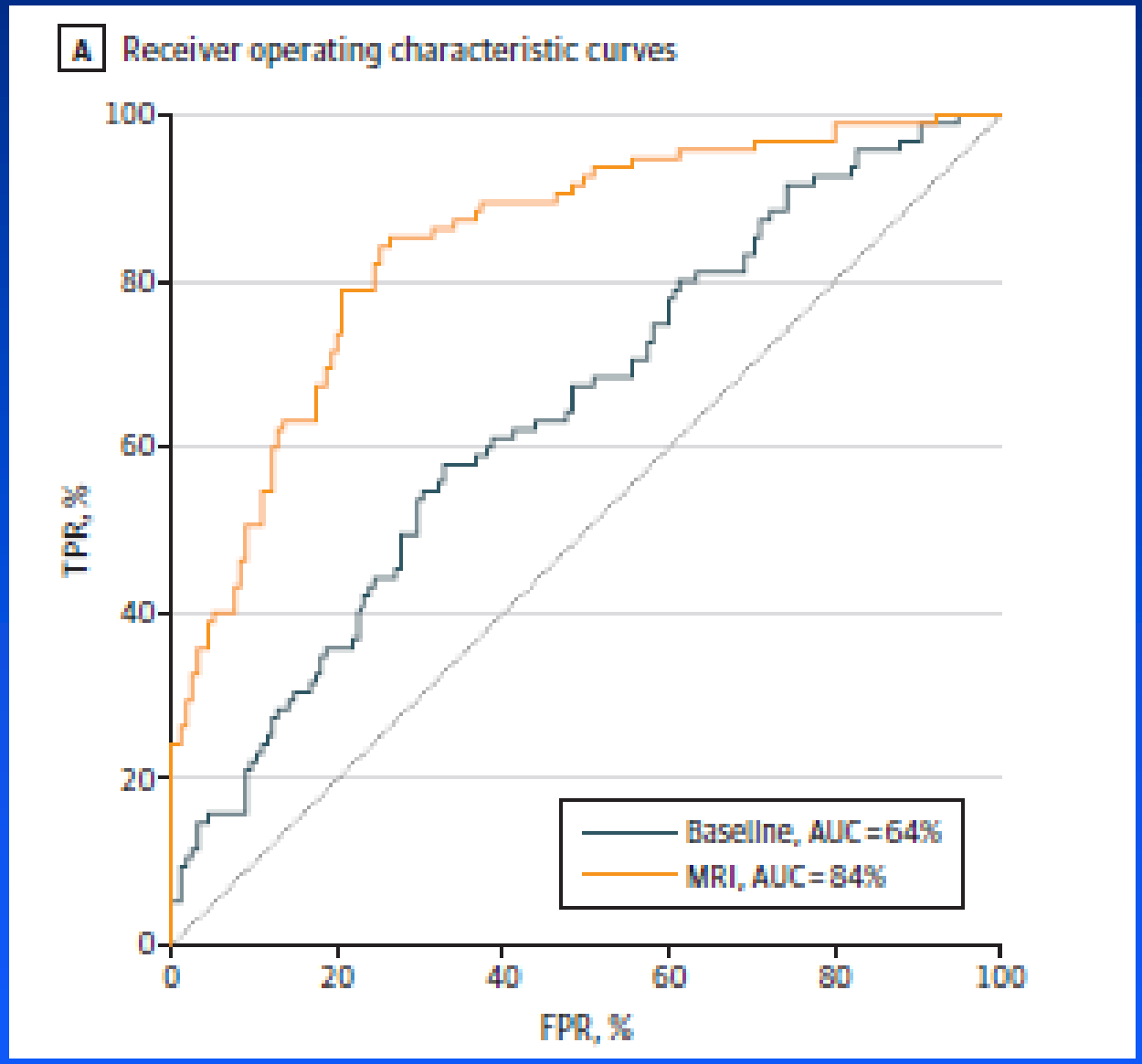
JAMA Oncol. doi:10.1001/jamaoncol.2017.5667
Published online February 22, 2018.


A
Receiver operating characteristic curves
100
80
60
40
20
0
TPR, %
0
20
40
60
80
100
FPR, %
Baseline, AUC = 64%
MRI, AUC = 84%

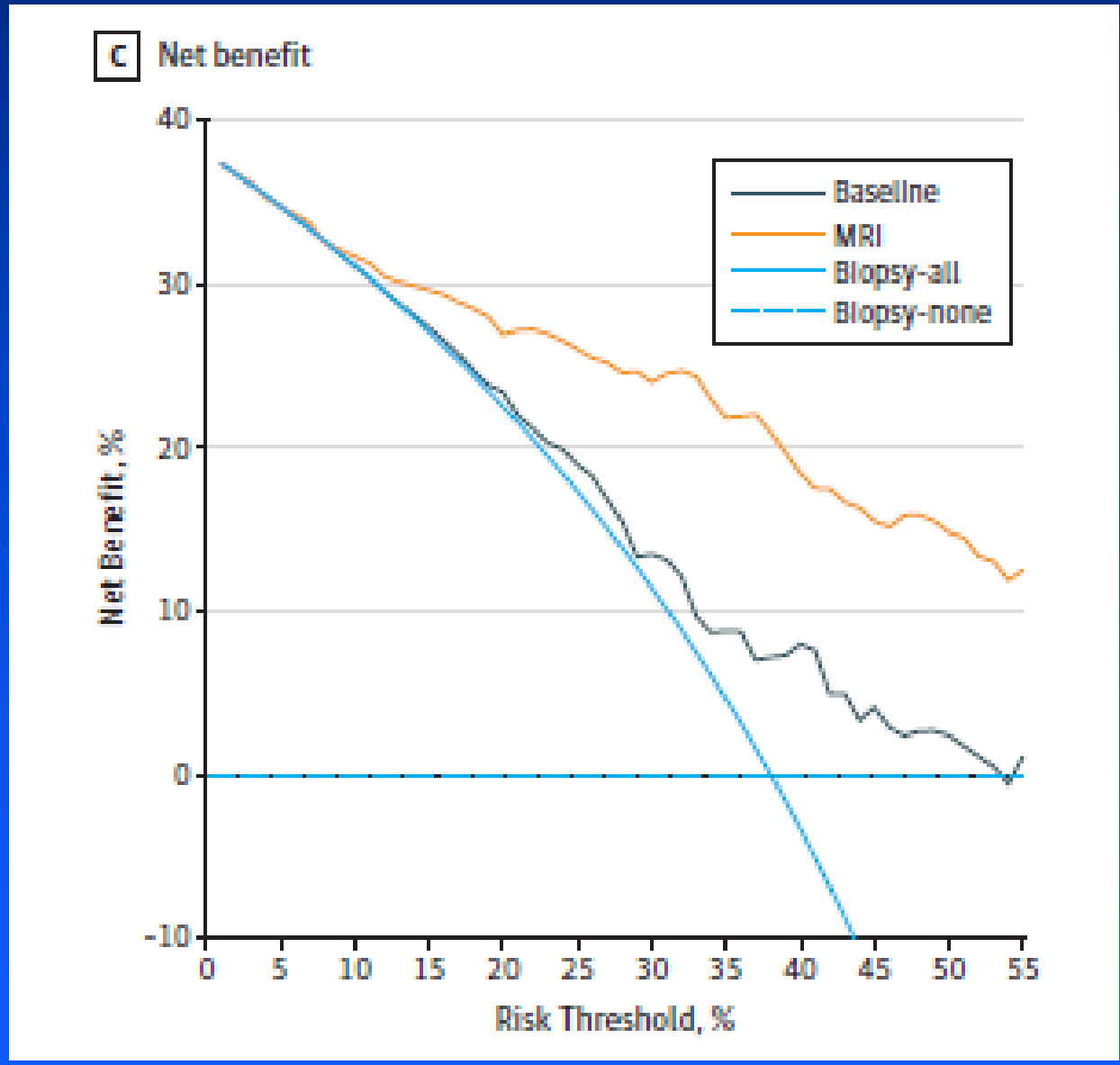

C
Net benefit
40
30
20
10
0
-10
Net Benefit, %
0
5
10
15
20
25
30
35
40
45
50
55
Risk Threshold, %
Baseline
MRI
Biopsy-all
Biopsy-none

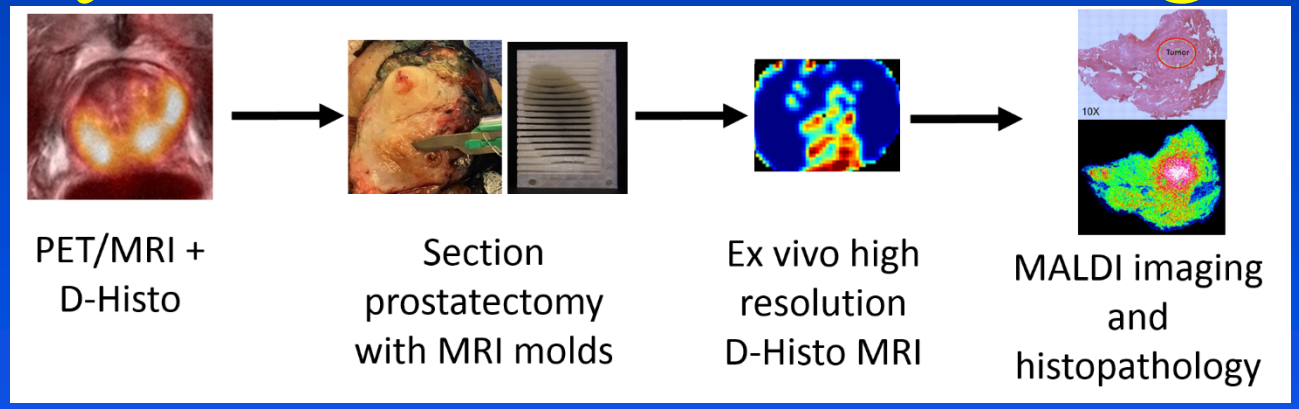
Table 3.1 Summary of radiologist and team accuracy based on various cutoffs for PI-RADS classification and Gleason score

Cutoffs	Radiologist #1	Radiologist #2	Radiologist #3	Radiologist #4	p-value
PIRADS 3+, Gleason 6+	59.4%	75.0%	71.9%	56.3%	0.31
PIRADS 3+, Gleason 7+	62.5%	71.9%	75.0%	46.9%	<0.01
PIRADS 4+, Gleason 6+	62.5%	71.9%	56.3%	59.4%	0.02
PIRADS 4+, Gleason 7+	59.4%	75.0%	65.6%	56.3%	0.41

Table 4.1 Summary of studies examining radiologists' accuracy and variability.
PACS = picture archiving and communication system

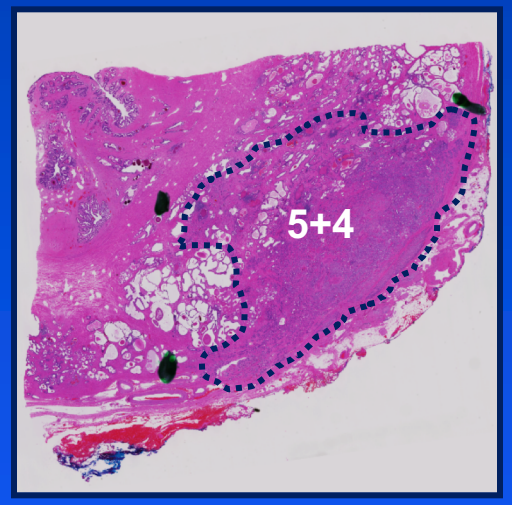
Study	Patients	Radiologists	Image Reviewed	Pathology Reference	Scoring System	Accuracy	kappa
Rosenkrantz et al. [14]	120	6	screen capture	MRI/US fusion biopsy	PIRADS v 2	56%	0.56
Muller et al. [15]	94	5	screen capture	MRI/US fusion biopsy	PIRADS v 2	78%	0.46
Schimmoller et al. [16]	67	3	circled lesion	in-bore MRI biopsy	PIRADS v 1	76%	0.65
Garcia-Reyes et al. [17]	31	5	PACS access	prostatectomy	Gleason 6 vs. 7+	55-74%	
Greer et al. [18]	34	5	PACS access	prostatectomy	PIRADS v 2		0.72
Current study	32	4	PACS access	MRI/US fusion biopsy	PIRADS v 2	66%	0.29

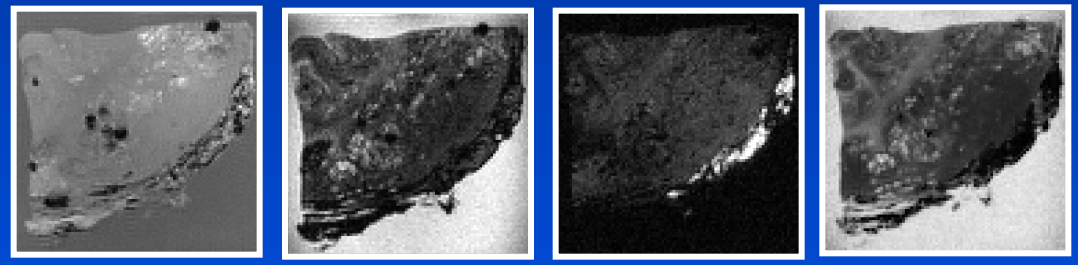
Prostate Cancer Foundation Funded Pilot Project Hybrid MR/MALDI imaging of



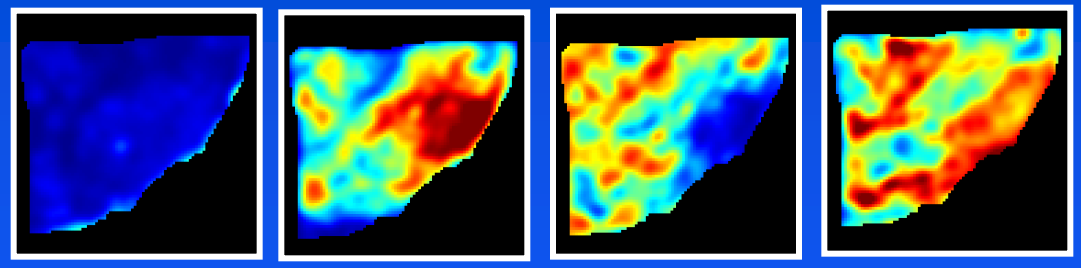
- **10 patients**
- **Gleason 8-10**
- **Preoperative clinical imaging performed**
- **Postoperative D-Histo prostate imaging performed on formalin fixed tissue**
- **Direct histopathologic correlation to imaging**
- **Incorporation of new prognostic markers with MALDI imaging**

Patient #1 C9





T1W | T2W | DWI | DTI - ADC



highly restricted (inflammation) | Restricted (PCa) | Hindered (Benign) | Anisotropic (Stroma)

Summary

- Current TRUS techniques need improvement
  - "Random" transrectal office biopsy should be avoided
  - Transperineal approach effective at finding Ca P and characterizing Gleason score and location
    - Eliminates sepsis as complication
    - Can it be done efficiently in office w local anes?
- MRI targeting improves Bx but is imperfect
  - Misses some cancer
  - Radiologist variation
  - cost
- PET imaging holds promise for primary diagnosis