Should mpMRI be used to Monitor Active Surveillance?

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NATIONAL® CANCER INSTITUTE

23st PCa Symposium
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NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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- NIH research lab and Philips have a CRADA (Cooperative Research and Development Agreement) which resulted in the development of UroNav (MRI - TRUS prostate fusion biopsy system)

NIH Collaboration

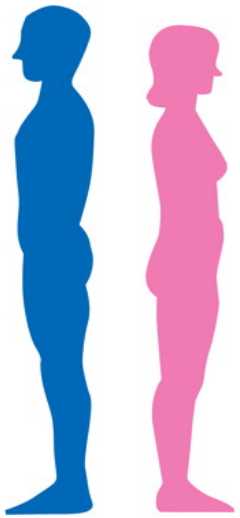
- **Molecular Imaging**
  - Peter Choyke, M.D.
  - Baris Turkbey, M.D.
  - Marcelino Bernado, Ph.D.
  - Tom Pohida, Ph.D.
- **Pathology**
  - Maria Merino, M.D.
- **Interventional Radiology**
  - Bradford Wood, M.D.
  - Jochen Krueker, Ph.D.
  - Pingkun Yan, Ph.D.
  - Sheng Xu, Ph.D.
- **Biometric Research Branch**
  - Richard Simon, D.Sc.

NIH Collaboration

- **Urologic Oncology Branch**
  - W. Marston Linehan, M.D.
  - Ram Srinivasan, M.D., Ph.D.
  - Piyush Agarawal, M.D.
- **Medical Oncology Branch**
  - Bill Dahut, M.D.
  - James Gulley, M.D., Ph.D.
  - Ravi Madan, M.D.
  - Anna Couvillon, CRNP
- **Radiation Oncology**
  - Deborah Citrin, M.D.
  - Aradhana Kaushal, M.D.
  - James Mitchell, Ph.D.
  - Murali Krishna Cherukuri, Ph.D.

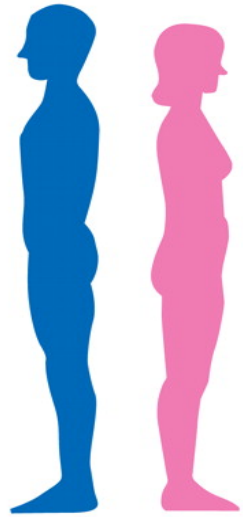
Estimated New Cases*

Males				Females		
Prostate	217,730	28%		Breast	207,090	28%
Lung & bronchus	116,750	15%		Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%		Colon & rectum	70,480	10%
Urinary bladder	52,760	7%		Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%		Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%		Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%		Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%		Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%		Ovary	21,880	3%
Pancreas	21,370	3%		Pancreas	21,770	3%
All Sites	**789,620**	**100%**		**All Sites**	**739,940**	**100%**



Estimated Deaths

Males				Females		
Lung & bronchus	86,220	29%		Lung & bronchus	71,080	26%
Prostate	32,050	11%		Breast	39,840	15%
Colon & rectum	26,580	9%		Colon & rectum	24,790	9%
Pancreas	18,770	6%		Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%		Ovary	13,850	5%
Leukemia	12,660	4%		Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%		Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%		Uterine Corpus	7,950	3%
Urinary bladder	10,410	3%		Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%		Brain & other nervous system	5,720	2%
All Sites	**299,200**	**100%**		**All Sites**	**270,290**	**100%**



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 19, 2012 VOL. 367 NO. 3

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

Compared to observation, prostatectomy did not significantly improve overall or cancer specific survival over a 12 year period (PSA era) in localized **low risk** prostate cancer.. **ACTIVE SURVEILLANCE ?**

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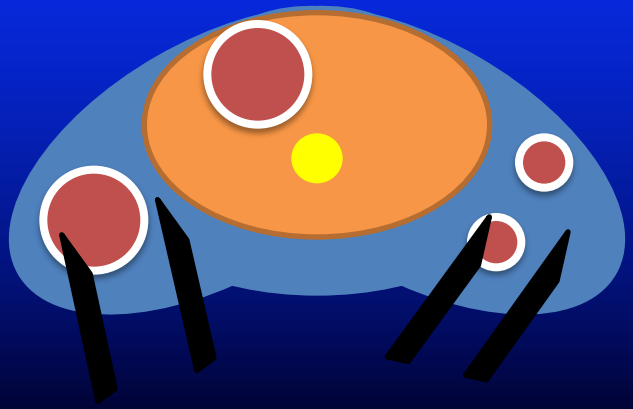
Urology has a detection and treatment selection problem, MRI can help men enroll and stay on active surveillance.

Current Method to Screen and Detect Prostate Cancer

- PSA leads to a systematic 12 core prostate biopsy blind to the tumor(s) location
  - Prostate cancer is the only solid-organ tumor diagnosed without image guidance in the hopes of accidentally “hitting” the tumor
  - Often miss the lethal tumors and over detect clinically insignificant cancer



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European Association of Urology

Platinum Priority – Collaborative Review – Prostate Cancer

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

Active Surveillance for Prostate Cancer: A Systematic Review of the Literature

Marc A. Dall'Era [a,], Peter C. Albertsen [b], Christopher Bangma [c], Peter R. Carroll [d], H. Ballentine Carter [e], Matthew R. Cooperberg [d], Stephen J. Freedland [f,g], Laurence H. Klotz [h], Christopher Parker [i], Mark S. Soloway [j]*

Active Surveillance for Prostate Cancer: A Systematic Review of the Literature

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Table 1 – Inclusion criteria for active surveillance by institution*

Institution	Clinical stage	PSA	Gleason grade	Total positive cores	Single core positivity	Other
Johns Hopkins [7,8]	≤T2a	–	≤3 + 3	≤2	≤50%	PSA DT ≤0.15
University of Toronto [9]	NS	≤10	≤3 + 3*	NR	NR	–
UCSF [10]	≤T2a	≤10	≤3 + 3	≤33%	≤50%	–
ERSPC (PRIAS criteria) [11]	≤T2a	≤10	≤3 + 3	≤2	NR	PSA DT ≤0.2
Royal Marsden Hospital [12]	≤T2a	≤15	≤3 + 4	≤50%	NR	–
MSKCC [13]	≤T2a	≤10	≤3 + 3	≤3	≤50%	–
University of Miami [14,15]	≤T2a	≤10	≤3 + 3	≤2	≤20%	–

PSA = prostate-specific antigen; PSA DT = prostate-specific antigen doubling time; NS = not stated; NR = not recorded; UCSF = University of California, San Francisco; MSKCC = Memorial Sloan-Kettering Cancer Center.

* Prior to 2000, men >70 yr of age with a PSA ≤15 and Gleason score ≤3 + 4 were included.

Active Surveillance for Prostate Cancer: A Systematic Review of the Literature

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Table 2 – Summarized key findings from the largest published series within the past 2 yr

Institution	Yr	Age, median	*n*	Follow-up, yr, median	No. treated (%)	Time to treatment, median	Primary trigger for treatment	Treated at 2 yr, %	PCSM, %	ACM, %
Johns Hopkins [8]	2011	66	769	2.7	255 (33)	2.2	Histology	19	0	2
University of Toronto* [9]	2010	70.3	450	6.8	135 (30)	NR	PSA	16	1	21.4
UCSF [24]	2011	61.9	649	3.9	113 (30)**	3.5	Histology	–	0	3
ERSPC* [25]	2009	66	988	3.9	197 (32)	2.6	NR	22	0.2	11.2
Royal Marsden Hospital* [12]	2008	67	326	1.8	65 (20)	1.3	PSA	NR	0	2
MSKCC [13,26]	2011	62	238	1.8***	25 (11)	NR	Histology	NR	NR	NR
University of Miami [15,27]	2011	64	272	2.9	67 (25)	2.6	Histology	NR	0	2

PCSM = prostate cancer–specific mortality; ACM = all-cause mortality; NR = not recorded; PSA = prostate-specific antigen; UCSF = University of California, San Francisco; ERSPC = European Randomized Study of Screening for Prostate Cancer; MSKCC = Memorial Sloan-Kettering Cancer Center.

* Studies with some men having Gleason >3 + 3 disease.

** Percentage treated is of 337 men meeting strict inclusion criteria.

*** Median follow-up for patients without progression.

VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort With Localized Prostate Cancer

Laurence Klotz, Liying Zhang, Adam Lam, Robert Nam, Alexandre Mamedov, and Andrew Loblaw

- Published 2010
- 450 men
- Median f/u 6.8 yrs (1 to 13 yrs)
- Overall survival 78.6%
- 10 yr actuarial PCa survival 97.2%

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer

Laurence Klotz, Danny Vesprini, Perakaa Sethukavalan, Vibhuti Jethava, Liying Zhang, Suneil Jain, Toshihiro Yamamoto, Alexandre Mamedov, and Andrew Loblaw

- Published 2015
- 993 men
- Median f/u 6.4 yrs (0.2 to 19.8 yrs)
- # of deaths due to PCa was 15
- 10 yr actuarial PCa survival 98.1%
- 15 yr actuarial PCa survival 94.3%

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

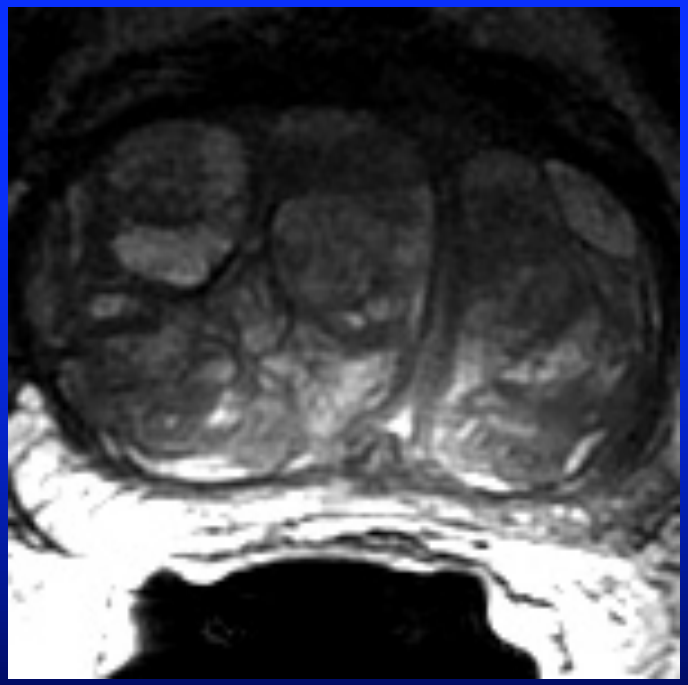
How much better can MRI or any other biomarker make this and at what economic cost ??

- 993 men
- Median f/u 6.4 yrs (0.2 to 19.8 yrs)
- # of deaths due to PCa was 15
- 10 yr actuarial PCa survival 98.1%
- 15 yr actuarial PCa survival 94.3%

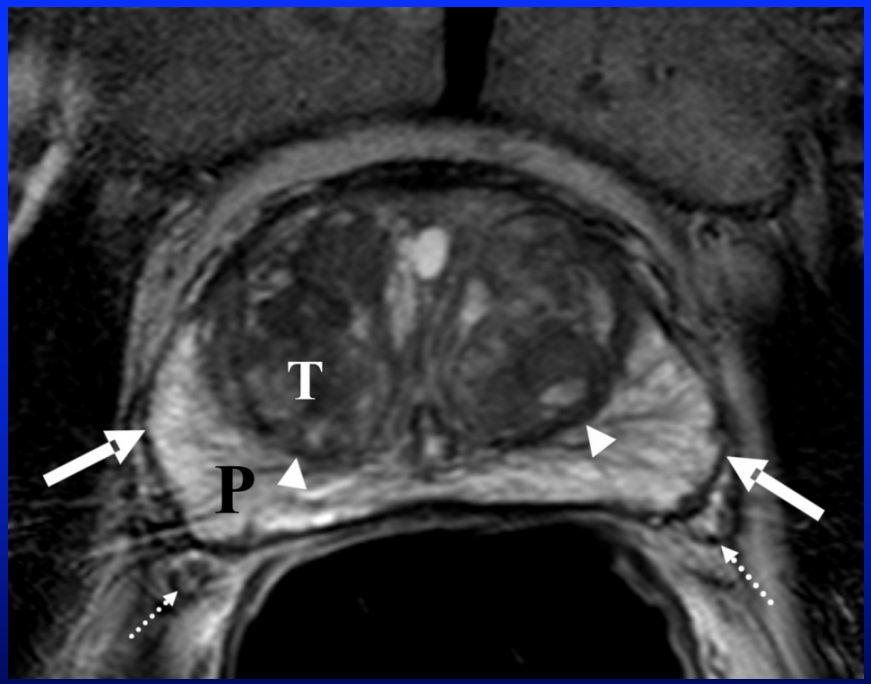
MRI of the Prostate

- High resolution imaging of the prostate

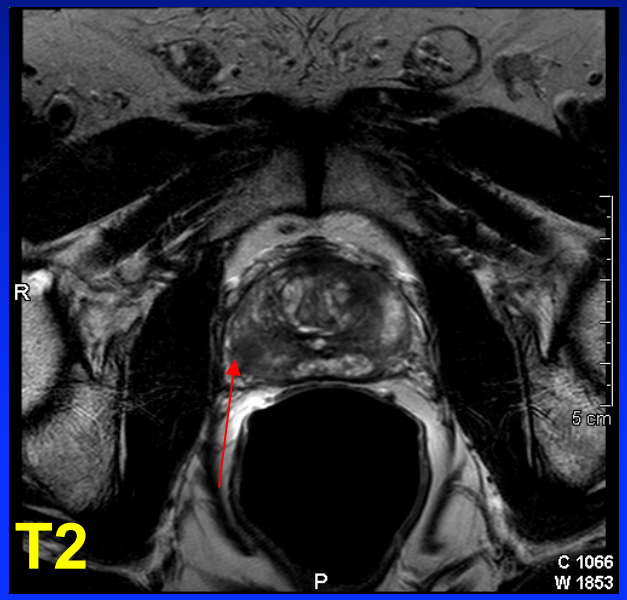
- **Bad** Technique

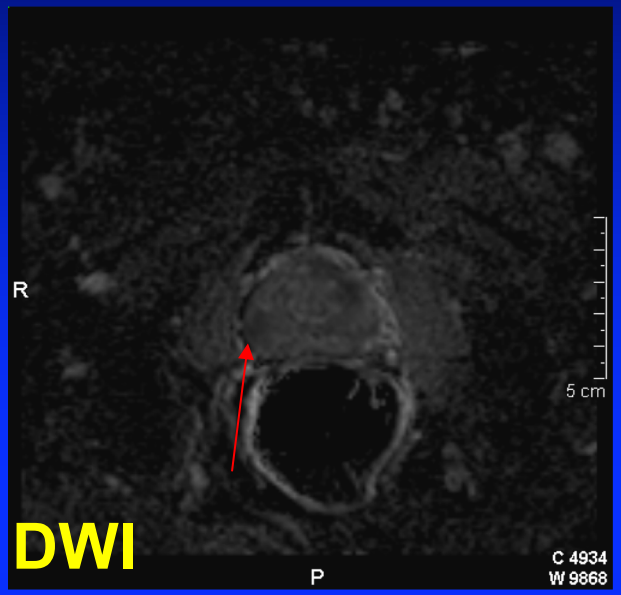


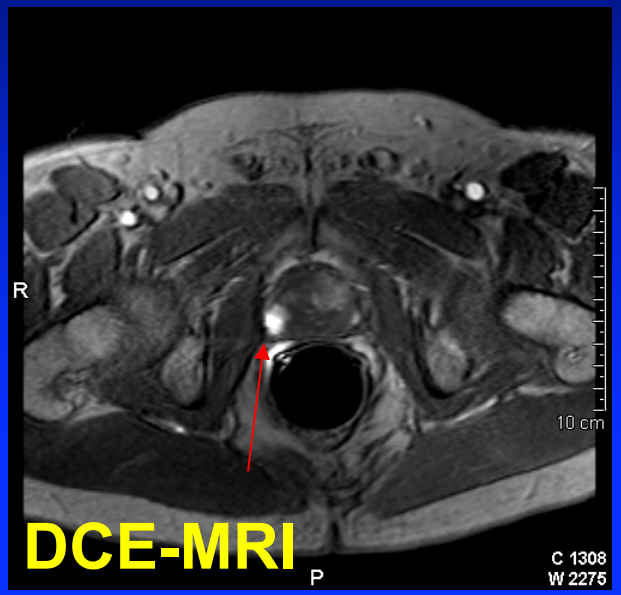
- **Good** Technique



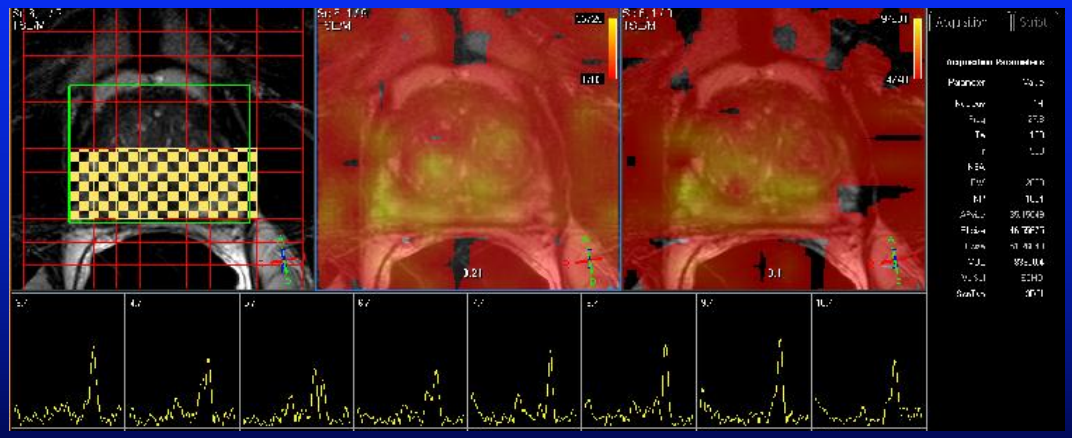
Multi-parametric 3Tesla endorectal MR Imaging of the prostate



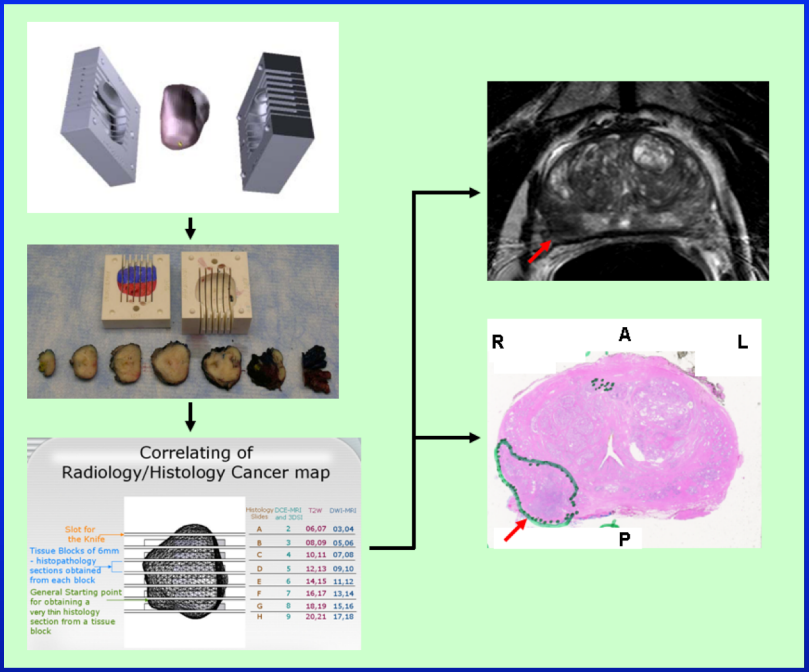




Spectroscopy



MRI Prostate Cancer Correlation with Patient Specific Histopathological Specimen Molds



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MRI-TRUS Fusion Tumor Targeting

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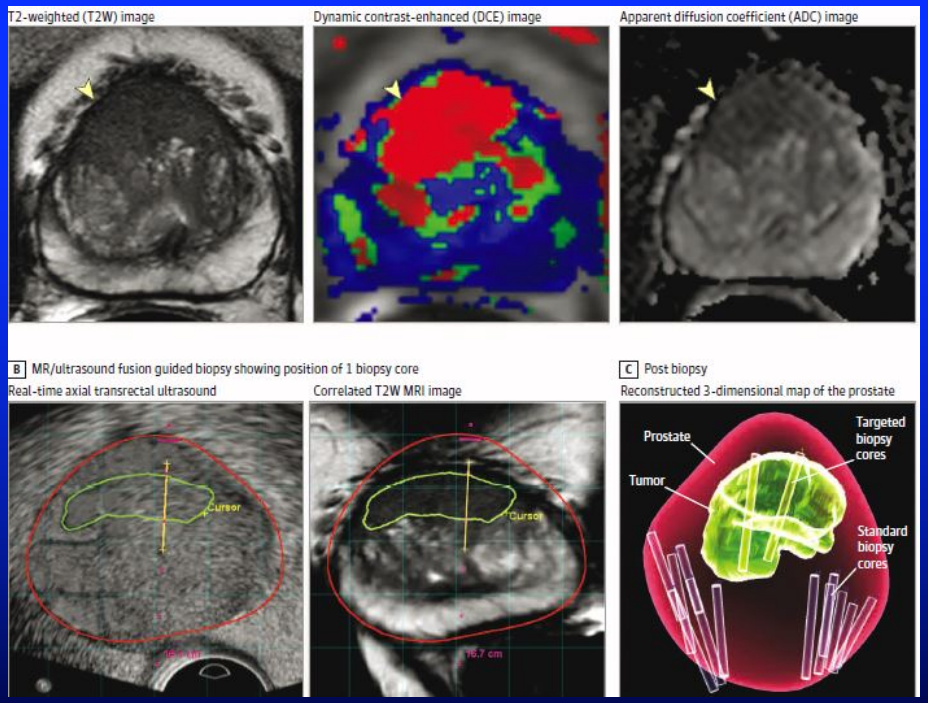


Original Investigation

Comparison of MR/Ultrasound Fusion–Guided Biopsy With Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer

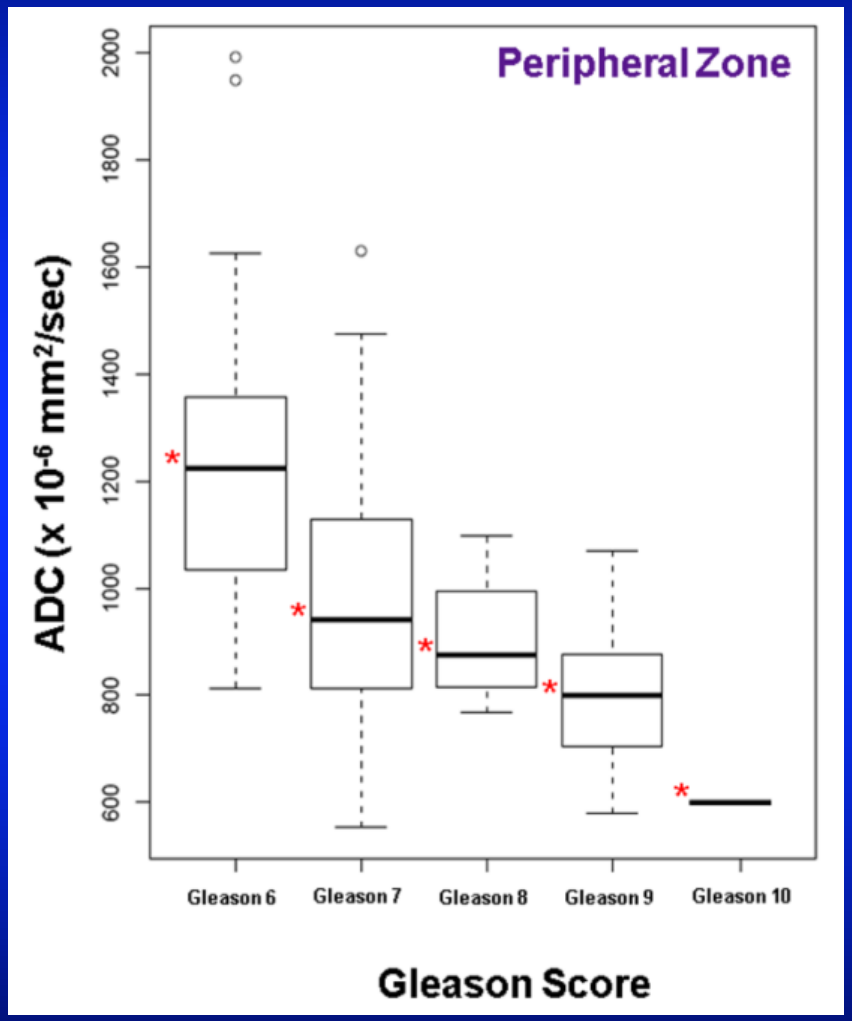
M. Minhaj Siddiqui, MD; Soroush Rais-Bahrami, MD; Baris Turkbey, MD; Arvin K. George, MD; Jason Rothwax, Nabeel Shakir, BS; Chinonyerem Okoro, BS; Dima Raskolnikov, BS; Howard L. Parnes, MD; W. Marston Linehan, MD; Maria J. Merino, MD; Richard M. Simon, DSc; Peter L. Choyke, MD; Bradford J. Wood, MD; Peter A. Pinto, MD

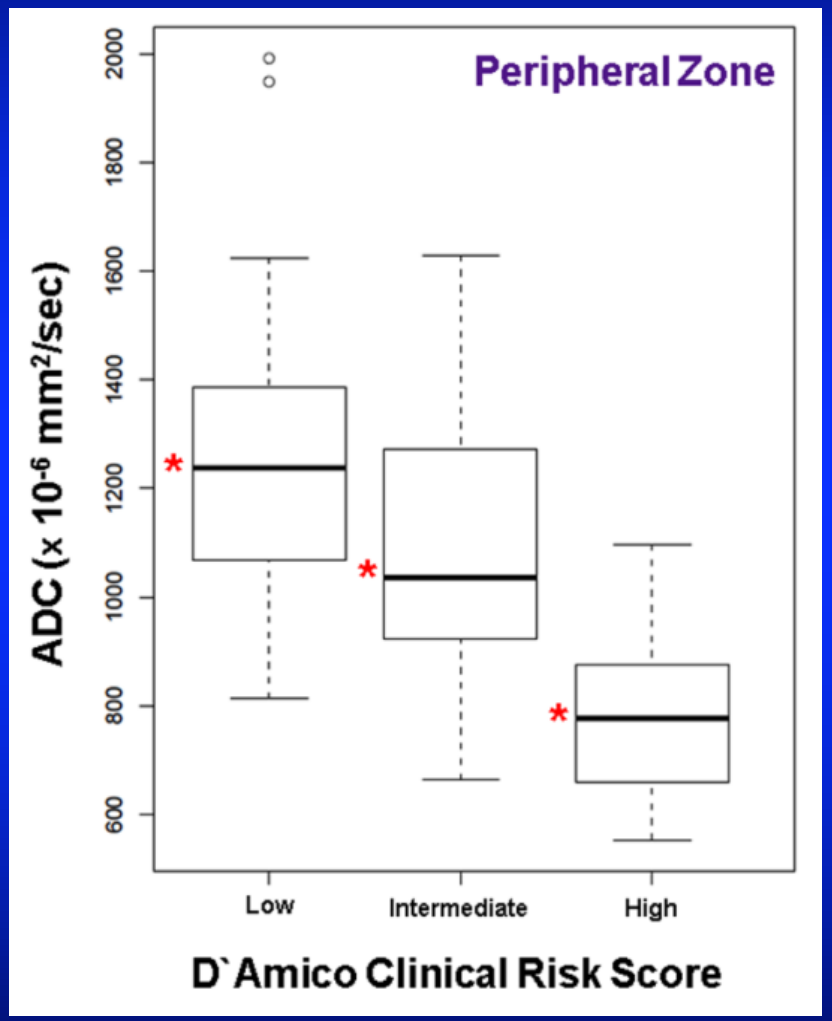
JAMA®
The Journal of the American Medical Association

- MRI / TRUS targeted biopsy diagnosed 30% more high risk cancer (GI score $\geq$ 4+3) than standard TRUS biopsy and 17% fewer low risk cancer
- MRI / TRUS targeted biopsy better predicted whole-gland pathology after prostatectomy than standard TRUS biopsy

JAMA 313: 2015

DWI-ADC Maps Correlates with Tumor Grade





Turkbey B, et al. Radiology 2011

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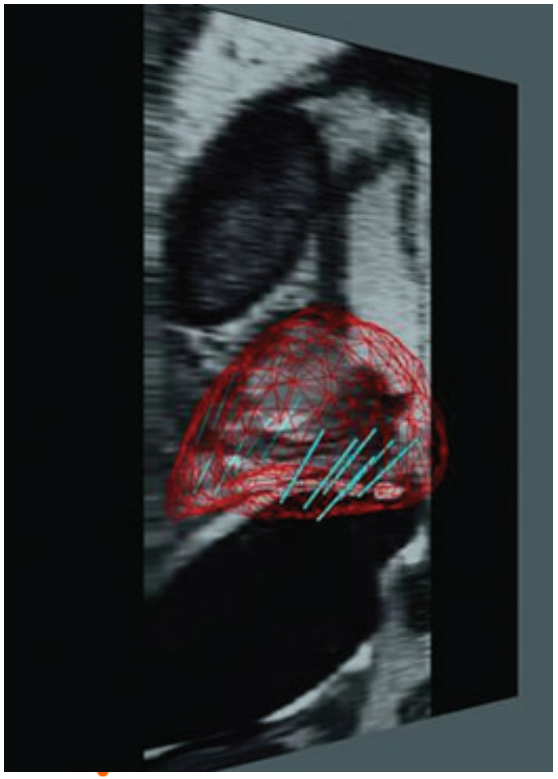
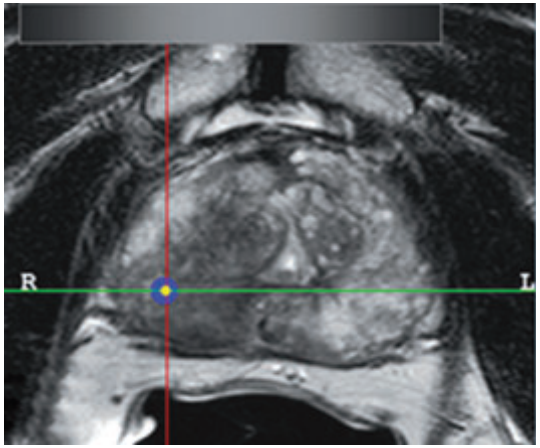
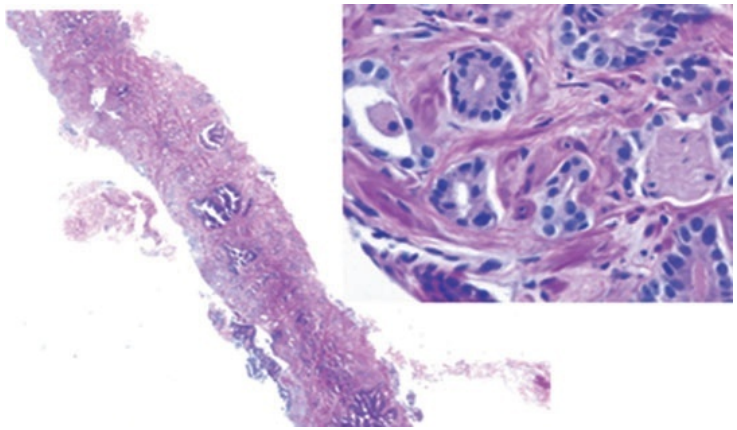
Documenting the location of prostate biopsies with image fusion

Baris Turkbey*, Sheng Xu†, Jochen Kruecker†, Julia Locklin‡, Yuxi Pang§, Marcelino Bernardo*,¶, Maria J. Merino††, Bradford J. Wood‡, Peter L. Choyke* and Peter A. Pinto‡‡

**Molecular Imaging Program, ††Laboratory of Pathology, and ‡‡Urologic Oncology Branch, NCI, NIH, ‡Center for Interventional Oncology, NCI and Radiology and Imaging Sciences, Clinical Center, NIH, Bethesda, MD, †Philips Research North America, Briarcliff Manor, NY, §Philips Healthcare, Cleveland, OH, and ¶SAIC-Frederick, NCI-Frederick, Frederick, MD, USA*







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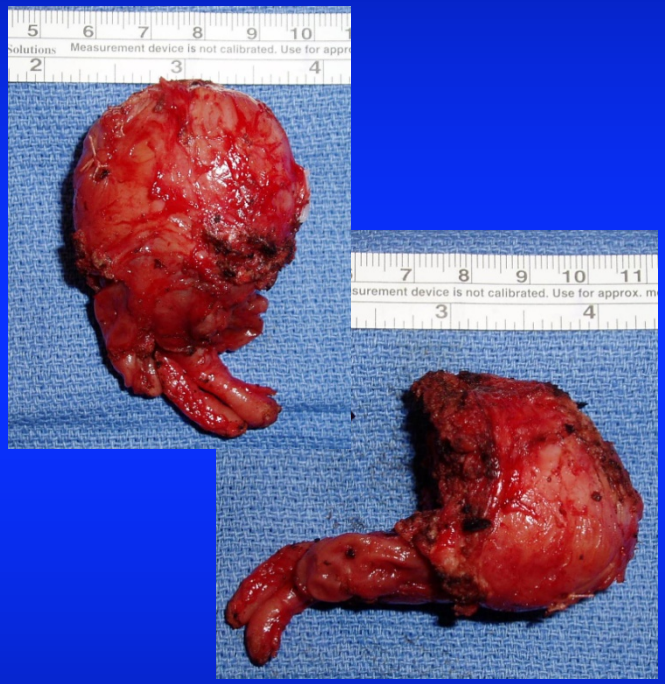
Treatment Methods for Localized Prostate Cancer in MRI era

- Surgery
  - Retropubic Prostatectomy
  - Perineal Prostatectomy
  - Laparoscopic Prostatectomy
  - Robotic Assisted Prostatectomy
- Radiation Therapy
  - External Beam
  - Proton Beam
  - Interstitial Seed Implantation
- Ablation: Whole Gland or Focal
  - Cryo, HIFU, Laser, PDT, IRE, …..
- **Active Surveillance**



Prostate Cancer Treatment

- Radical treatment (surgery or radiation)
  - Results in known harms that may not outweigh the potential benefit
- Concern is overtreatment
- Patients and physicians seeking less morbid treatment modalities today such as active surveillance
- Fear is standard TRUS biopsy underestimates tumor volume and grade for AS patients

Active Surveillance

- Established treatment option for low grade low volume prostate cancer
- How can MRI help ?
  - Detect higher grade or volume tumors who would be theoretically disadvantaged if put on AS
  - Allow ***patients*** to feel more comfortable with AS
  - Allow ***urologists*** to feel more comfortable with AS
  - Use MRI to decrease the frequency of biopsies

Does Multiparametric MRI and Subsequent MRI – TRUS Fusion Guided Biopsy Allow Urologists to Improve How They Enroll and Monitor Active Surveillance Patients than TRUS Alone ?

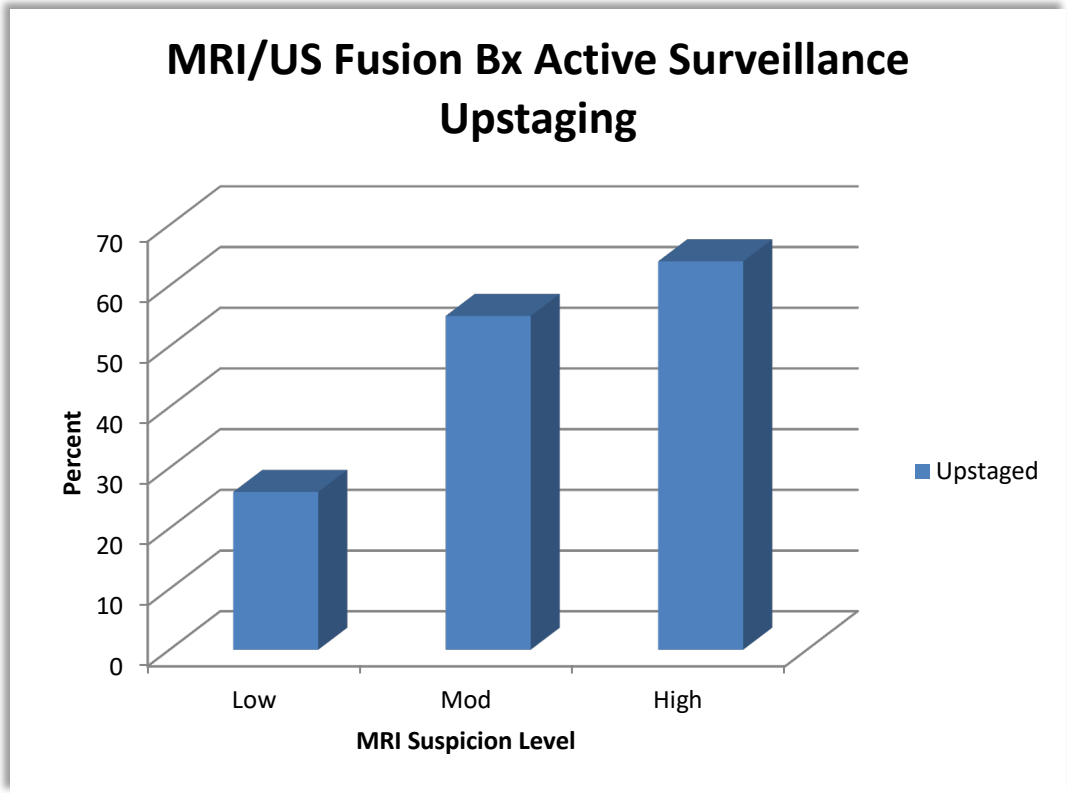
Active Surveillance Inclusion Criteria

Institution	Inclusion Critera	NCI Pt. Cohort Met Criteria
Johns Hopkins	Gleason ≤ 6; PSAD ≤ 0.15; cT 1; ≤ 2 cores +; ≤ 50% any core	74

Pt. Demographics	
N	74
Mean Age	60.5
Race	
White	63
African American	11
Clinical Stage	
T1c	74
Mean PSA	4.79
Mean PSA Density	0.09
Mean MRI Volume	52

NCI Results

- MRI/US fusion bx was median 8 mo from initial OSH Bx
- 41% of patients re-staged & no longer AS candidates based on grade/volume
- Risk of staging out of AS increases based on MRI suspicion level
- *But are we helping our hurting patients?*



NIH mpMRI followed by MRI-TRUS Fusion Targeted Prostate Biopsy Active Surveillance Trial

Primary Objective:
Detect Progression in Men on Active Surveillance for Low and Intermediate Risk Prostate Cancer

AS Criteria Definitions

AS Criteria	Clinical Stage	PSA	Gleason grade	Total Positive cores	Single core positivity	PSA DT
NIH Low risk	≤T2a	-	≤3+3	-	-	-
NIH Expanded	≤T2a	-	≤3+4	-	-	-
Epstein	≤T1c	-	≤3+3	≤2	≤50%	≤0.15
Toronto	-	≤10	≤3+3	-	-	-
PRIAS	≤T2a	≤10	≤3+3	≤2	-	≤0.2
Royal Marsden	≤T2a	≤15	≤3+4	≤50%	-	-

Baseline Patient Characteristics

	Low Risk	Intermediate Risk	P value
N	128	38	
Mean Age, years (SD)	61.7 (6.6)	65.7 (6.7)	0.0013
Mean PSA, ng/ml (SD)	5.69 (4.19)	6.16 (3.54)	0.53
Mean PSAD, ng/ml/g (SD)	0.12 (0.09)	0.13 (0.08)	0.67
Mean # MRI lesions (SD)	2.6 (1.3)	2.7 (1.4)	0.85
MRI Suspicion Score, N (%)			0.013
Low	36 (28.1)	4 (10.5)	
Moderate	86 (67.2)	33 (86.8)	
High	6 (0.05)	1 (0.03)	
Number of Cores with Gleason 7, N (%)			
1	N/A	26 (68)	
2	N/A	7 (18)	
3	N/A	2 (7)	
4	N/A	3 (8)	

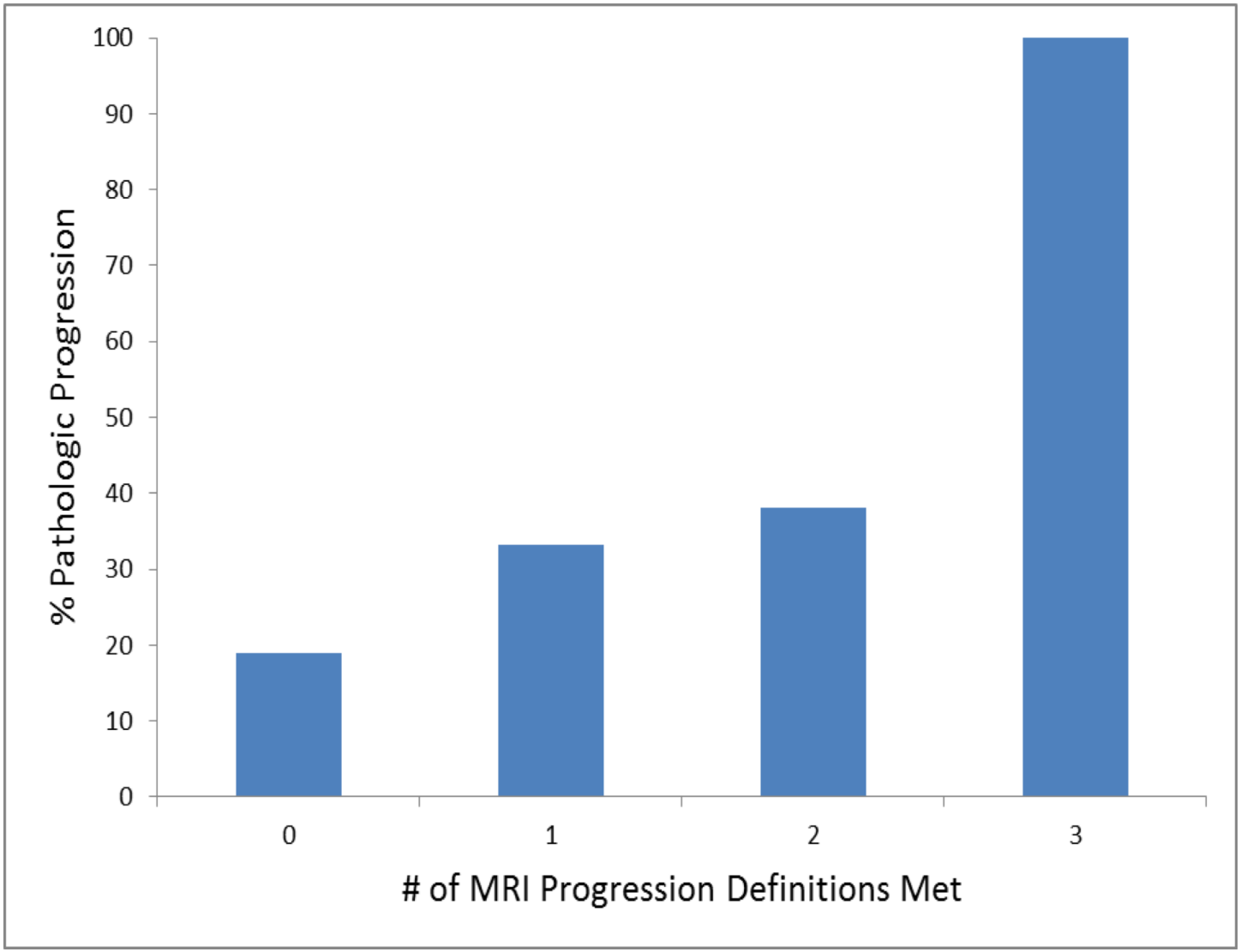
Risk of Pathologic Progression

	LR	IR
Number to Progress, N (%)	**37 (29.0)**	**12 (31.5)**
Progress by Systematic Bx Alone (%)	**12 (32.4)**	**3 (25)**
Progress by Target Bx Alone (%)	**14 (37.8)**	**8 (66.7)**
Progress by Both Target and Systematic (%)	**11 (29.7)**	**1 (8)**
Mean time to progression, years (SD)	**2.7 (1.8)**	**1.8 (1.1)**

Comparison to other AS criteria

	N (% of entire cohort)	N (%) progressed
NIH Low-risk cohort	**128 (77)**	**37 (29.1)**
NIH Expanded cohort	**166 (100)**	**49 (29.5)**
Epstein	**88 (69)**	**25 (28.4)**
Toronto	**111 (87)**	**33 (29.7)**
PRIAS	**95 (75)**	**26 (27.3)**
CAPRA low risk	**121 (73)**	**34 (28)**
Royal Marsden	**150 (90)**	**46 (27.7)**

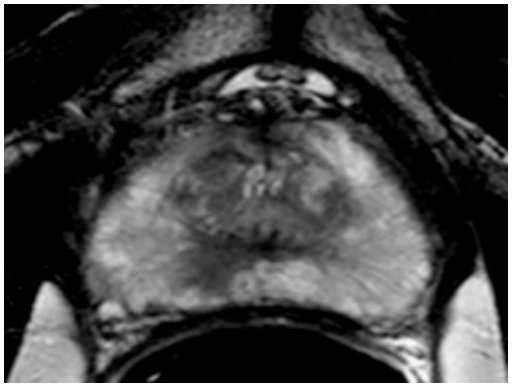
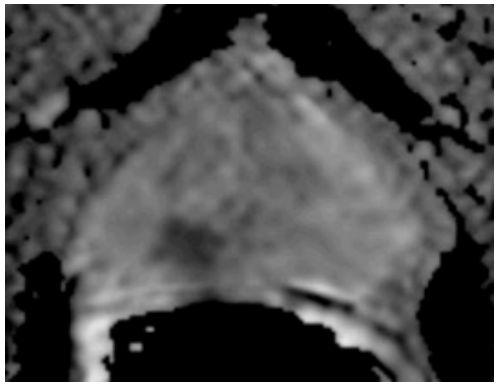
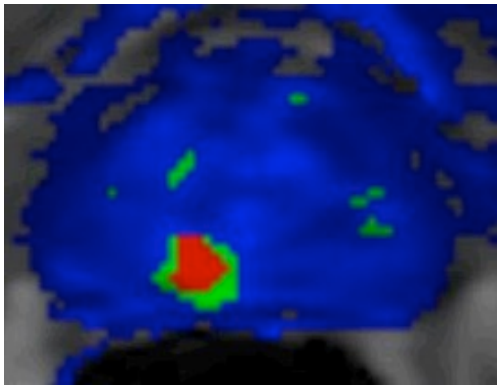
Risk of pathologic progression increases with increasing MRI progression



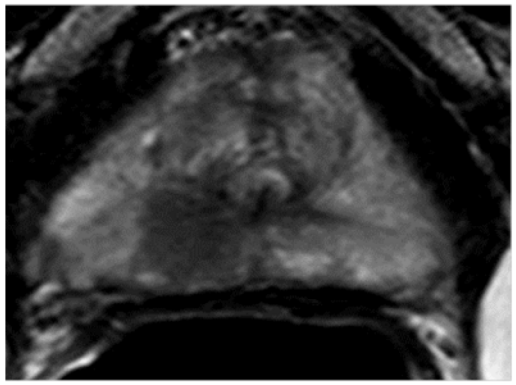
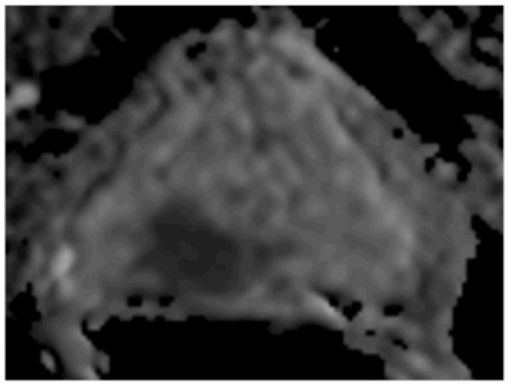
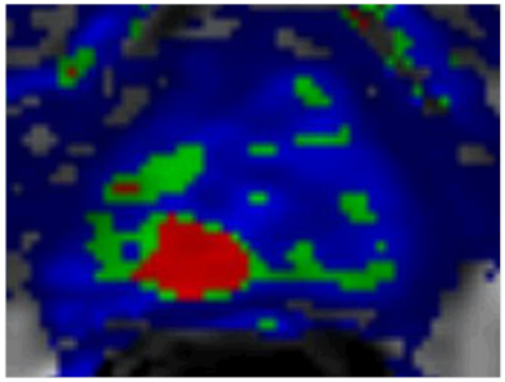
Predictors of pathologic progression

Variable	No Progression	Progression	Univariate P value	Multivariate P value
MRI progression (N)	69	38	0.013	0.04
PSAD progression ≥0.15	11	6	0.58	-
PSA Doubling Time <2 years	11	6	0.59	-
PSA Velocity >2ng/ml/yr	12	8	0.29	-
Initial PSA (ng/ml, mean)	5.95	5.48	0.50	-
Initial PSAD (ng/ml/g, mean)	0.122	0.120	0.91	-
Age (years, mean)	62.1	64.1	0.07	0.22
Highest % core >50%	10	8	0.34	-
Positive biopsy cores >33%	26	19	0.16	0.34

61 y.o. PSA 3.04 Gleason 3+4=7 from 2 MRI-TRUS fusion cores, all systematic biopsies were negative. Enrolled on NIH AS trial.

18 month later PSA 3.28 but the MRI showed progression. Targeted biopsy revealed Gleason 4+4=8. RARP demonstrated Gleason 4+4=8 organ confined with negative margins.

Summary

- mpMRI can help select the best patient for active surveillance
- mpMRI can help the patient and urologist feel more comfortable undergoing active surveillance
- mpMRI can predict progression on active surveillance
- BUT will this technology and additional cost really be necessary ??

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For a copy of the slides from this talk email

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Ask for “MRI Active Surveillance” Talk