Focal Therapy for Prostate Cancer

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Disclosures

- None

Objectives

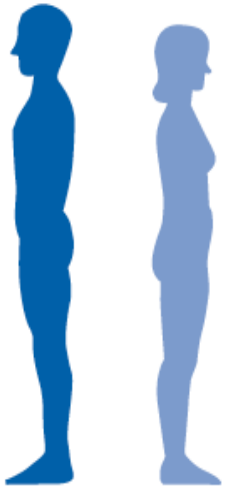
- Introduction
- Rationale for Focal Therapy in Prostate Cancer
- Multiparametric MRI of Prostate
- Image guided focal/partial gland therapy
- Conclusion

Introduction

Prostate Cancer Incidence and mortality

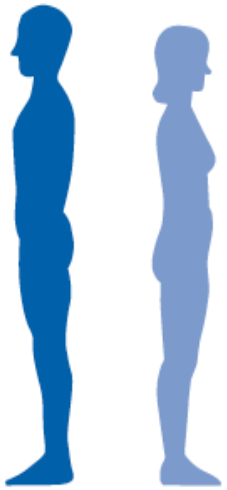
Estimated New Cases

Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All sites	**856,370**	**100%**	**All sites**	**878,980**	**100%**



Estimated Deaths

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	**323,630**	**100%**	**All sites**	**286,010**	**100%**



Probability of developing invasive cancer

		Birth to 49	50 to 59	60 to 69	70 and older	Birth to death
All sites†	Male	3.4 (1 in 30)	6.1 (1 in 16)	13.4 (1 in 7)	32.2 (1 in 3)	39.7 (1 in 3)
	Female	5.5 (1 in 18)	6.1 (1 in 16)	9.9 (1 in 10)	26.0 (1 in 4)	37.6 (1 in 3)
Breast	Female	1.9 (1 in 52)	2.3 (1 in 43)	3.4 (1 in 29)	6.8 (1 in 15)	12.4 (1 in 8)
Colon & rectum	Male	0.3 (1 in 287)	0.7 (1 in 145)	1.2 (1 in 85)	3.4 (1 in 29)	4.5 (1 in 22)
	Female	0.3 (1 in 306)	0.5 (1 in 194)	0.8 (1 in 122)	3.1 (1 in 32)	4.2 (1 in 24)
Kidney & renal pelvis	Male	0.2 (1 in 456)	0.4 (1 in 284)	0.6 (1 in 155)	1.3 (1 in 74)	2.1 (1 in 48)
	Female	0.1 (1 in 706)	0.2 (1 in 579)	0.3 (1 in 320)	0.7 (1 in 136)	1.2 (1 in 83)
Leukemia	Male	0.2 (1 in 400)	0.2 (1 in 573)	0.4 (1 in 260)	1.4 (1 in 71)	1.8 (1 in 56)
	Female	0.2 (1 in 515)	0.1 (1 in 887)	0.2 (1 in 446)	0.9 (1 in 111)	1.3 (1 in 80)
Lung & bronchus	Male	0.1 (1 in 682)	0.7 (1 in 154)	1.9 (1 in 54)	6.1 (1 in 16)	6.9 (1 in 15)
	Female	0.2 (1 in 635)	0.6 (1 in 178)	1.4 (1 in 70)	4.8 (1 in 21)	5.9 (1 in 17)
Melanoma of the skin‡	Male	0.5 (1 in 218)	0.5 (1 in 191)	0.9 (1 in 106)	2.6 (1 in 38)	3.6 (1 in 27)
	Female	0.7 (1 in 152)	0.4 (1 in 254)	0.5 (1 in 202)	1.1 (1 in 91)	2.4 (1 in 42)
Non-Hodgkin lymphoma	Male	0.3 (1 in 382)	0.3 (1 in 349)	0.6 (1 in 174)	1.8 (1 in 54)	2.4 (1 in 42)
	Female	0.2 (1 in 545)	0.2 (1 in 480)	0.4 (1 in 248)	1.3 (1 in 74)	1.9 (1 in 54)
Prostate	Male	0.2 (1 in 403)	1.7 (1 in 58)	4.8 (1 in 21)	8.2 (1 in 12)	11.6 (1 in 9)
Thyroid	Male	0.2 (1 in 517)	0.1 (1 in 791)	0.2 (1 in 606)	0.2 (1 in 425)	0.6 (1 in 160)
	Female	0.8 (1 in 124)	0.4 (1 in 271)	0.3 (1 in 289)	0.4 (1 in 256)	1.8 (1 in 56)
Uterine cervix	Female	0.3 (1 in 368)	0.1 (1 in 845)	0.1 (1 in 942)	0.2 (1 in 605)	0.6 (1 in 162)
Uterine corpus	Female	0.3 (1 in 342)	0.6 (1 in 166)	1.0 (1 in 103)	1.3 (1 in 75)	2.8 (1 in 35)

Introduction

- >30 % of new diagnosis are low risk
- Majority of patients receive definitive therapy
  - Treatment related morbidity

Focal therapy for prostate cancer

- Focal therapy:
  - treatment that aims to eradicate known cancer within the prostate and at the same time preserve uninvolved prostatic tissue with the aim of preserving genitourinary function.
- Male “lumpectomy” that adequately treats disease and maintains QoL.
- Hypothesis: tissue preservation = functional preservation.

Predicting 15-Year Prostate Cancer Specific Mortality After Radical Prostatectomy

Scott E. Eggener,* Peter T. Scardino, Patrick C. Walsh, Misop Han, Alan W. Partin, Bruce J. Trock, Zhaoyong Feng, David P. Wood,† James A. Eastham, Ofer Yossepowitch, Danny M. Rabah, Michael W. Kattan, Changhong Yu, Eric A. Klein and Andrew J. Stephenson‡

Gleason 6 (low risk)

Gleason 7 (intermediate risk)

Gleason 8 (high risk)

Active Surveillance

Whole Gland Therapy

J Urol 2011. 185:869

Predicting 15-Year Prostate Cancer Specific Mortality After Radical Prostatectomy

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Gleason 6 (low risk)

Active Surveillance

Gleason 7 (intermediate risk)

Focal Therapy

Gleason 8 (high risk)

Whole Gland Therapy

J Urol 2011;185:869

BUT.....

- Prostate cancer is multifocal (60-80%)
- Cannot accurately localize prostate cancer

Rationale for Focal Therapy

Index lesion

- Prostate cancer is multifocal but index lesions drives biology
- Typically the largest lesion in prostate specimen containing highest stage, grade, volume
- Potential for being targeted

NEJM 2009; 361:1704-6

Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy

M Karavitakis[1,2], M Winkler[3], P Abel[1,3], N Livni[4], I Beckley[3] and HU Ahmed[5]

- 100 consecutive RP

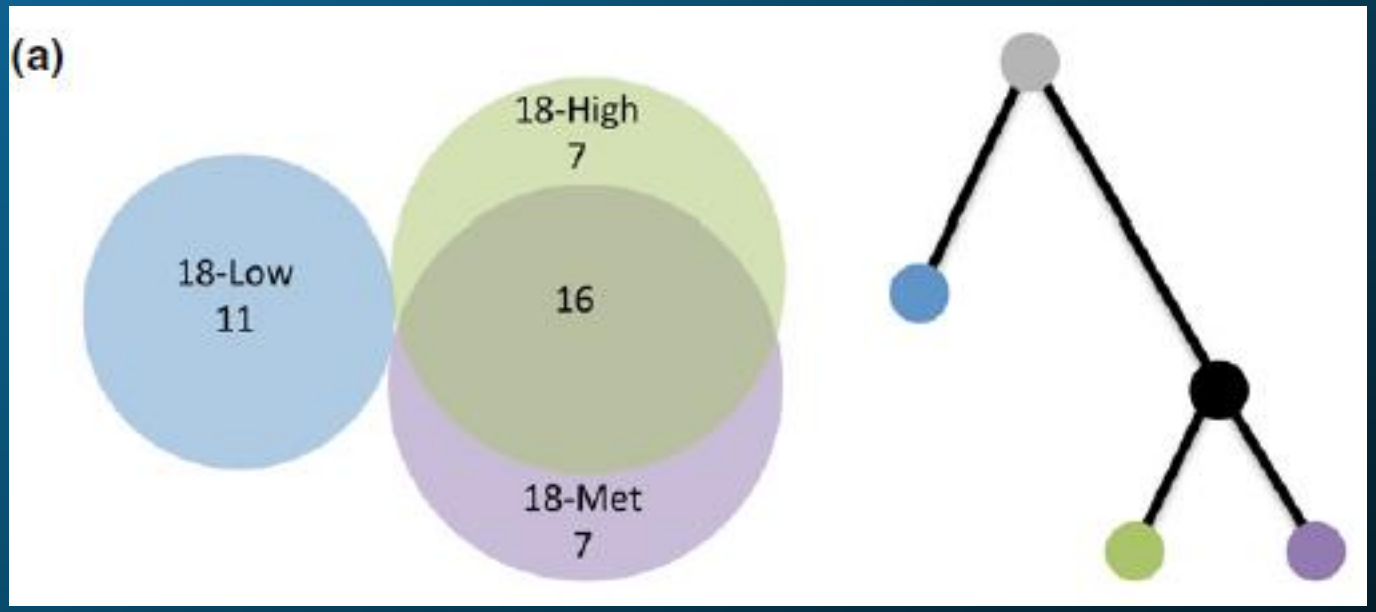
Tumour type	*Total*	*Gleason ⩾7*		*Gleason ⩽6*		*Volume ⩾0.5 cm³*		*ECE*		*SVI*	
		N	%	N	%	N	%	N	%	N	%
Unifocal	22	7	31.8	15	68.2	18	81.8	5	22.7	7	31.9
Index lesions	78	24	30.7	54	69.3	66	84.6	13	16.6	5	6.4
Secondary lesions	170	1	0.6	169	99.4	22	12.9	2	1.1	0	0
Total	270	32		238		106		20		12	

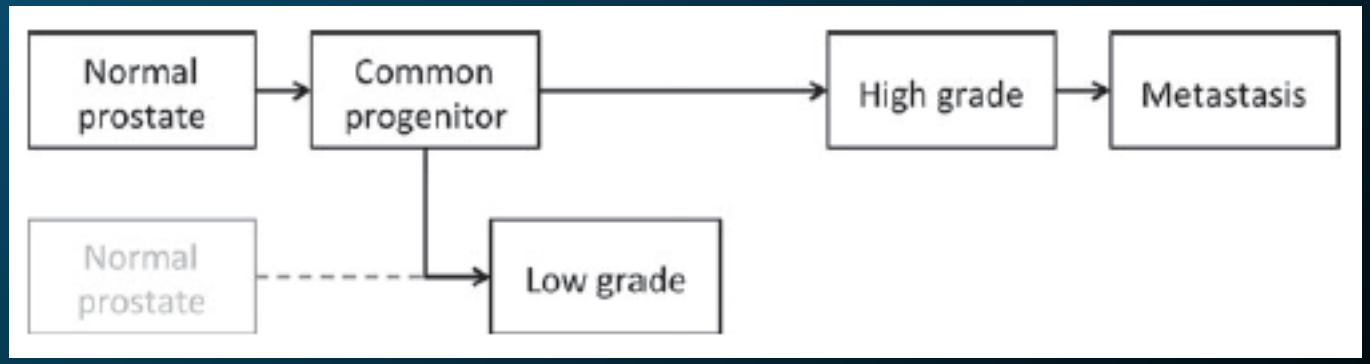
- Tumor volume, Gleason score and pathological stage were almost invariably defined by the index lesion of the specimen
- 51% suitable for FT

Prostate Cancer and Prostatic Dis. 2011;14:46

Low-grade prostate cancer diverges early from high grade and metastatic disease

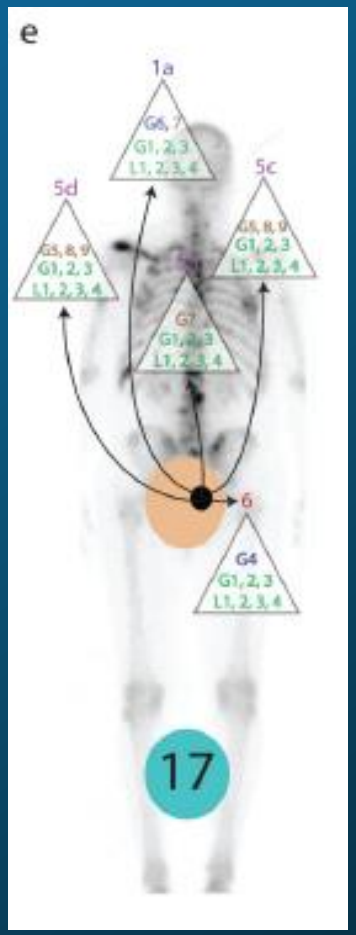
David J. VanderWeele,[1,2] Christopher D. Brown,[1,3,6] Jerome B. Taxy,[4,7] Marc Gillard,[2] David M. Hatcher,[5] Westin R. Tom,[5] Walter M. Stadler[2] and Kevin P. White[1,2,3]

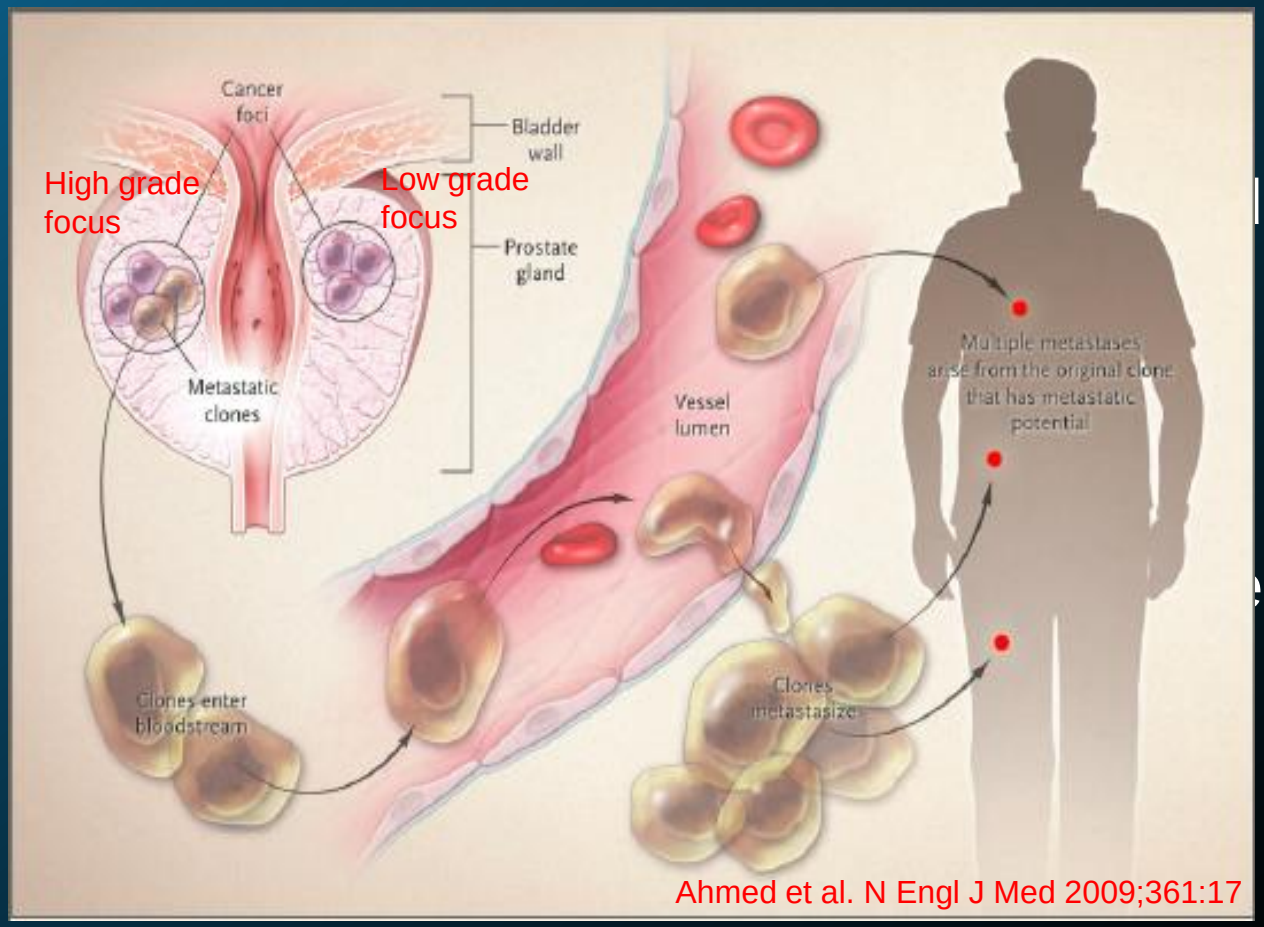




Copy Number Analysis Indicates Monoclonal Origin of Lethal Metastatic Prostate Cancer

Wennuan Liu[¶,1], Sari Laitinen[¶,2], Sofia Khan[3], Mauno Vihinen[3], Jeanne Kowalski[7], Guoqiang Yu[8], Li Chen[8], Charles M. Ewing[5], Mario A. Eisenberger[6], Michael A. Carducci[6], William G. Nelson[6], Srinivasan Yegnasubramanian[6], Jun Luo[5,6], Yue Wang[8], Jianfeng Xu[1], William B. Isaacs[5,6], Tapio Visakorpi[2], and G. Steven Bova[4,5,6]





Patient selection

- Identifying Index lesions and targeting these lesions effectively is paramount to achieving success in focal therapy
- How to accurately localize index lesion preop?

- Random or extended sextant bx inaccurate
- In a study of 201 RP specimens for unilateral positive biopsies unilateral PCA was confirmed only in 28%
- 40% of multifocal cases, had CS disease on contralateral side

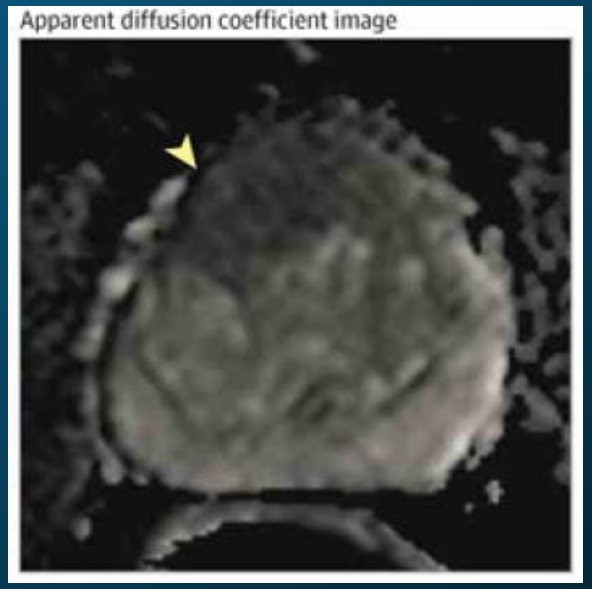
Sinnott et al. The Prostate 2012.72:1179

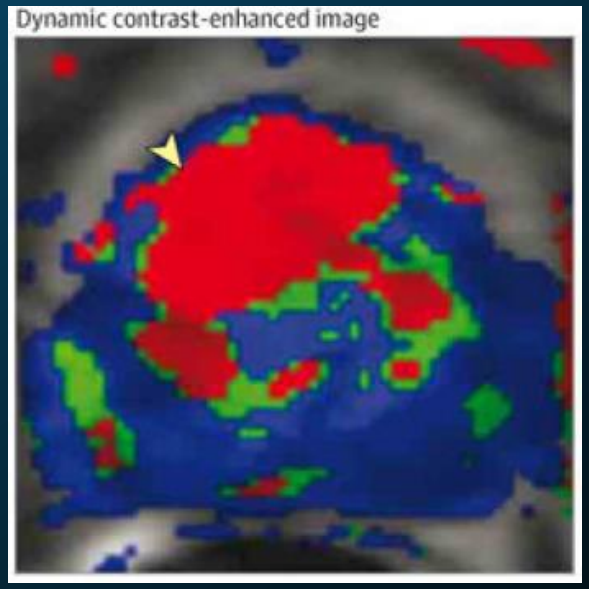
Prostate Imaging

Multi-parametric Prostate MRI

- Anatomic and functional
- T2 Weighted Imaging
  - Anatomical detail, gland substructure
- Dynamic Contrast Enhancement
  - Vascularity, esp arterial hyperenhancement
- Diffusion Weighted Imaging
  - Used to calculate Apparent Diffusion coefficient
  - Reflection of cellular density

Multiparametric Magnetic Resonance Imaging





Targeted Bx: Cognitive fusion, in-bore and Ultrasound fusion

Siddiqui et al. JAMA 2015; 313: 390

JAMA The Journal of the American Medical Association

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, BS, 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, and Peter A. Pinto, MD

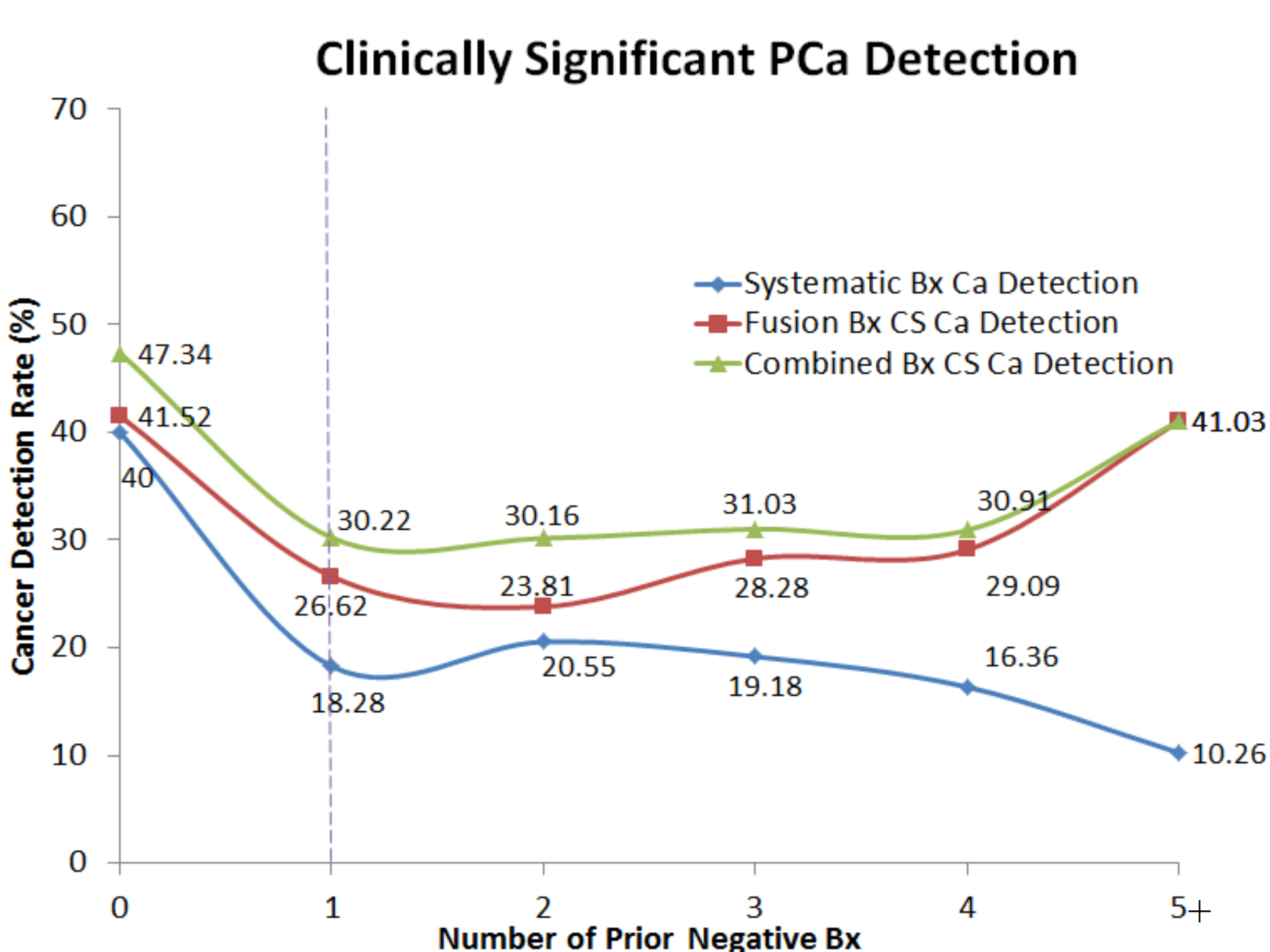
- 1003 men, underwent MRI targeted bx for one or more lesions identified on MpMRI
- 69% agreement between targeted and systemic
- Targeted bx diagnosed
- 30% more high-risk cancers, and
- 17% fewer low-risk cancers

JAMA 2015; 313: 390

Fusion prostate biopsy outperforms 12-core systematic prostate biopsy in patients with prior negative systematic biopsy: A multi-institutional analysis

Abhinav Sidana, M.D.[a,b,*,1], Matthew J. Watson[a,c,1], Arvin K. George[d], Ardeshir R. Rastinehad[e], Srinivas Vourganti[f,g], Soroush Rais-Bahrami[h], Akhil Muthigi[a,i], Mahir Maruf[a], Jennifer B. Gordetsky[h], Jeffrey W. Nix[h], Maria J. Merino[j], Baris Turkbey[k], Peter L. Choyke[k], Bradford J. Wood[l], Peter A. Pinto[a]

- NCI, UAB, SUNY Upstate, Mount Sinai
- All patients without prostate cancer
- 779- patients
- Fusion biopsy outperformed systematic biopsy
- Clinically significant cancer detection by systematic biopsy decreased with increased number of prior biopsies. Yield of fusion biopsy stayed constant


Clinically Significant PCa Detection
Cancer Detection Rate (%)
70
60
50
40
30
20
10
0
0
1
2
3
4
5+
Number of Prior Negative Bx
Systematic Bx Ca Detection
Fusion Bx CS Ca Detection
Combined Bx CS Ca Detection
47.34
41.52
40
30.22
26.62
18.28
30.16
23.81
20.55
31.03
28.28
19.18
30.91
29.09
16.36
41.03
10.26

PROMIS (Prostate MRI Imaging Study)

- Level Ib evidence
- Prospective, paired-cohort
- 576 biopsy naïve, 11 center in UK
- MpMRI followed by TRUS and TPM (reference)
- MpMRI: sens-93%,
- TRUS-biopsy was less sensitive at 48%
- MP-MRI as a triage test can identify one quarter of men (27%) who might safely avoid unnecessary biopsy

Ahmed et al. J Clin Oncol 2016; 34 (suppl; abstr 5000)

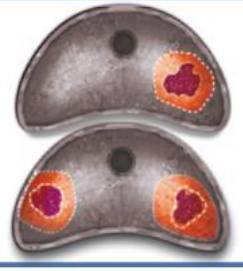
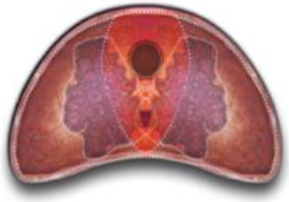
Multiparametric Magnetic Resonance Imaging (MRI) and MRI–Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen

- 120 RP patients
- 120 index, 71 non index
- MpMRI-TRUS fusion 92% index lesion
- Combination with saturation bx increased detection to 96%
- Combined approach detected 97% CS Pca

Radtke et al. Eur Urol 2016 (epub)
Rosenkrantz et al. J Urol 2012;187:2032

Image Guided Focal/Partial Gland Therapy

Focal/partial gland ablation

Focal	ablation volume <30% of prostate volume	mono-/bifocal	
Hemi-ablation	ablation volume <60% of prostate volume	safety margin	
Total	ablation volume ≈ 100% of prostate volume	TURP before	

Energy Delivery

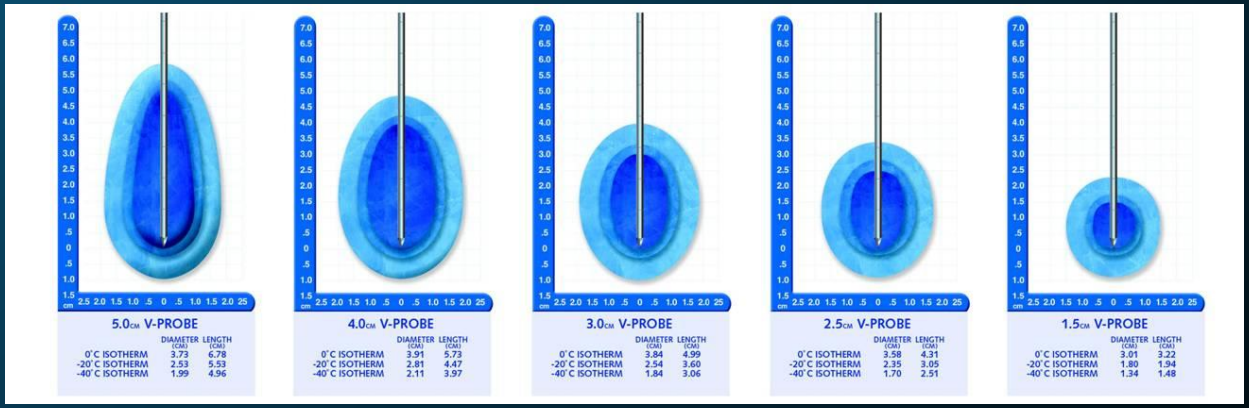
- High Intensity focused Ultrasound
- Laser Interstitial Thermal Therapy
- Cryotherapy
- Brachytherapy
- Water vapor
- Photodynamic Therapy
- And several more……

Cryoablation

- Cancer treatment modality, uses freezing temperatures.

- Induces cell death-
  - Direct damage to membranes.
  - Indirectly by causing vascular compromise in tissue (microthrombosis).

- Minimally invasive, minimal morbidity



Outcomes of Focal Cryoablation (COLD)

- 317 Gleason 6, 166 Gleason 7
- Freedom from PSA failure: 70-73% (5 year), 14% positive bx
- Continence- 95-99%
- Sufficient erections- 46.8-69% (2 years)
- 0-1 Fistula

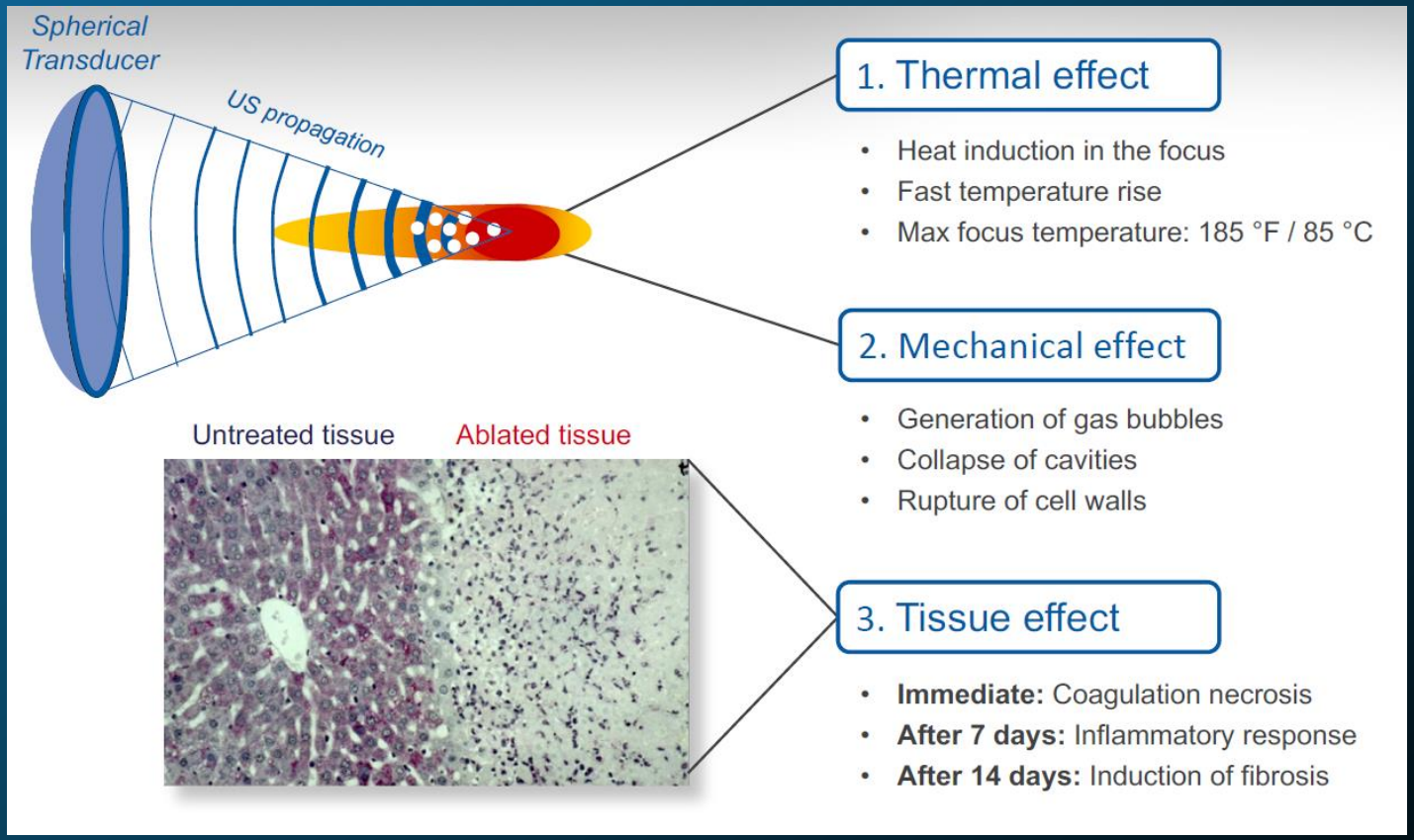
Mendez et al. J Endourol. 2015;29(10):1193-8

Tay et al. J Endourol. 2017;31(6):564-571

HIFU

- High energy ultrasound waves destroy tissue at focal point of a transducer without injuring the intervening tissues.
- Inaudible sound range and 10,000 times stronger than diagnostic ultrasound.
- At focal point, US energy is concentrated, and generates temp that can exceed 80 C, resulting in coagulative necrosis and destruction of tissue.
- Minimal damage to adjacent tissue.

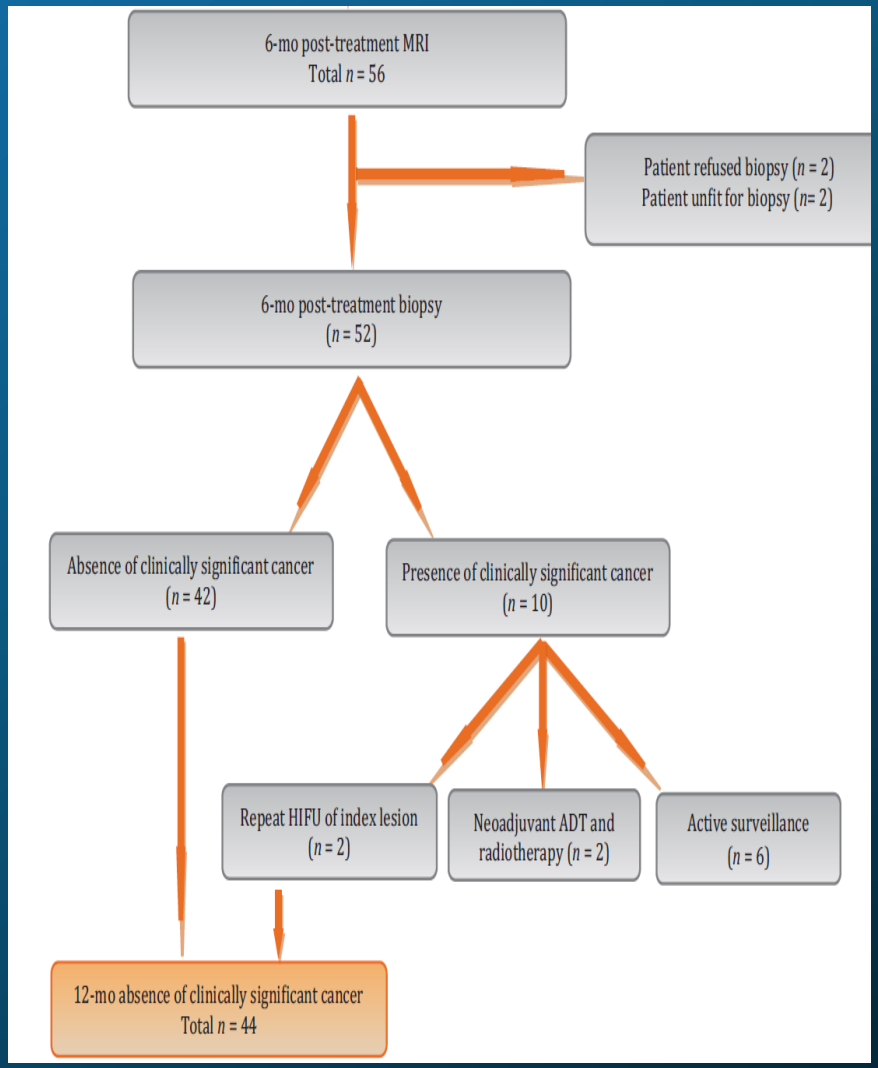
Mechanism

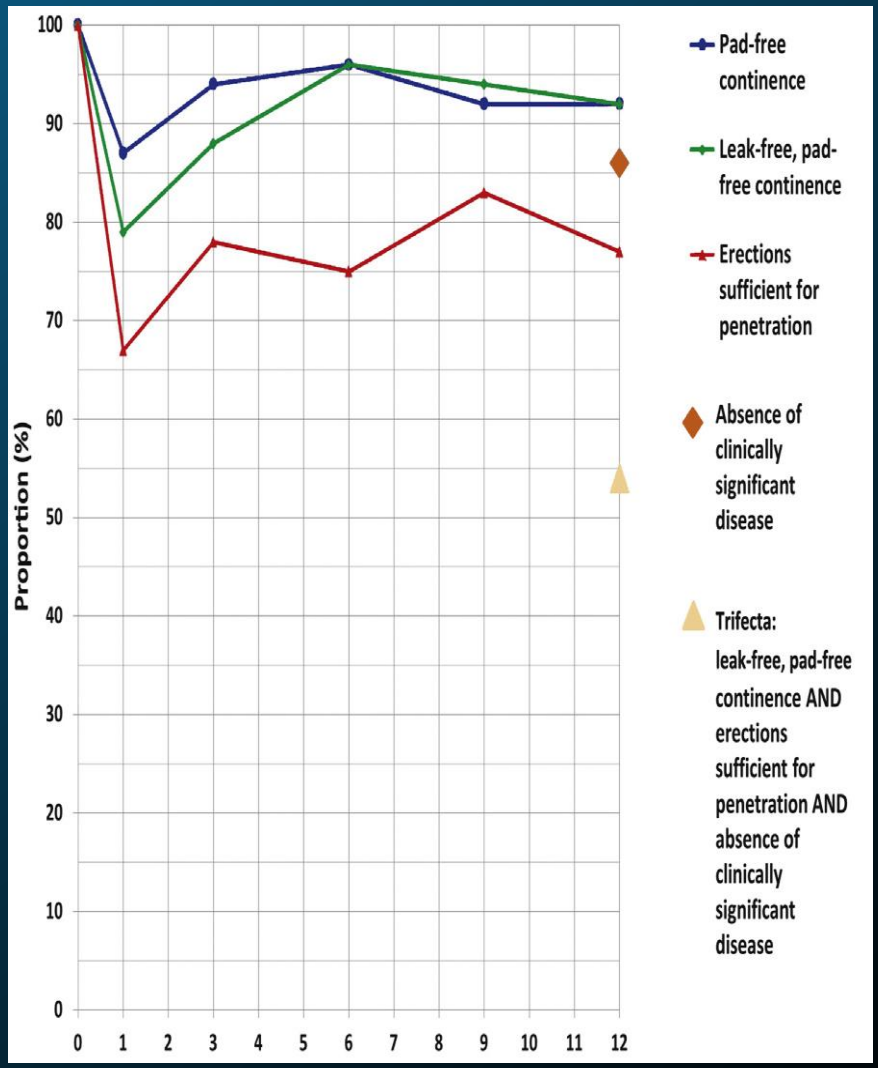

Spherical
Transducer
US propagation
Untreated tissue
Ablated tissue
1. Thermal effect
• Heat induction in the focus
• Fast temperature rise
• Max focus temperature: 185 °F / 85 °C
2. Mechanical effect
• Generation of gas bubbles
• Collapse of cavities
• Rupture of cell walls
3. Tissue effect
• **Immediate:** Coagulation necrosis
• **After 7 days:** Inflammatory response
• **After 14 days:** Induction of fibrosis

Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: a Prospective Development Study

Hashim U. Ahmed [a,b,†,], Louise Dickinson [a,b,†], Susan Charman [c,d], Shraddha Weir [b], Neil McCartan [b], Richard G. Hindley [e], Alex Freeman [f], Alex P. Kirkham [g], Mahua Sahu [b], Rebecca Scott [a], Clare Allen [g], Jan Van der Meulen [c,d], Mark Emberton [a,b]*

- Treatment naïve, PSA<20,Gleason≤4+3, ≤T3aN0M0, n = 56
- Focal HIFU delivered via Sonablate 500® (index lesion)
- 1° outcome: Composite outcome of genitourinary side effects
- 2° outcomes: Presence of cancer 6-mo biopsy, CS disease on mpMRI at 6 and 12 mo, PSA kinetics


6-mo post-treatment MRI
Total n = 56
Patient refused biopsy (n = 2)
Patient unfit for biopsy (n= 2)
6-mo post-treatment biopsy
(n = 52)
Absence of clinically significant cancer
(n = 42)
Presence of clinically significant cancer
(n = 10)
Repeat HIFU of index lesion
(n = 2)
Neoadjuvant ADT and
radiotherapy (n = 2)
Active surveillance
(n = 6)
12-mo absence of clinically significant cancer
Total n = 44


Proportion (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Pad-free continence
Leak-free, pad-free continence
Erections sufficient for penetration
Absence of clinically significant disease
Trifecta: leak-free, pad-free continence AND erections sufficient for penetration AND absence of clinically significant disease

Who do we offer focal/partial gland treatment at UC?

- Motivated patient
- Understands the need for intense followup
- Realistic expectations
- Cancer criteria:

  -MRI fusion biopsy demonstrating Gleason 7 (3+4, 4+3) or significant Gleason 6 in the MR visible lesion

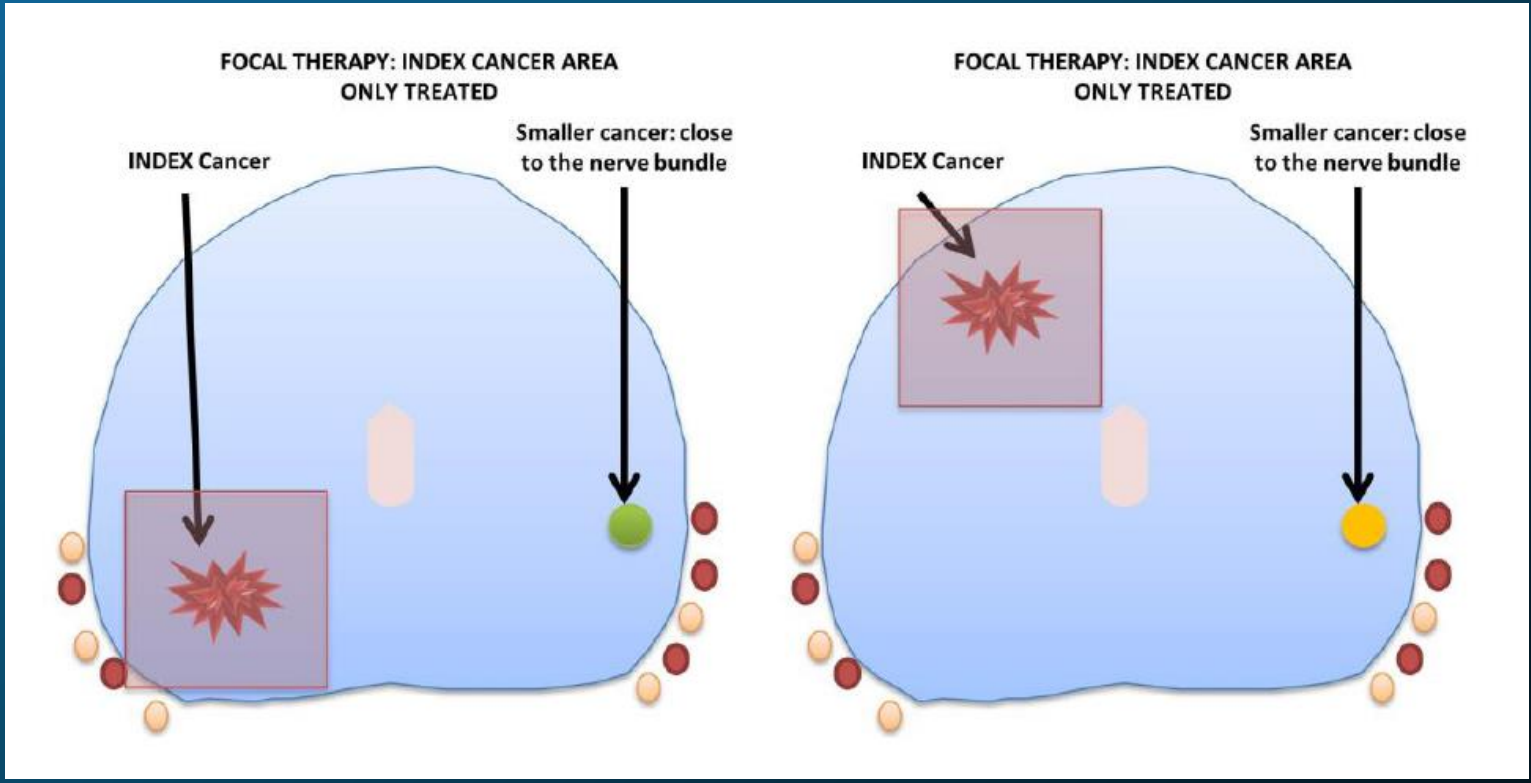
  -Absence of Gleason 7 or high volume Gleason 6 outside of planned treatment area

  - PSA <15 ng/ml

  -Treatment would spare atleast one neurovascular bundle and avoid injury to urethra and sphincter

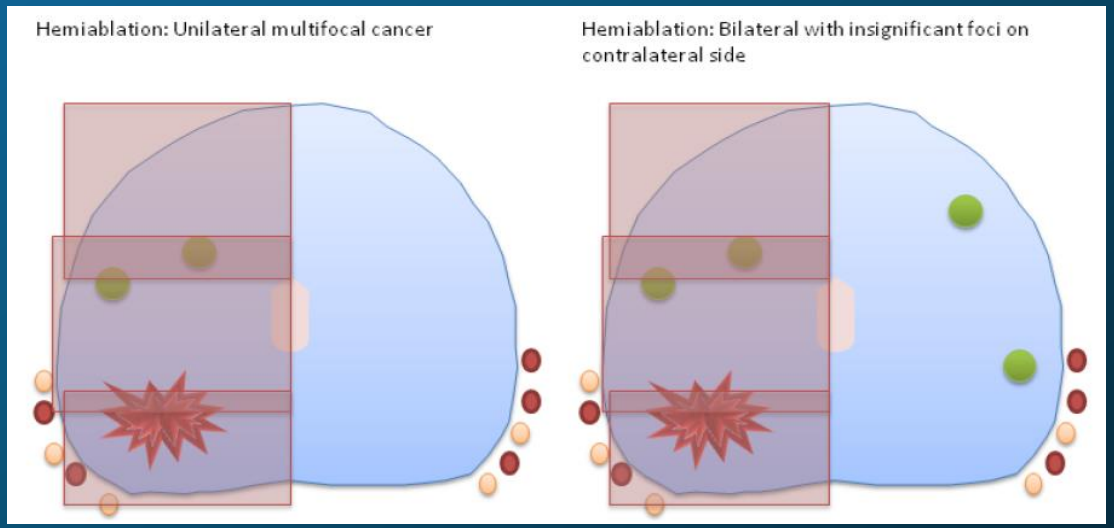
  -Radiation failures will need additional imaging

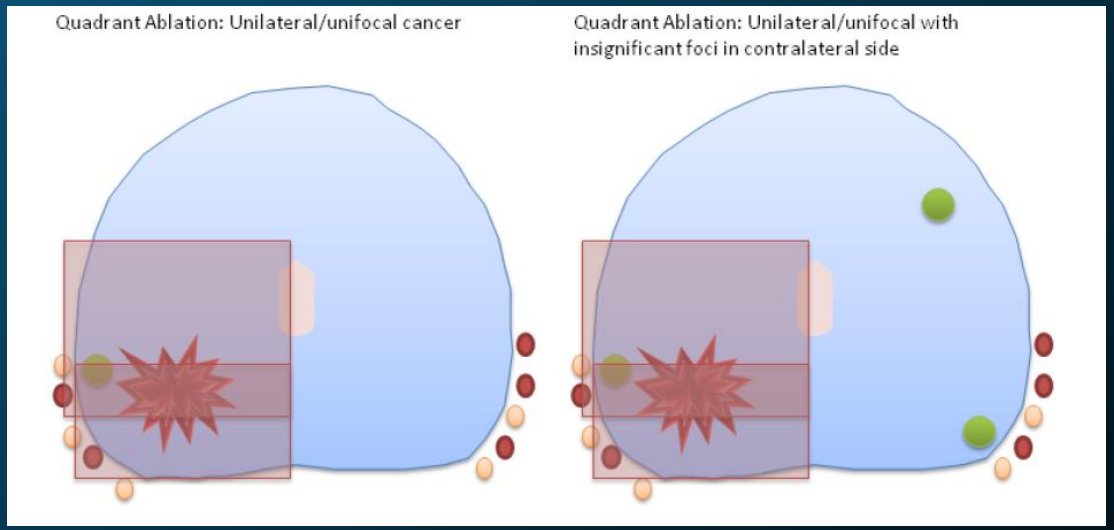
Pure focal ablation



Ahmed et al. Eur Urol 2015.68:927

Partial gland (or template) ablation





Ahmed et al. Eur Urol 2015.68:927

HIFU vs Cryo

- Prostate size
- Cancer location
- Functional outcomes
- **Affordability**

  - Cryoablation is approved by all insurances

  - HIFU is approved partly by Medicare

  - At the minimum 5-10K out of pockets, can be as high as 25K

Conclusion

Conclusion

- Focal ablation of prostate cancer is safe and feasible with encouraging short term oncological outcomes and excellent preservation of functional outcomes.
- Prostate MpMRI's ability to accurately detect and localize clinically significant cancer has potentiated this approach.
- MpMRI has also facilitated follow up after focal therapy.
- Scarcity of long term data, need for higher level of evidence.
- Further research to improve patient selection and localization of prostate cancer.

Thank you