Organ Preservation in the Management of Prostate Cancer

John F. Ward, MD, FACS

Professor

Division of Surgery, Department of Urology

The University of Texas, M. D. Anderson Cancer Center

Houston, TX

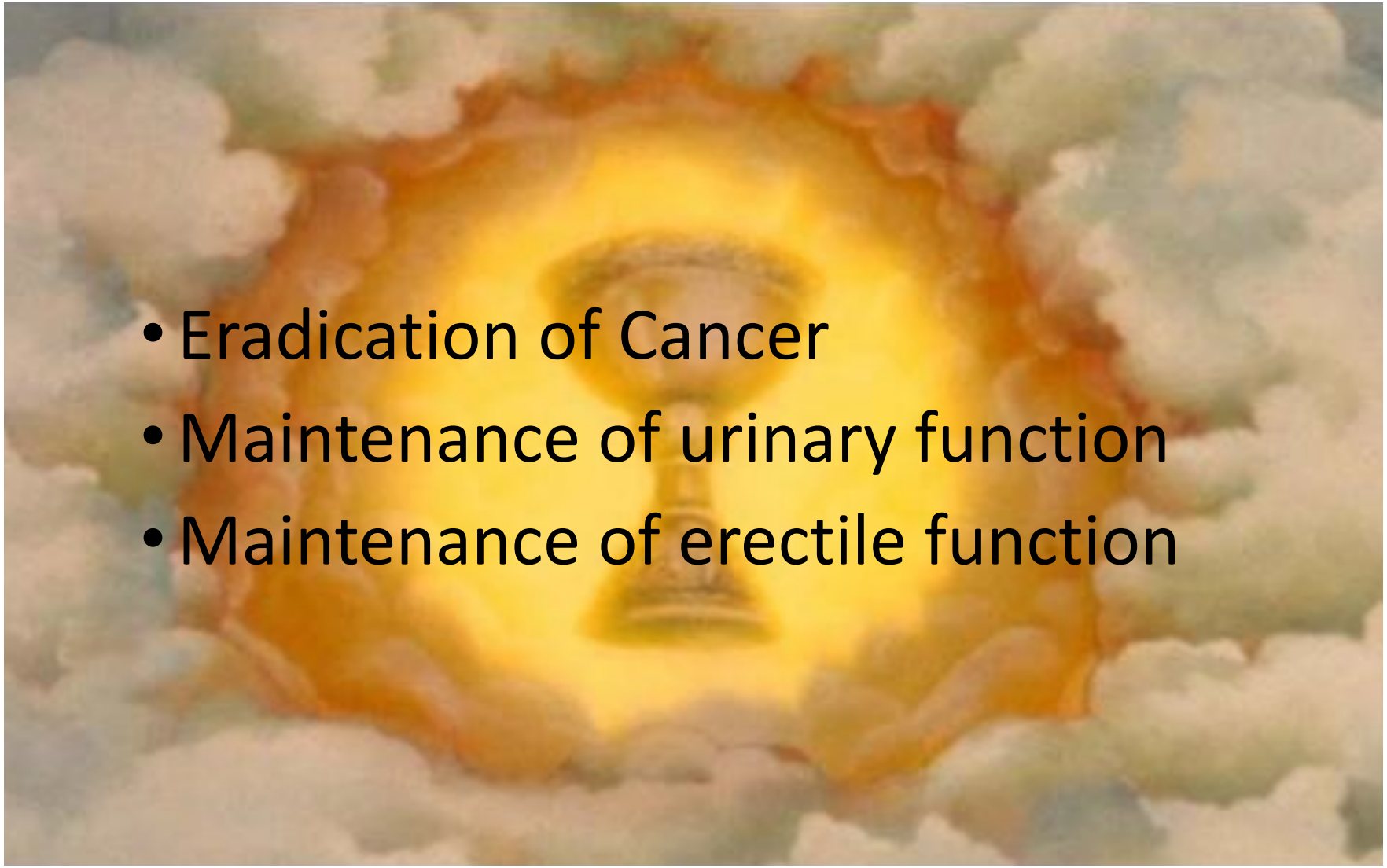
USA

Overarching Theme of Prostate Cancer in 2018

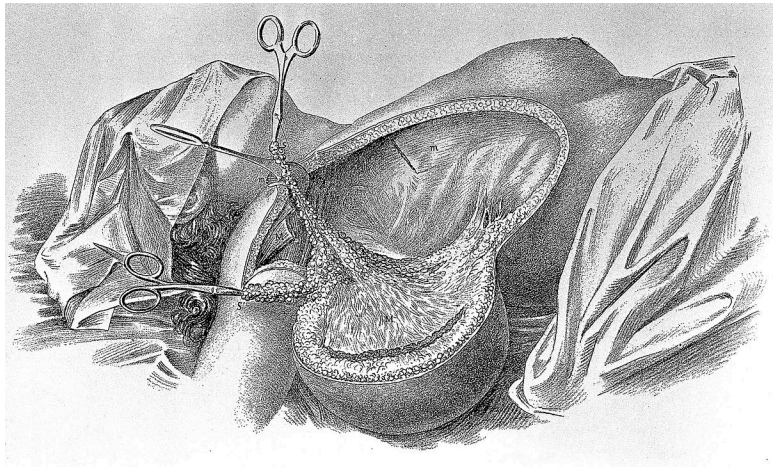
* Just as a failure to under-treat a potentially lethal prostate cancer is generally considered inappropriate, over-treatment of lower-risk cancers is also not in the patient's best interest.

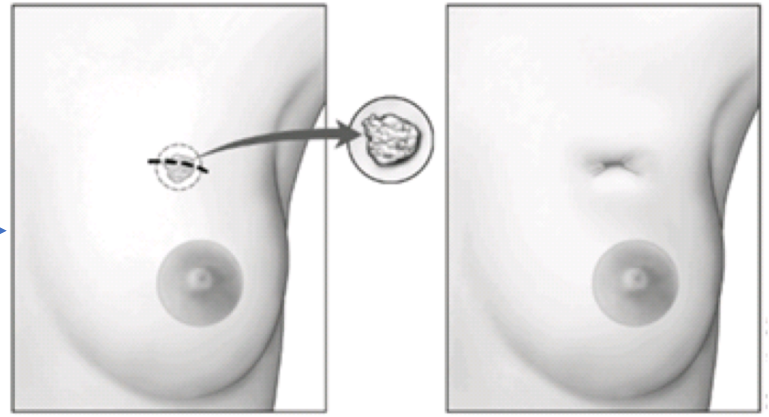
* For some men with early stage prostate cancer, radical surgery or radical radiation may result in substantial negative effects without a survival benefit

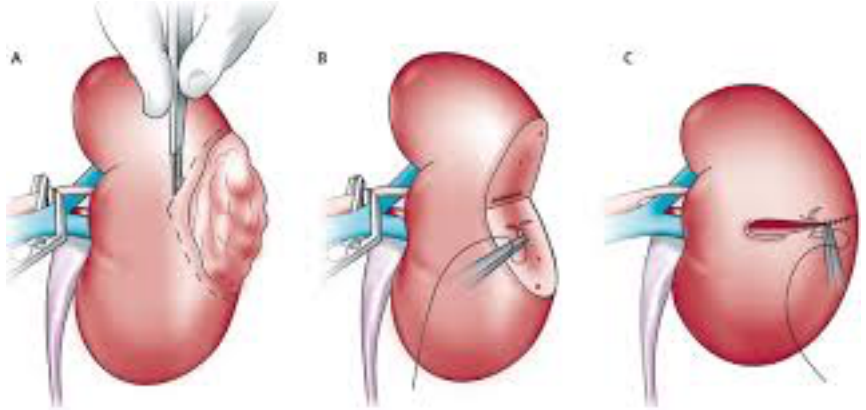
The Holy Trinity of Prostate Cancer Therapy



Evolution of organ preservation in oncologic surgery







What is the objective of organ preservation in prostate cancer?

- Complete eradication of all localized prostate cancer(s).
- Elimination of Index tumor
- Chronic disease management
- Functional Outcomes
- Part of Multi-modal treatment

Oncologic Efficacy

- Measure of success = Negative prostate Bx
  - Even after Targeted Focal therapy IS the random nature of prostate biopsy still dominating the outcome measurement (False Negative).

Houston, we have a problem….

- TRUS Bx are blind mining
- Subject to random and systematic errors
- ”Wrong” results about half the time
- Clinically insignificant cancers are identified by chance
- Important cancers are incorrectly classified as unimportant

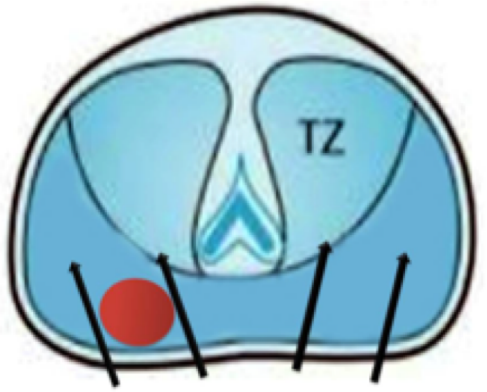


Figure 3a: Random deployment of the needle leads to a clinically significant tumour being missed in the PZ

Figure 2: Random deployment of the needle leads to detection of small clinically insignificant tumours

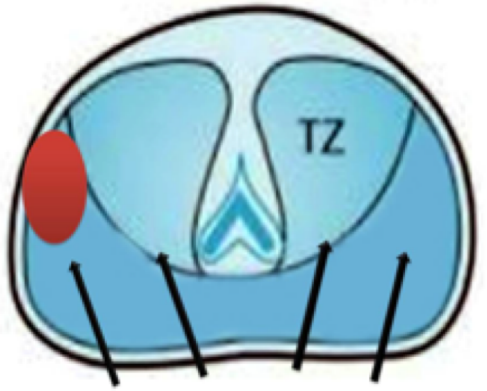
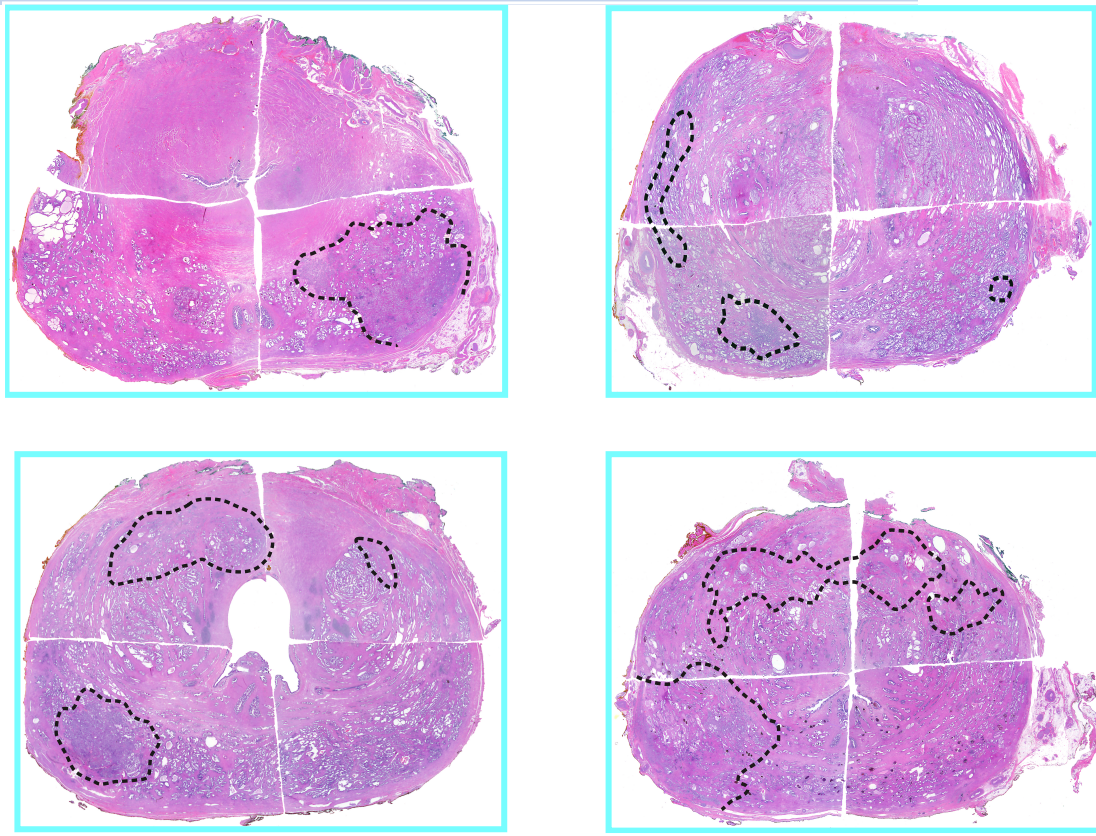


Figure 3b: Random deployment of the needle leads to a clinically significant tumour being missed in the anterior PZ horn

Figure 4: Random deployment of the needle leads to a clinically significant tumour being under-sampled and categorised as low volume

Prostate Cancer Multifocality

- Meta-analysis of 12 RP series[#]
  - 2,388 RP Specimens
  - Multifocality 33%-87% (Avg. 67%)
- RP specimens +/- 20% tumors unilateral[*^]
  - 1186 RP specimens with 19% unilateral PCA's*
    - 72% occupy less than 5% of prostate
  - 1000 RP specimens with 18% unilateral PCA^
    - ECE always associated with Index lesion



Meiers I, Bostwick DG; Urology 70(supp 6A) 2007
* Mouraviev V, et al.; Cancer 110(4) 2007
^ Ohori M, et al.; J Urol 175(Suppl) 2006

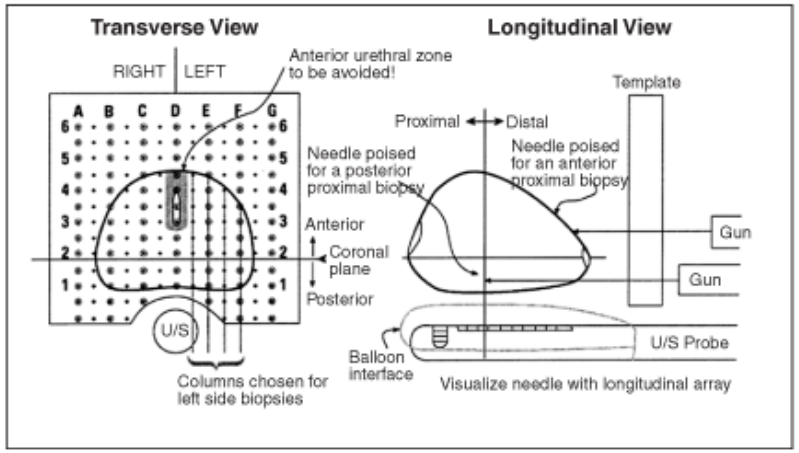
Prostate Cancer Multifocality

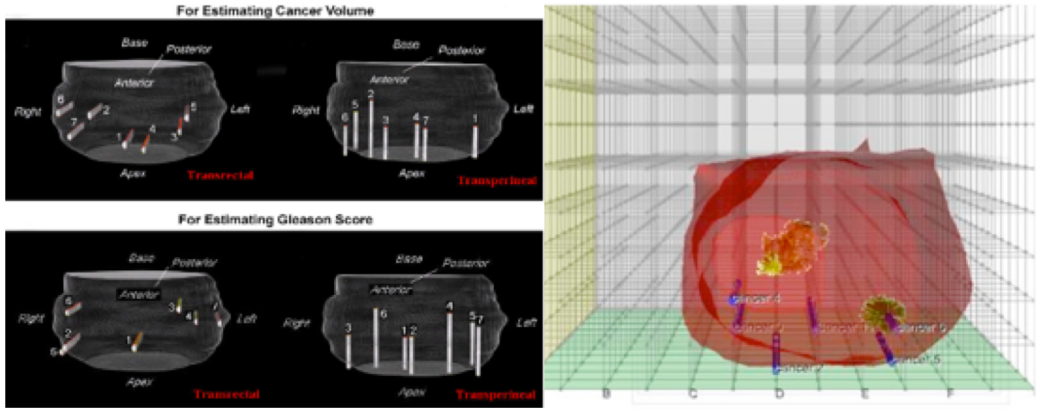
M.D. Anderson Cancer Center

- Unilateral + Biopsy --> RP Specimens*
  - 2,095 extended scheme biopsy (no prior diagnosis)
  - 35% (731/2095) positive for cancer
  - 21% (442/2095) unilateral positive for cancer
  - 40% (180/442) prostatectomy at MDACC
- Tumor foci = 3 (1-8) [median, range]
- Total tumor volume = 0.73cc
  - Dominant tumor volume = 0.50cc
- 17% Uni-laterality
  - 83% Bilateral Disease DESPITE unilateral only + Bx

* Ward, JF, et al; BJU Int 104(4) 2009

Complete eradication

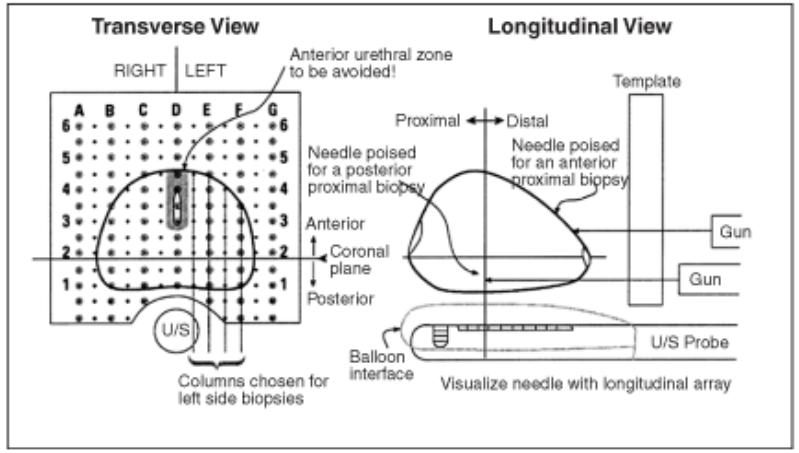


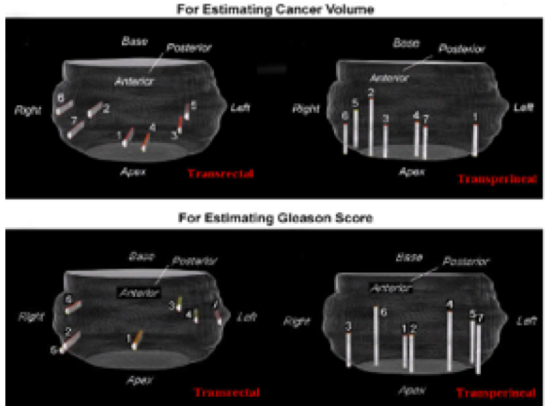


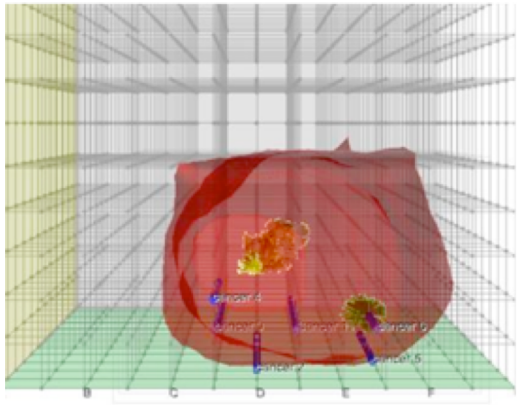
- "Battle Ship" the game
- Does Saturation biopsy accomplish this?
  - Respiratory movement
  - Capsular Deformation
  - Bevel deflection
  - 100 bx samples <1.5cc

Crawford et al, Prostate 2013

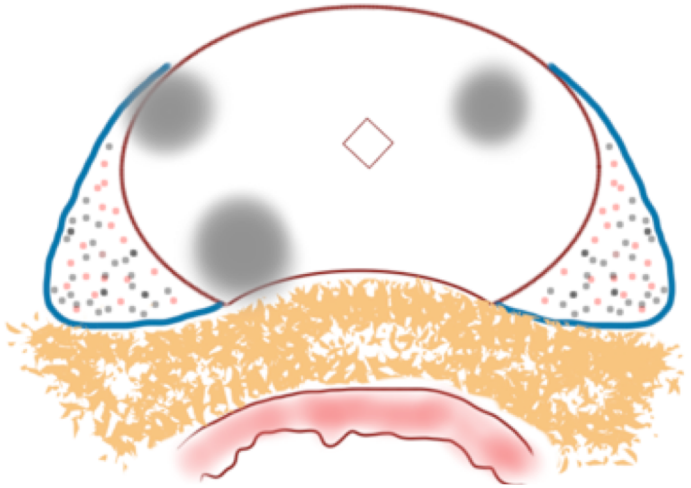
Targeted Focal Therapy







- Mimics radical therapy in therapeutic outcome
- Addresses Multi-focality issue

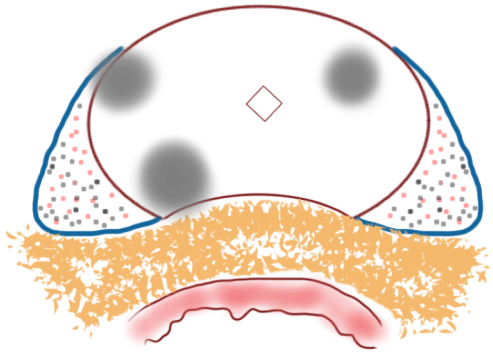


Crawford et al, Prostate 2013

Barqawi, et al.; J Urology, March2014

TARGETED FOCAL THERAPY IN THE MANAGEMENT OF ORGAN-CONFINED PROSTATE CANCER

- Targeted Focal Therapy (TFT)➔ the "complete ablation of all **clinically detected** cancer foci within the prostate. (recapitulate radical Tx)
- 3D-Transperineal Mapping Biopsy
  - 32-64 cores per patient
- Gold fiducial markers
- 3D reconstruction with PROview rendering software



Barqawi, et al.; J Urology, March2014

TARGETED FOCAL THERAPY IN THE MANAGEMENT OF ORGAN-CONFINED PROSTATE CANCER

- 62 Subjects (2006-2009)
- Ablative Energy: Cryotherapy
- 12-month, 12 core prostate biopsy (rather than 3D-mapping biopsy)
- Biochemical failure➔Any postoperative PSA value that exceeds the maximum preoperative PSA value

Barqawi, et al.; J Urology, March2014

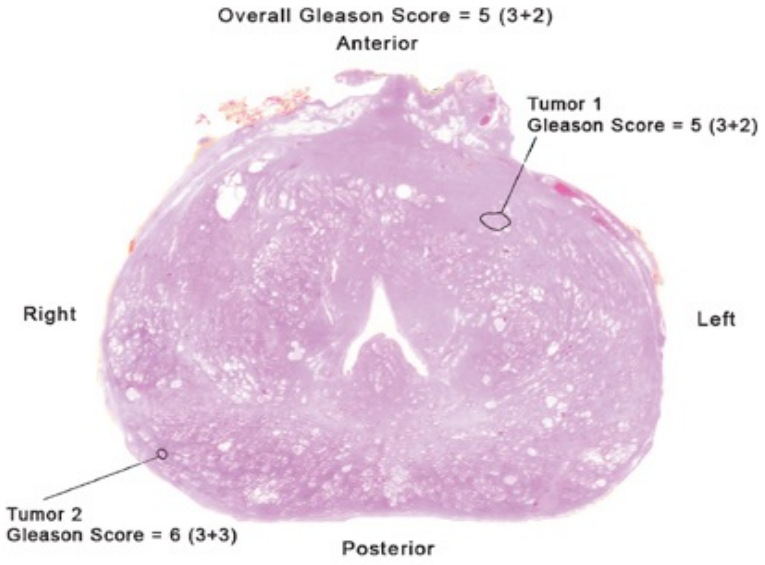
TARGETED FOCAL THERAPY IN THE MANAGEMENT OF ORGAN-CONFINED PROSTATE CANCER

- + Biopsy: 19% (12/50)
- + PSA recurrence: 29%
- Median AUA-SS: Decline 1.5% ($p<0.01$)
- No Change observed in SHIM score (sign test $p=0.6$)

Barqawi, et al.; J Urology, March2014

Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens

Examined the histologic details of small, independent cancers compared with the largest (index) tumor and their impact on PSA failure in 486 men treated only by prostatectomy



Wise et al. Urology 2002, 60(2)

Index + Synchronous Tumors

	Mean (cm^3)	IQ Range (cm^3)
Index tumor volume	4.16	1.37-5.11
Total tumor volume	4.78	1.73-6.28
Smaller tumor volume	0.63	0.01-0.85
Additional foci	2.92	1-4

- Pathologic evaluation of index lesion correctly predicted clinical course in >90% of patients regardless of synchronous tumors
- 80% of secondary tumors <0.5cc

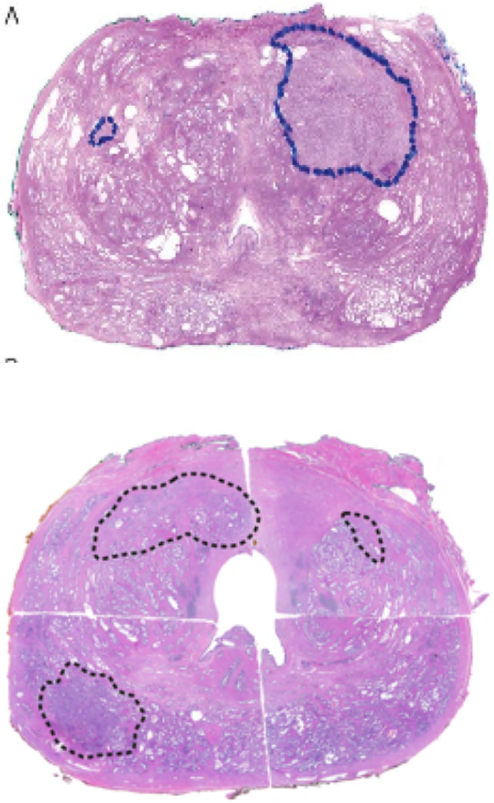
.Wise AM, et al.; Urology 60(2) 2002
.Villers A, et al.; Cancer 70 1992

Monoclonal or Multiclonal expansion of Tumor Cells

- Intraprostatic lesions appear to be multiclonal
  - Study allelic loss on 8p12-21 and BRCA1 on 17q21*
    - tumors arise within the prostate independently secondary to numerous independent mutations rather than proliferation and intraglandular spread of a single malignant transformed cell
- Metastatic lesions appears to be monoclonal#@

* Cheng L, et al.; JNCI 90(3) 1998
# Liu W, et al.; Nat Med 15(5) 2009
@ Mehra R, et al.; Cancer Res 68(10) 2008

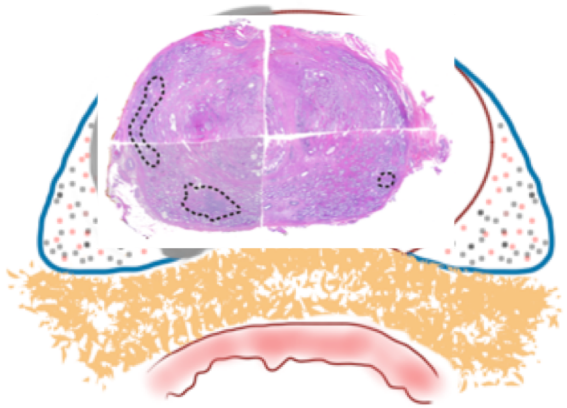
Elimination of Index Tumor



- Smaller cancers are not a significant predictor of PSA failure after radical prostatectomy
- The index cancer volume is equally predictive of PSA failure after radical prostatectomy as total cancer volume (index plus smaller cancers)
- Suggestion that the largest carcinoma may increase its volume by assimilation of adjacent independent tumors
- Many patients with multifocal disease have small volume secondary tumors of lower grade that are unlikely to affect clinical biology
- Pathologic landscape suggests that targeting index tumor can alter clinical course

Index Lesion Elimination

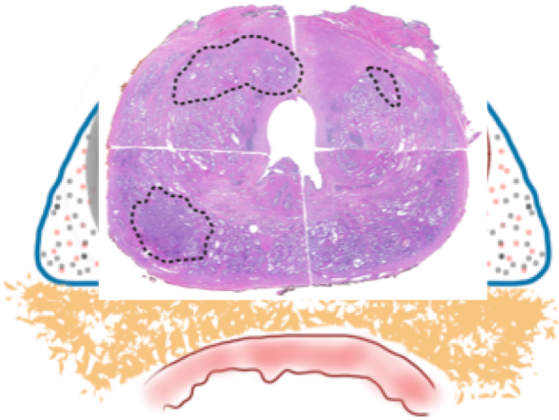
Hemisphere



ALL cancers --> 17%

INDEX cancers --> 89%

Hockey-Stick



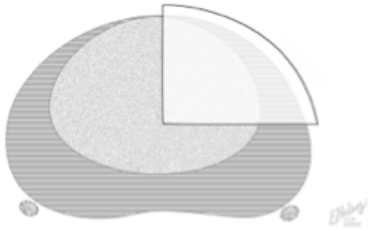
ALL cancers --> 47%

INDEX cancers --> 100%

180 RP specimens with Unilat +Bx

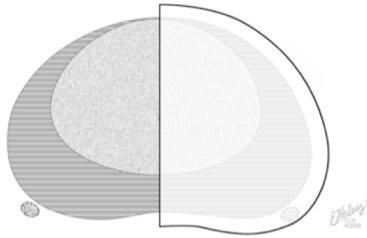
* Ward, JF, et al; BJU Int 104(4) 2009

Ablation Plan and Cancer Biology Dictates Degree of Precision Necessary

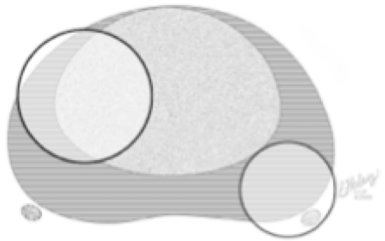


Zonal Ablation

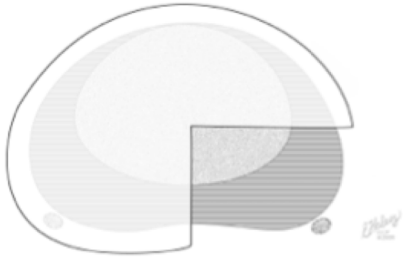
Nerve Sparing
(uni or bi)



Hemiablation



Targeted Focal Therapy
"TFT"



Hockey Stick
(Anterior)

Hockey Stick
(Posterior)

John F. Ward and J. Stephen Jones
Urology 75(6) 1258-60. June 2010

Prospective trial of organ preserving prostate cryoablation using anterior hockey-stick regional template

MD Anderson 2008-0244

- Gleason 3+3=6 or 3+4=7, and PSA<10ng/ml
  - Gleason ≤ 3+4 disease in less than ½ of unilateral cores and no more than 50% involvement of any single core. Contralateral Gleason 3+3 with <2mm involvement was also eligible.
- Confirmation biopsy is performed using the 3D Target Scan® biopsy system
- A hockey stick template (dominant side hemiablation with contralateral anterior wing) is employed
- Post-cryo biopsy performed using robotic guidance at 6-, 18- and 36 months following regional ablation.

Prospective trial of organ preserving prostate cryoablation using anterior hockey-stick regional template

MD Anderson 2008-0244

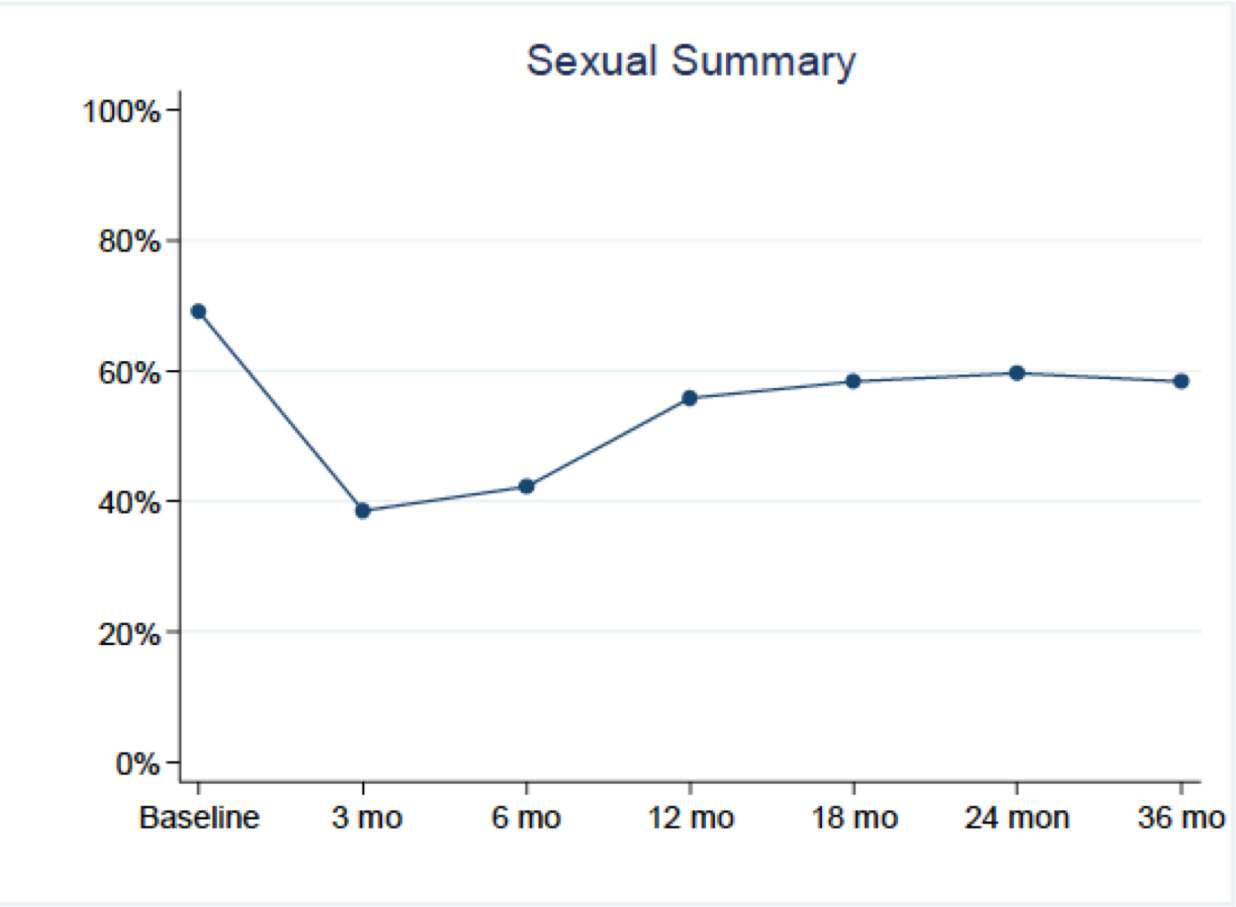
- 72 men were screened for trial eligibility
- 47 underwent confirmatory biopsy
- 23 were treated with regional (hockey-stick template) cryoablation.

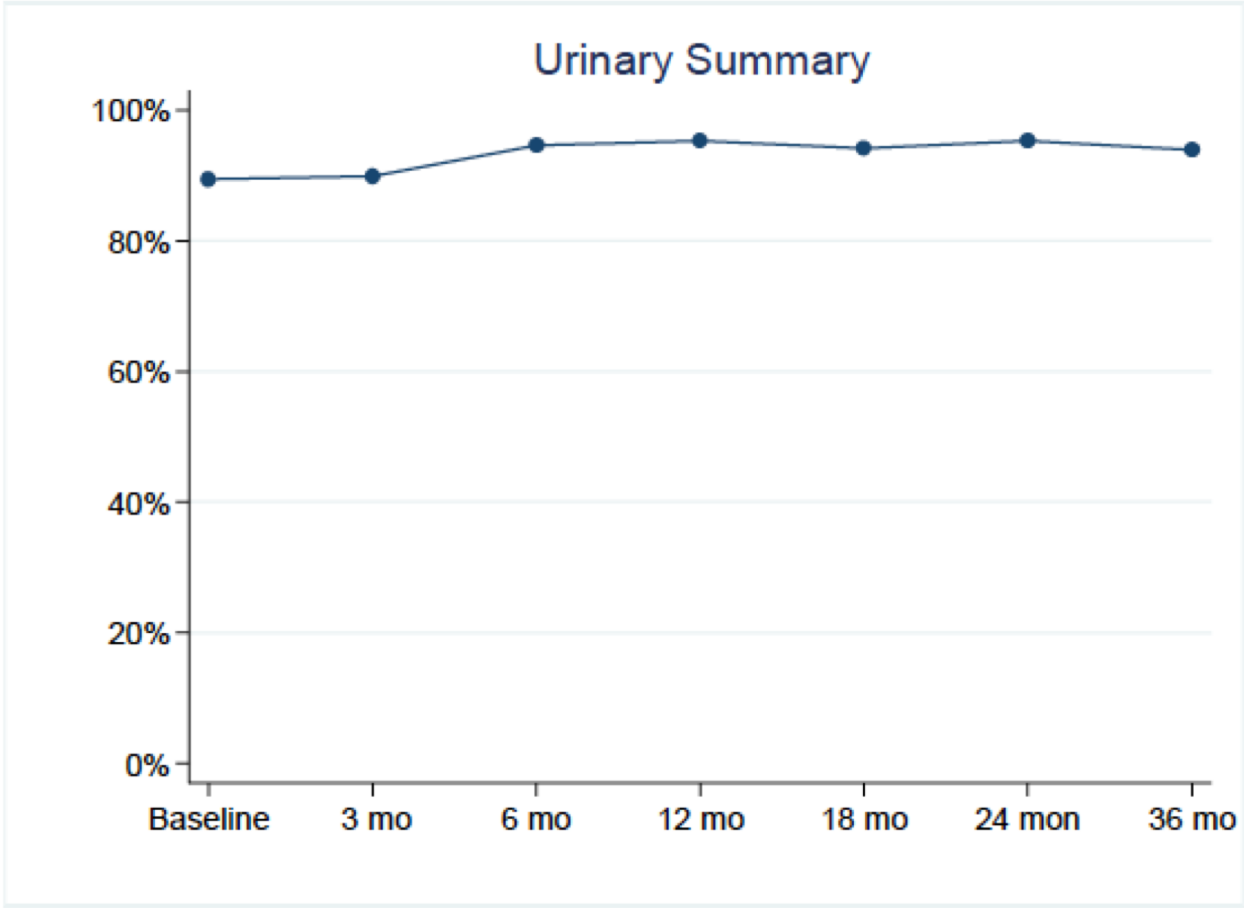
- Post ablation biopsy at 6, 18, and 36 months was performed in 21, 16 and 14 men, respectively.

- A single patient revealed In-Field <1mm positive biopsy with therapy effect (no Gleason Grade) at 36-months.

Prospective trial of organ preserving prostate cryoablation using anterior hockey-stick regional template

MD Anderson 2008-0244





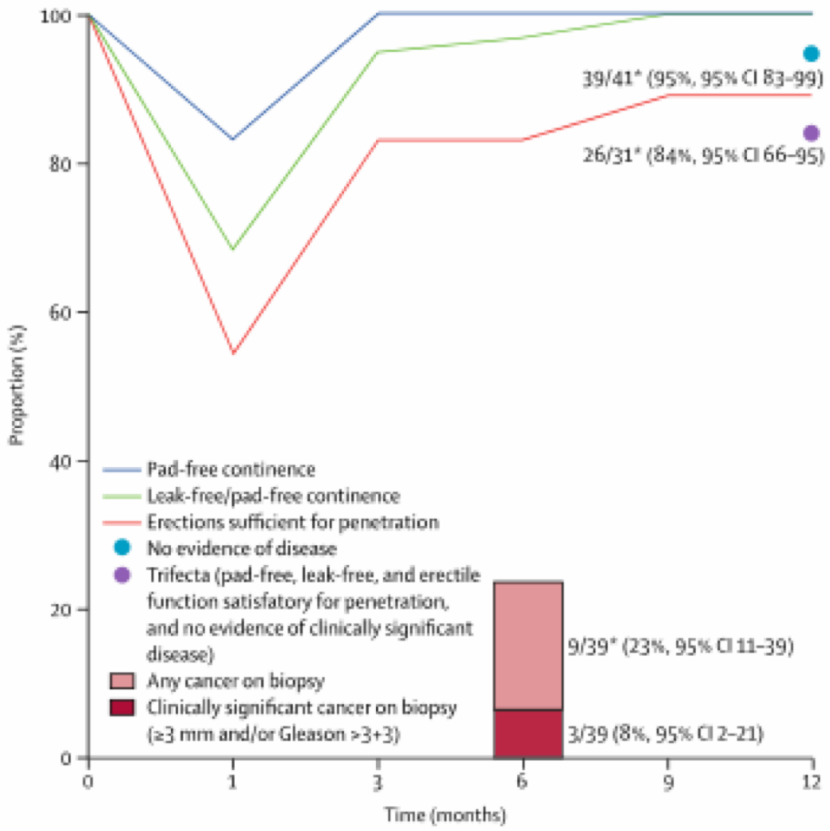
Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study

Hashim U Ahmed, Richard G Hindley, Louise Dickinson, Alex Freeman, Alex P Kirkham, Mahua Sahu, Rebecca Scott, Clare Allen, Jan Van der Meulen, Mark Emberton

- Prospectively performed
- Focal HIFU
- 42 men
  - Localized prostate cancer
  - PSA ≤ 15ng/mL
  - Gleason ≤ 4+3
  - Stage ≤ T2

Ahmed et al., Lancet Oncology April 2012

Functional Outcomes



Ahmed et al., Lancet Oncology April 2012

Cancer Outcomes

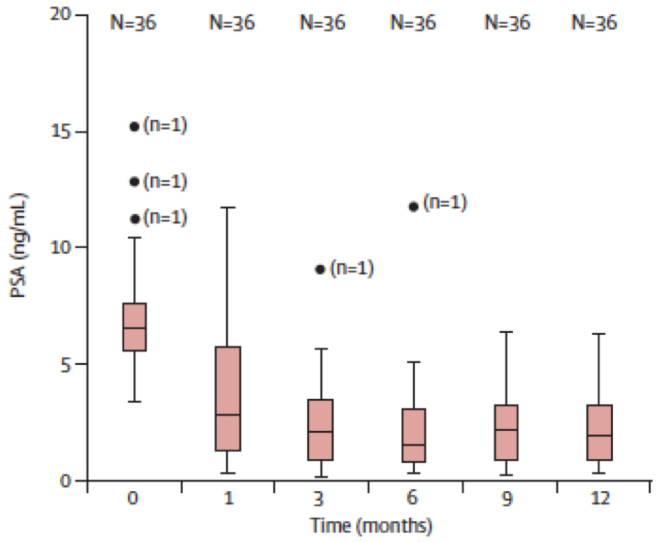
Biopsy Results

	Value
Number of cores taken	6·0 (5·0–7·0)
Absence of any cancer	30/39 (77%, 61–89)
Positive biopsy outcomes*	
Positive biopsies†	9/39 (23%, 11–39)
Maximum cancer core length (in positive cores), mm	1·0 (1·0–3·5)
Gleason (N)	
3+3	6
3+4	3
Absence of clinically significant disease‡	36/39 (92%, 79–98)
Other histological findings	
Prostatic acini	21/39 (54%, 37–70)
Atrophy	25/39 (64%, 47–79)
Fibrosis	35/39 (90%, 76–97)
Giant-cell reaction	4/39 (10%, 3–24)
Necrosis	15/39 (38%, 23–55)

Data are median (IQR) or number of patients/N (%, 95% CI). *Two men were not biopsied because of suprapubic catheter in situ in one patient and refusal by another. †Five men opted for surveillance. Of these, four had 1 mm of Gleason 3+3 and one had 2 mm of Gleason 3+4. Four men opted for retreatment. Of these, two had clinically significant cancer (5 mm and 6 mm of Gleason 3+4) and two had no more than 1 mm of Gleason 3+3. ‡As defined by Epstein criteria: Gleason >3+3, >2 cores positive, ≥3 mm cancer involvement.

***Table 3*: Histological outcomes at 6 months in men undergoing focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer**

PSA Response



Ahmed et al., Lancet Oncology April 2012

Along comes Multiparametric MRI

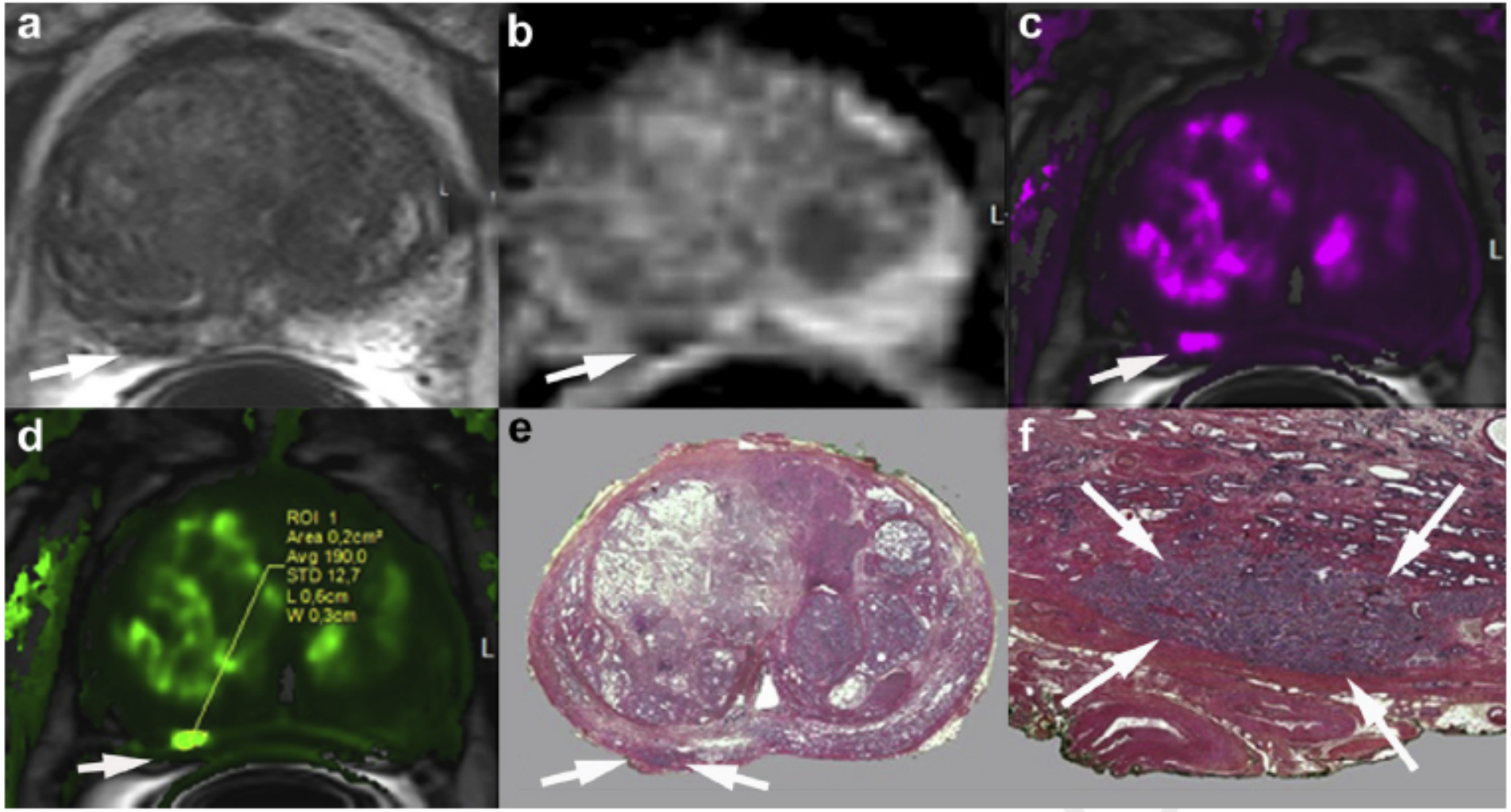
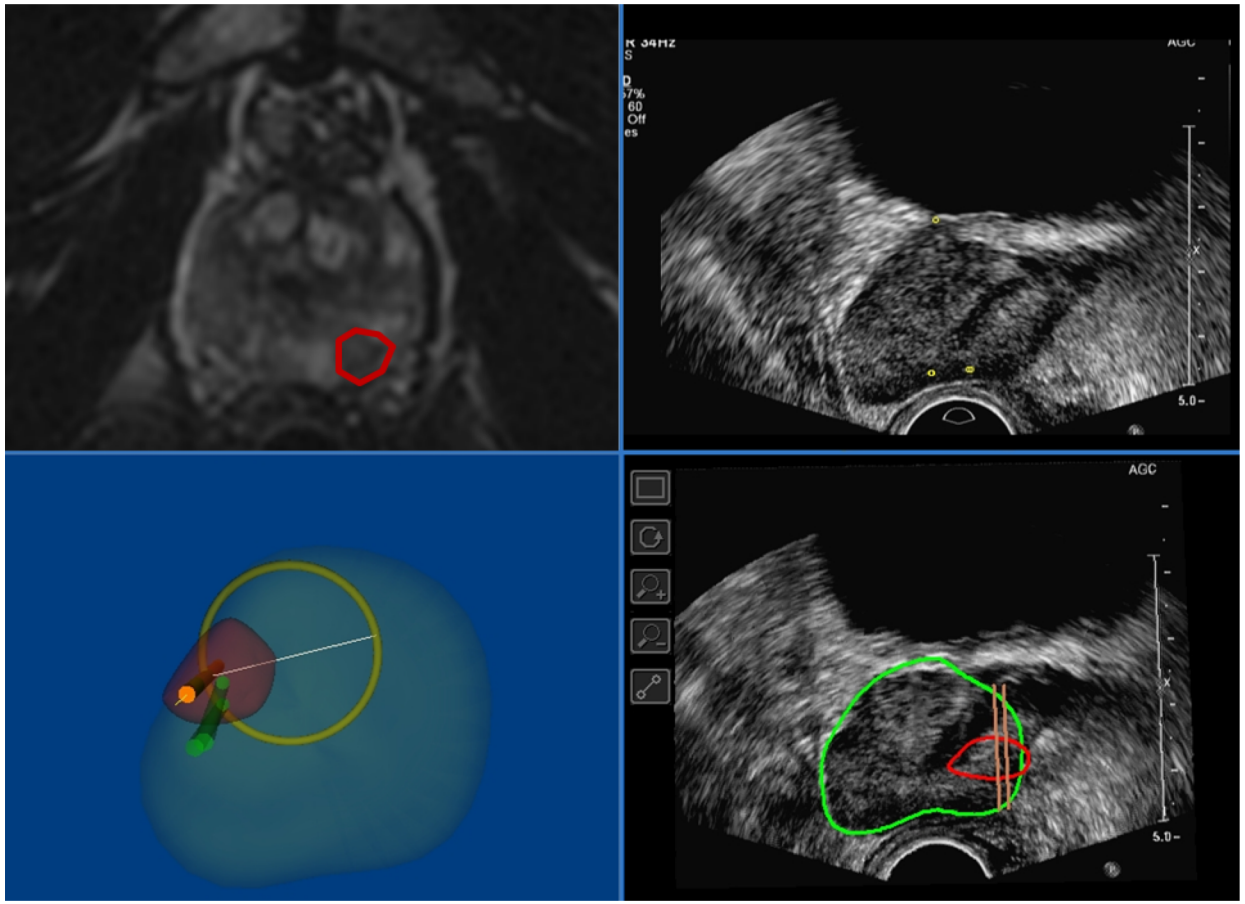


Image Guided Targeted Prostate Biopsy



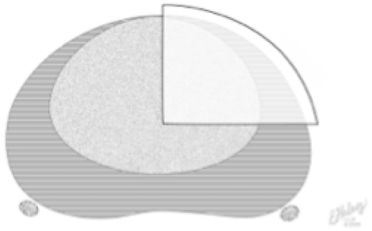
1. In-bore MRI guided Bx

2. Cognitive target Bx

3.MRI-US fusion-guided Bx

Cool et al. Radiology 2010; 254: 587

Ablation Plan and Cancer Biology Dictates Degree of Precision Necessary



Zonal Ablation

Nerve Sparing
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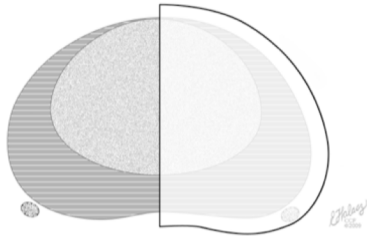
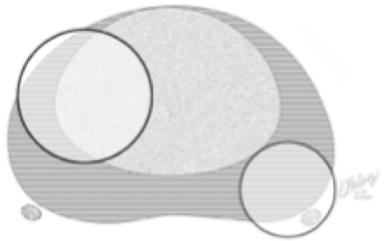
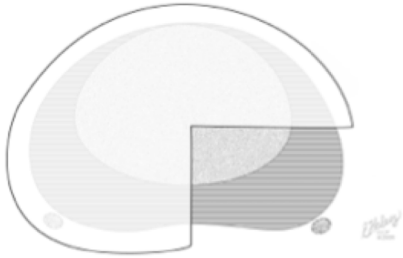


Hemiablation



Targeted Focal Therapy
"TFT"



Hockey Stick
(Anterior)

Hockey Stick
(Posterior)

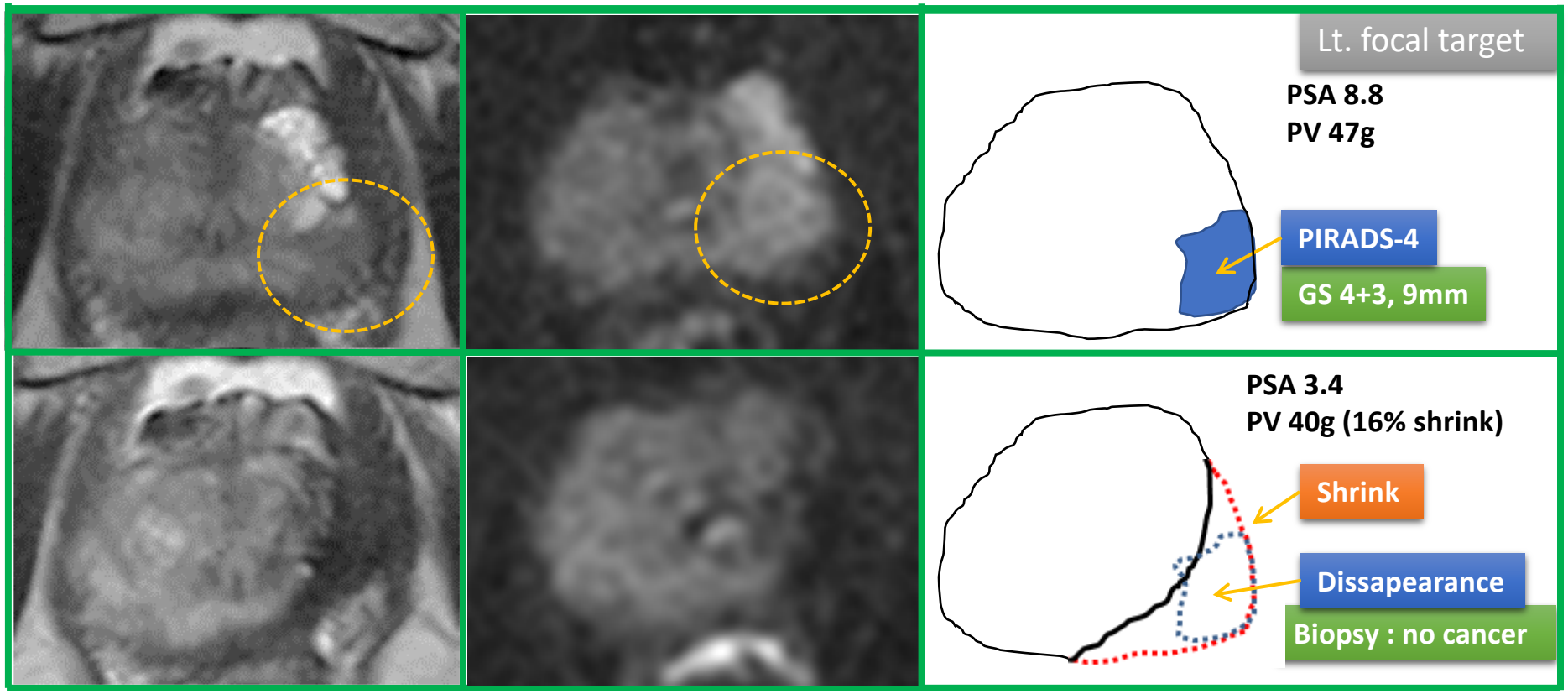
John F. Ward and J. Stephen Jones
Urology 75(6) 1258-60. June 2010

Targeted Focal Cryotherapy

In comparing the *pre- vs. post- mp-MRI* :

Disappearance of the lesion

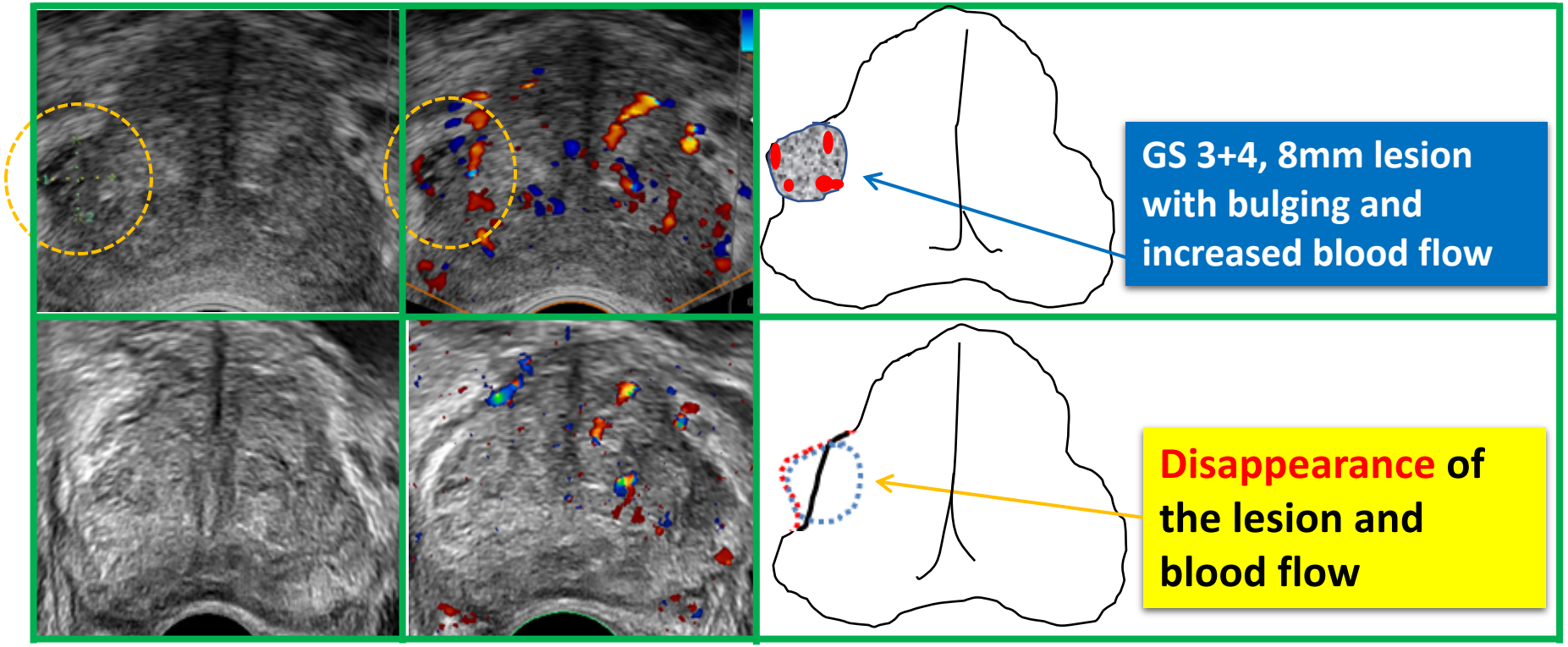
with shrinkage of the prostatic treated-side



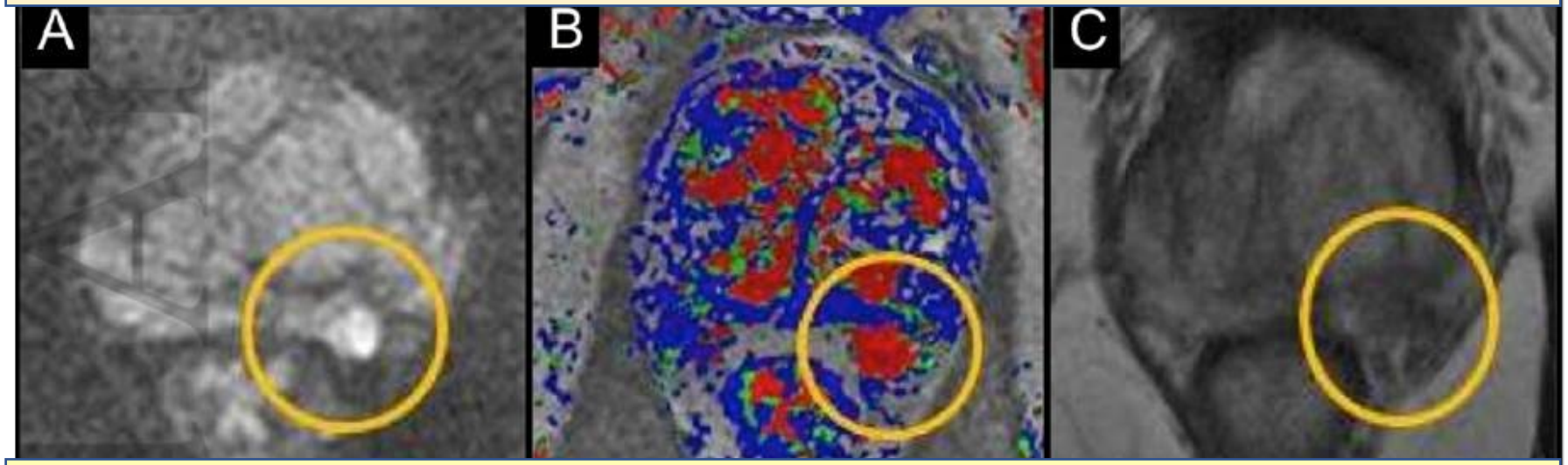
Targeted Focal Cryotherapy

In comparing the *pre- vs. post- mp-TRS* :

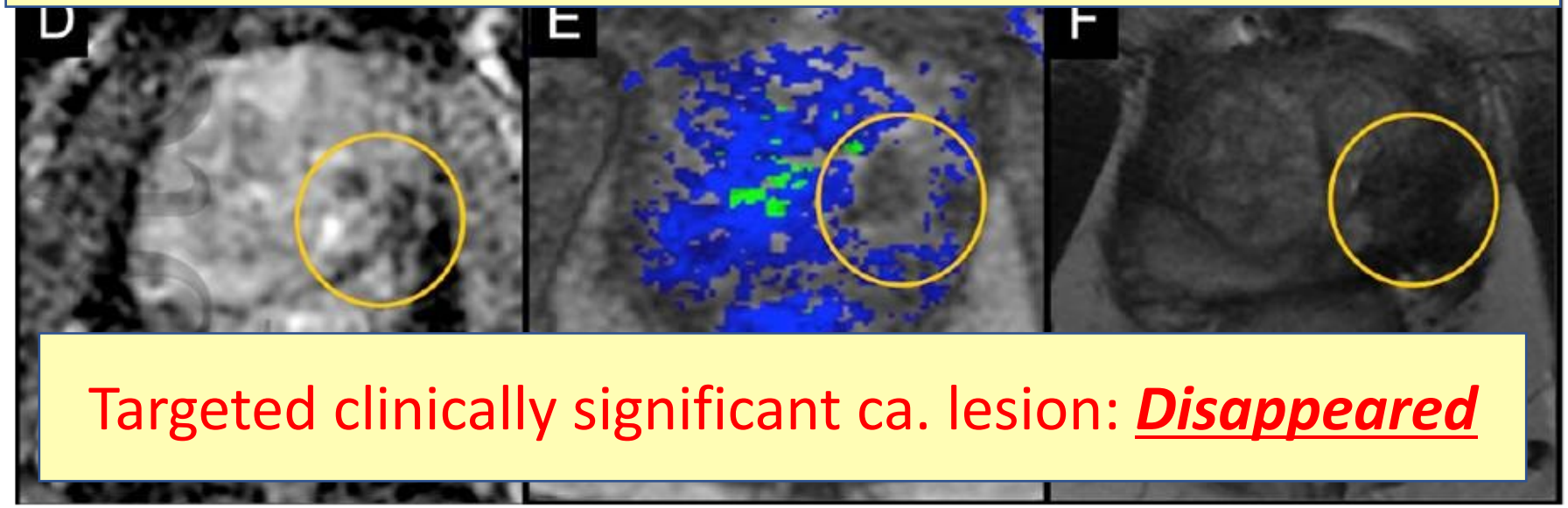
"Disappearance" of the lesion and "no" Doppler flow signal



Pre-



Post-



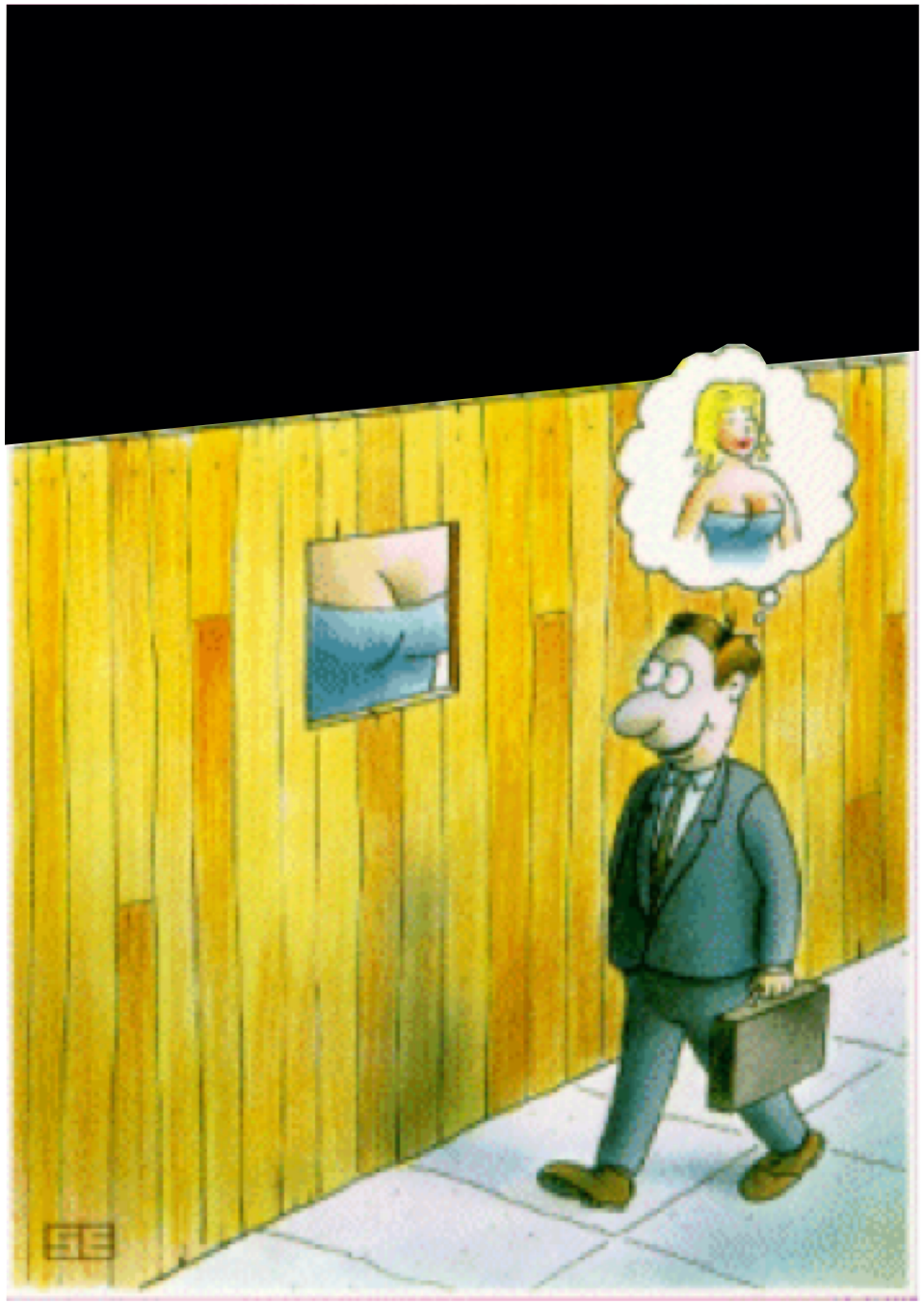
Targeted clinically significant ca. lesion: ***Disappeared***

BJU 2014: 114, 784-9

We again have to be careful about what we think we are seeing....

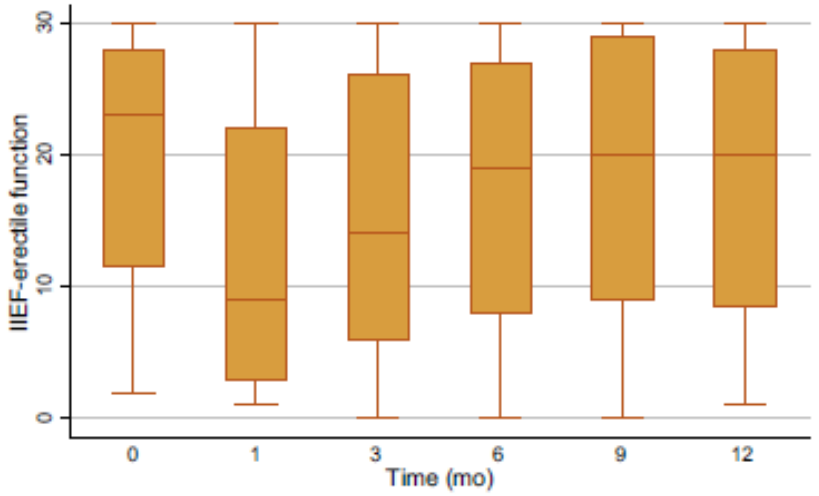
Inadequate (or inaccurate) information.....

.....may lead one to the wrong conclusions!!!



Does a smaller treatment field result in lower morbidity?

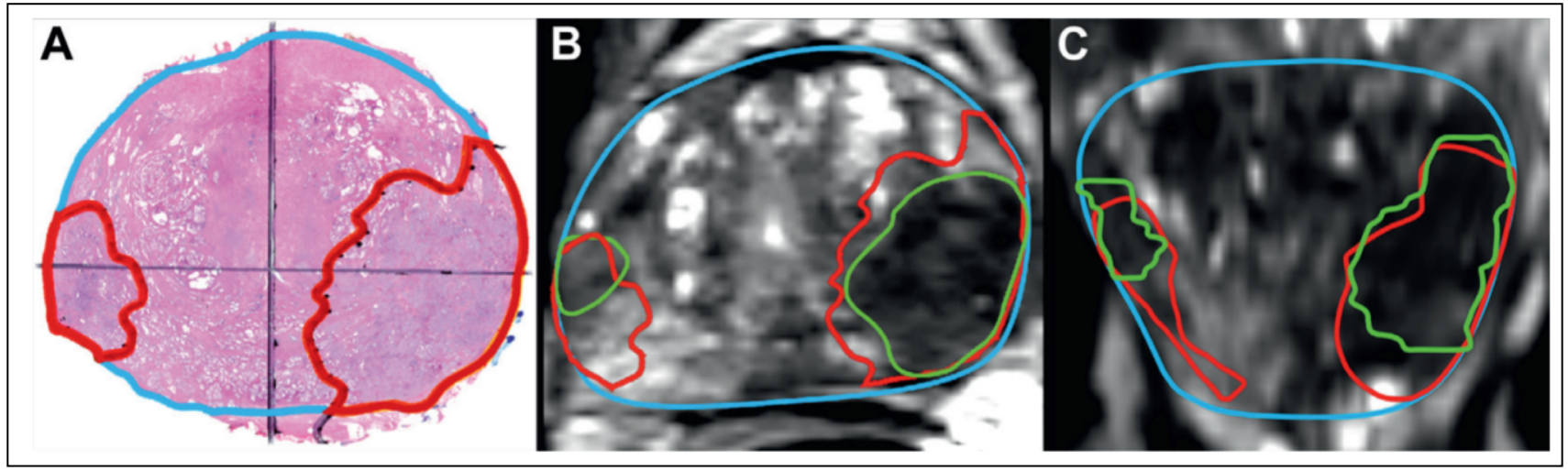
- N=118
- 3 Studies matched (Hemi, Focal, Index) using Sonablate
- IIEF-5 back to normal after 6 months
- 30% using PDF-5 Inhibitors
- **Recovery independent of treatment strategy !!!**



Yap et al. Eur Urol 2015

MRI v. Histology (Volume/Max Diam.)

- 114 Prostatectomy specimens
- Median PSA: 6.5 (4.6–8.7) Gleason: 6 (46%), 3+4(37%), 4+3(17%)
- Preop mpMRI (3 Tesla)
- MRI detected 118 out of 222 Tumors



Correlation of Tumordiamater and volume in MRI vs. Whole Mount Section

Priester et al, J Urol 2017

MRI v. Histology (Volume/Max Diam.)

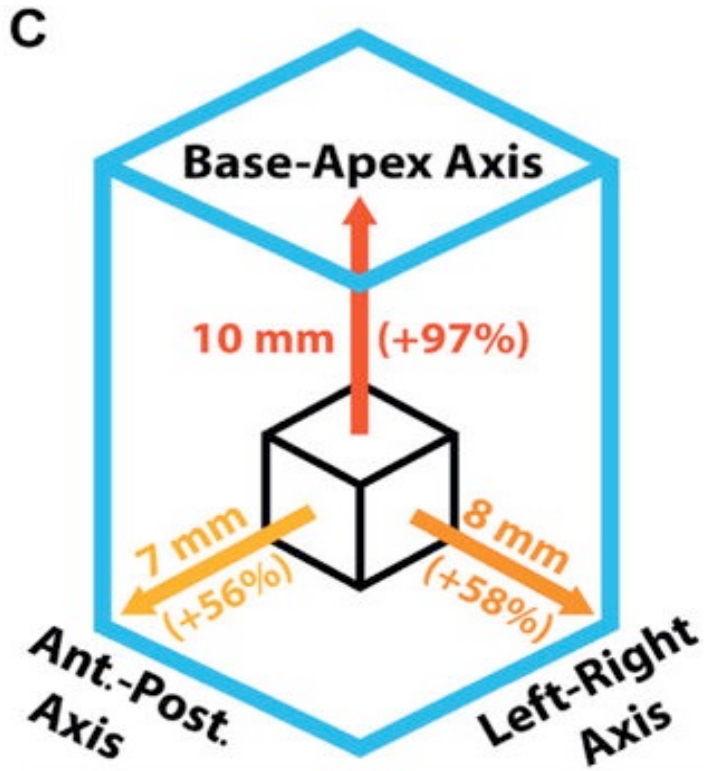
	Average (n = 118)	Gleason 3+3 (n = 22)	Gleason 3+4 (n = 61)	Gleason >= 4+3 (n = 32)
Volume (cc)				
Pathology	2.49	1.1	2.6	3.2
MRI	0.84	0.3	0.7	1.2
Difference	**1.65 cc**	**0.8cc**	**1.9cc**	**2.0cc**
Diameter (mm)				
Pathology	28.4	19.2	30.0	31.9
MRI	17	12.8	16.5	20.5
Difference	**11.4mm**	**6.4mm**	**13.5mm**	**11.4**

Priester et al, J Urol 2017

MRI v. Histology (Volume/Max Diam.)

Variation (mean) by axis

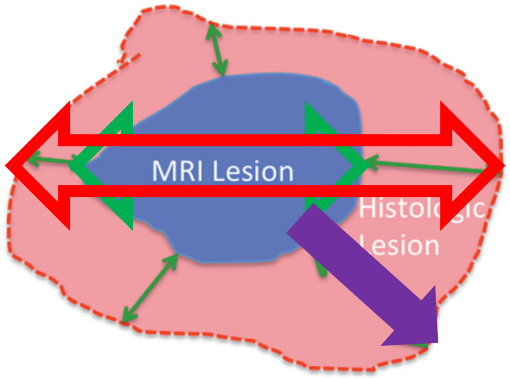
Base-Apex axis error: 10mm
Ant-Post. axis error: 7mm
Left-Right axis error: 8mm



Priester et al, J Urol 2017

MRI v. Histology (Volume/Max Diam.)

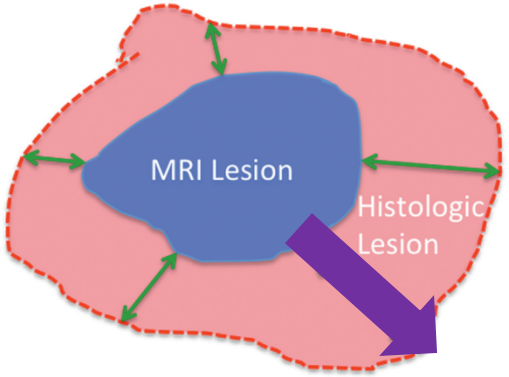
- Mean difference in Diameter: **11.4 mm**
- 50% of Tumors extended > **13.5 mm beyond ROI**



Priester et al, J Urol 2017

MRI v. Histology (Volume/Max Diam.)

- n=33 pts. /46 lesions
- T2WI versus pathology
- Higher Gleason score and tumor size > more safety distance!
- 9 mm safety margin would cover 100% of tumor



Le Bonin et al, J Urol 2015

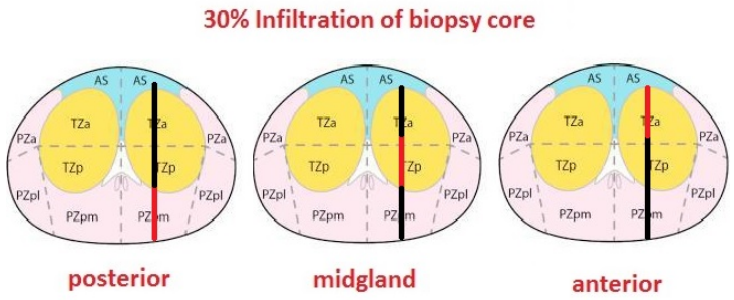
Safety margin based on MRI?

- MRI consistently underestimates the size and extent of prostate tumors.

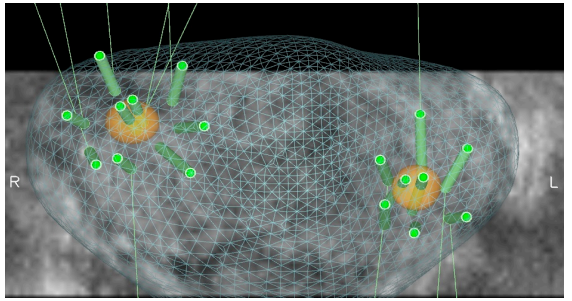
- **Safety margin?**
  5 mm *(Groenendaal et al Radiother Oncol 2010)*
  9 mm *(Le Bonin et al J Urol 2015)*
  More? *(Priesters et al J Urol 2017)*

How could we improve precision?

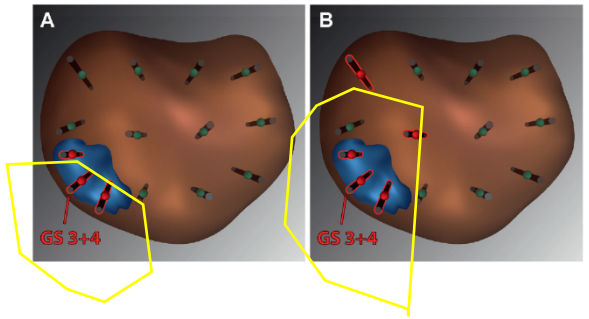
- Labelling of biopsy cores
  - (back/front) or (apex/base)



- Biopsies around lesions on MRI



- Simulation of ablation field prior to treatment based on:
  - Gleason, Tumorsize, MRI, Biopsy

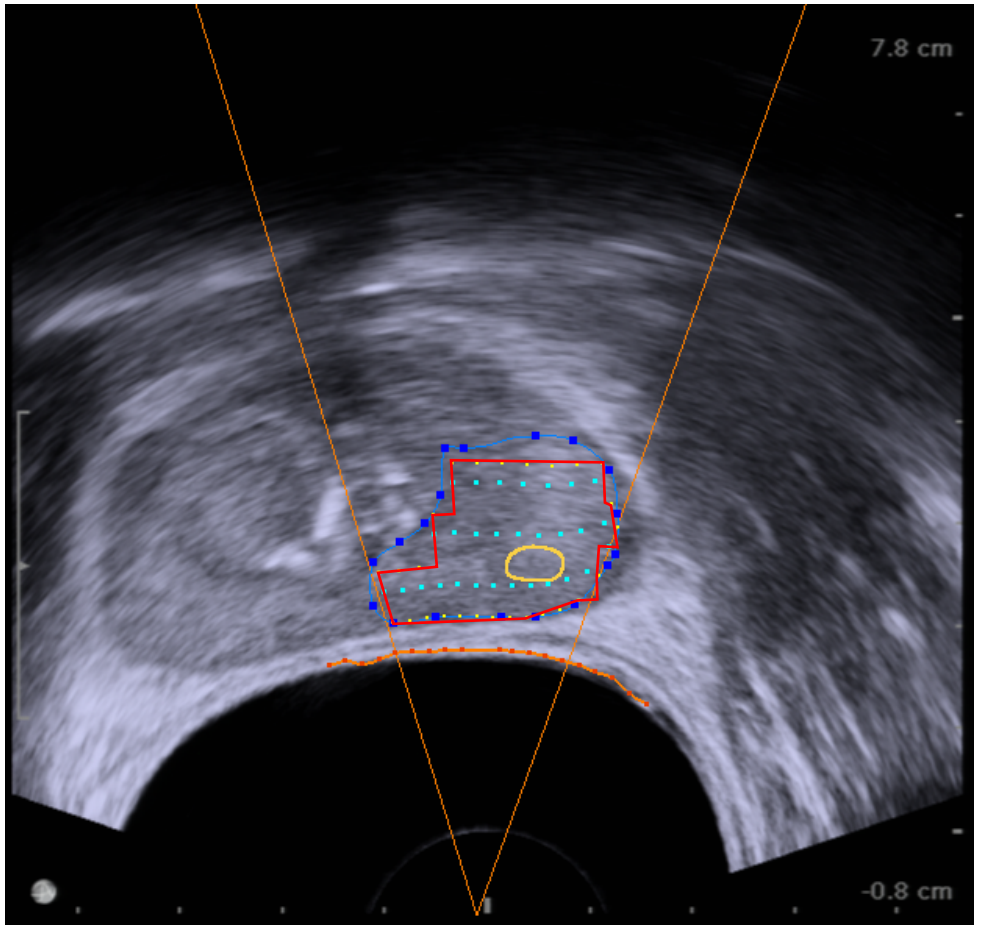


Nasiiri et al, J Urol 2018

HIFU

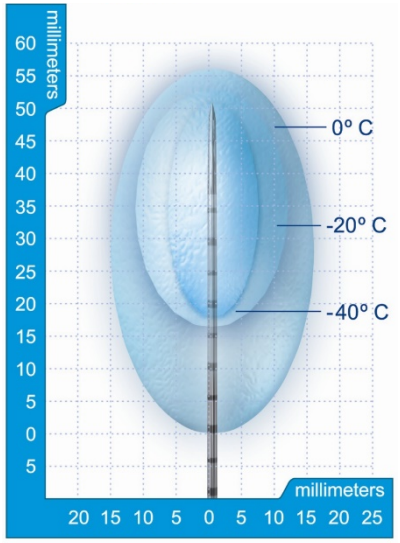
Single Lesion:

- Focal One
  - Hight 5mm
  - Diameter 1.7 mm
- Sonablate
  - Hight 10mm
  - Diameter 3 mm



Cryotherapy

- Lesion:
  - Oval Shaped
  - Time/Thaw cycles
  - Placement of needles



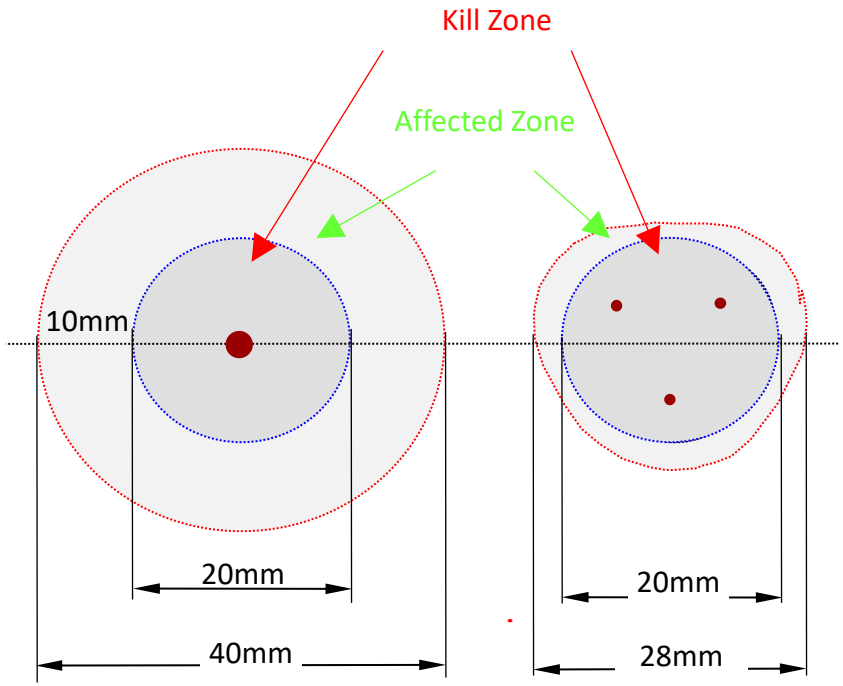
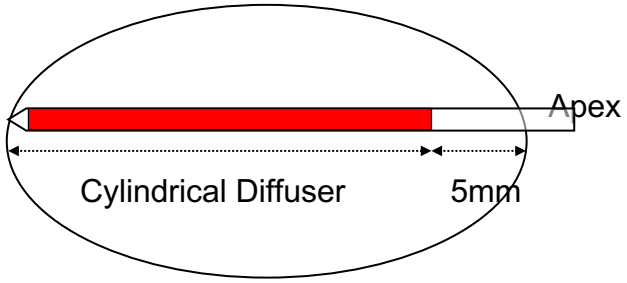
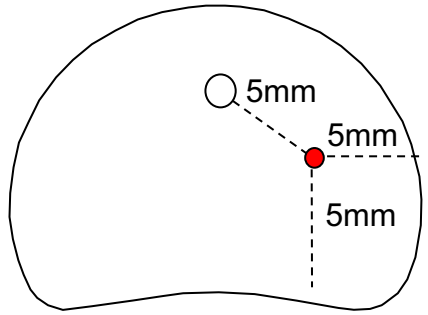
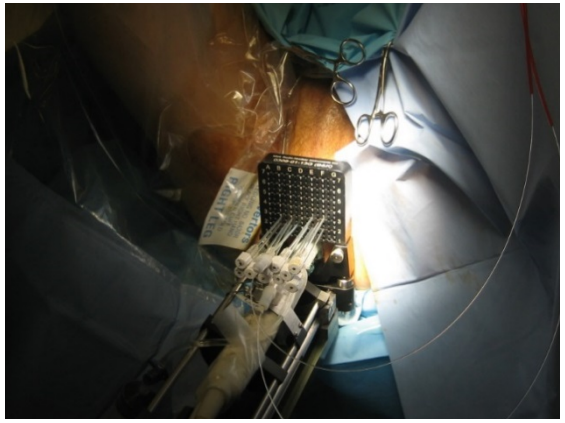


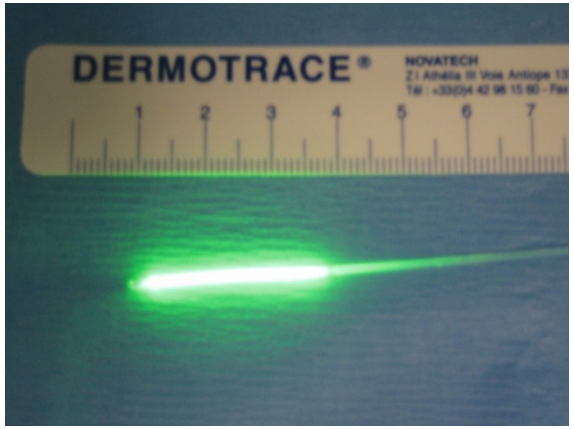
Photo dynamic therapy (PDT)

- Singe Lesion:
  - 5 mm radius around fiber
  - Length defined by length of fiber





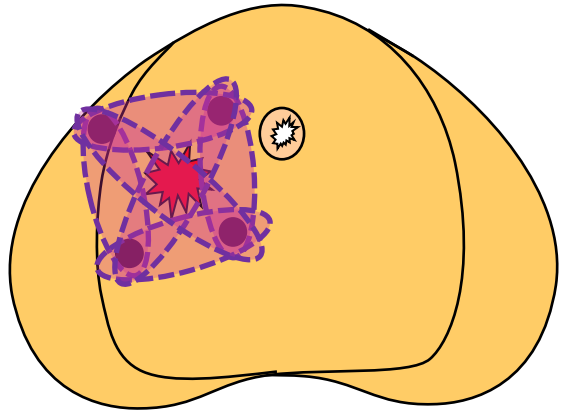




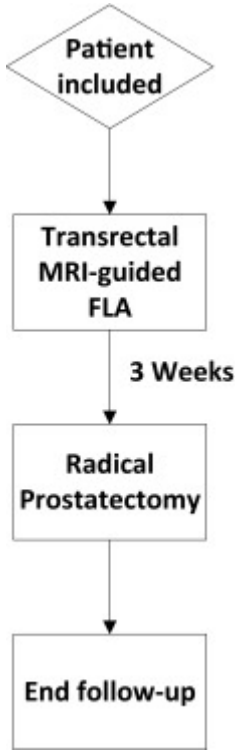
Irreversible Electroporation (IRE)

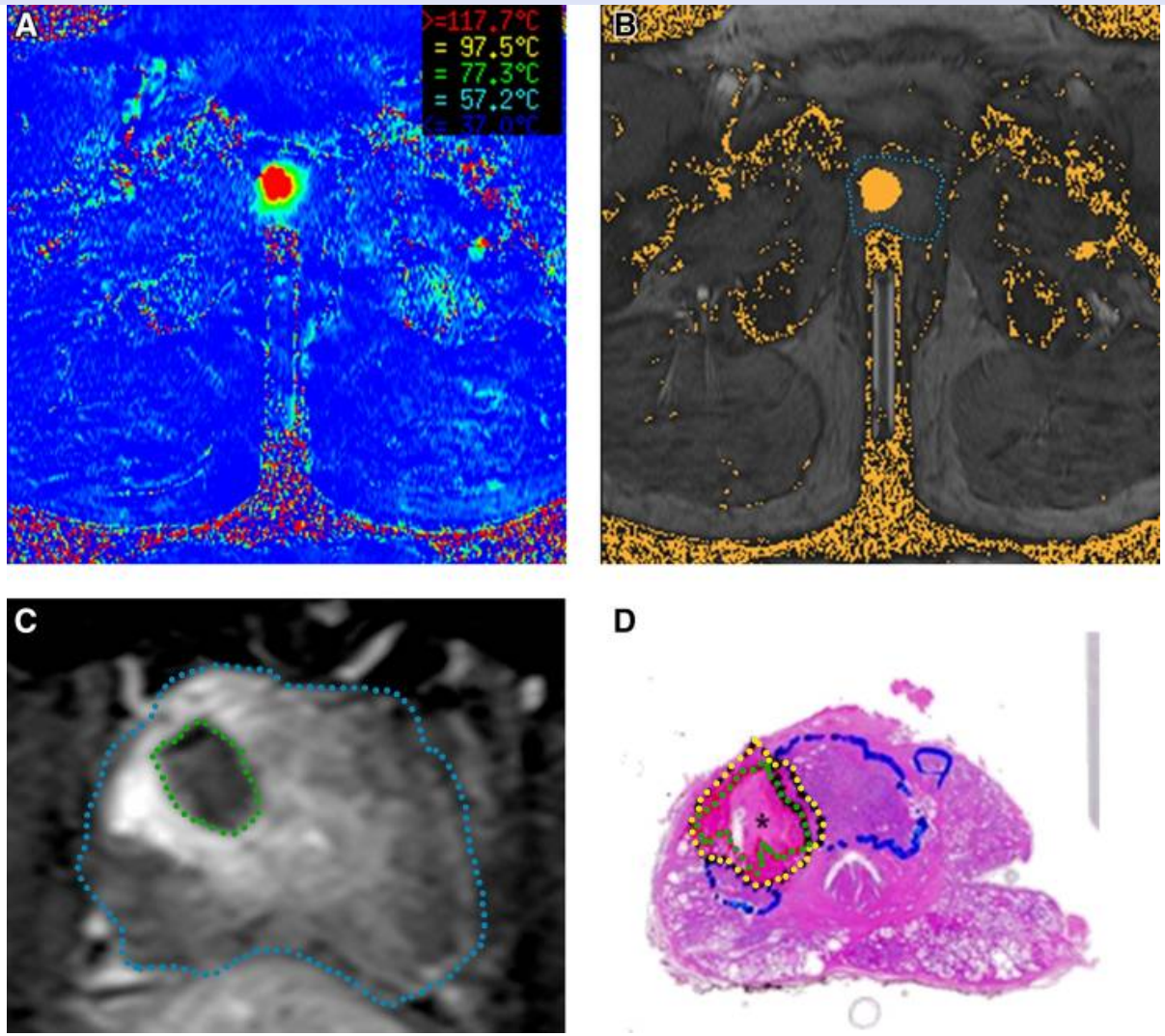
- Ablative field dependent on Probe placement

- Creation of rectangular lesions



MRI guided laser ablation

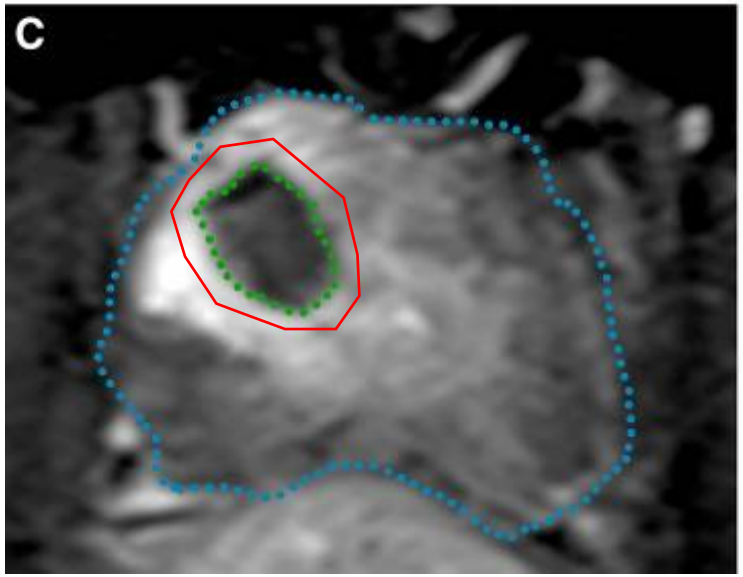


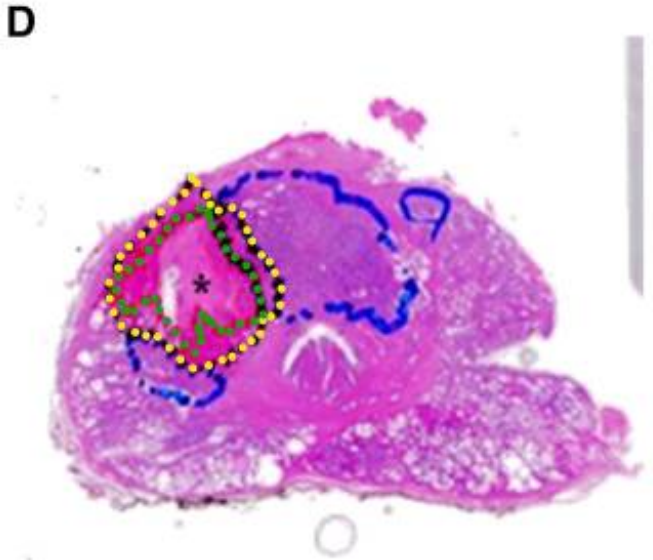


Bomers et al, World J Urol 2017

MRI guided Interstitial laser ablation

- Estimated damage: 8.77 cm3
- Ablated zone on T1: 5.85 cm3
- Transition zone 1-5 mm around necrotic tissue
- Poor correlation of lesion shape

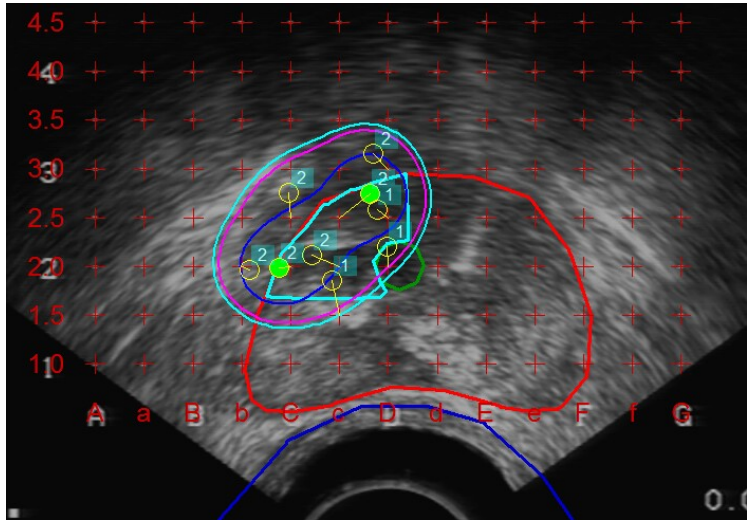


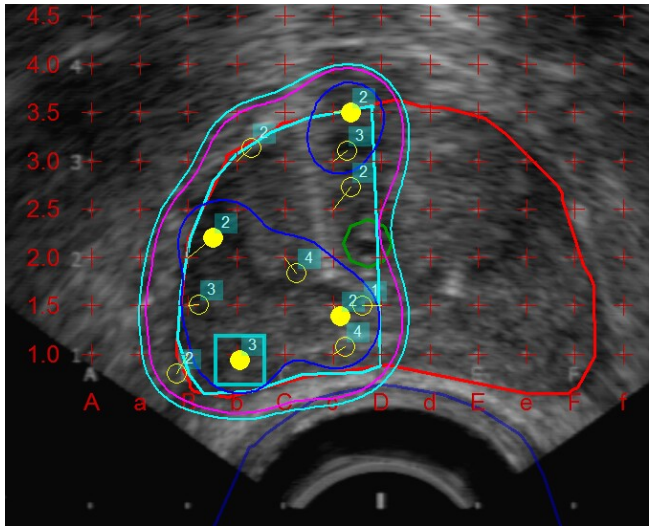


Bomers et al, World J Urol 2017

Brachytherapy

- Ultrafocal (Only Tumor)
- Focal (Hemiablation)
- Focused Therapy
  - Tumor: Ablative dose
  - Gland: Lower dose



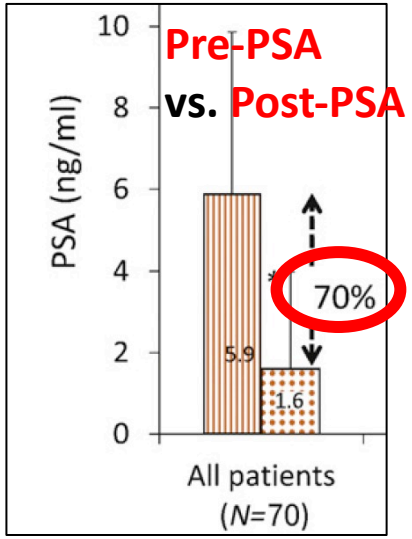


Langley et al, BJU 2012

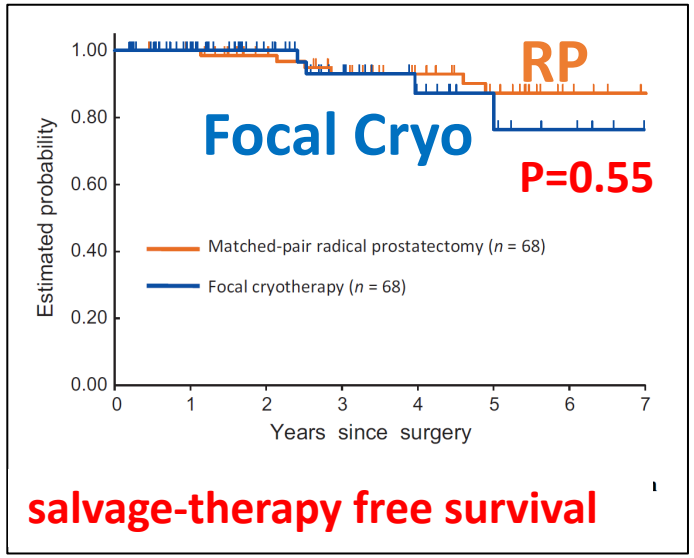
Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years

Duke Bahn [a,b], *Andre Luis de Castro Abreu* [a], *Inderbir S. Gill* [a], *Andrew J. Hung* [a], *Paul Silverman* [b], *Mitchell E. Gross* [a], *Gary Lieskovsky* [a], *Osamu Ukimura* [a,*]

Pre-PSA (5.9) decreased to 1.6 (70%down)



Pair-matched analysis with salvage-therapy free survival between RP vs. Focal Cryo



Eur Urol 62: 55-63-2012

Updated report:

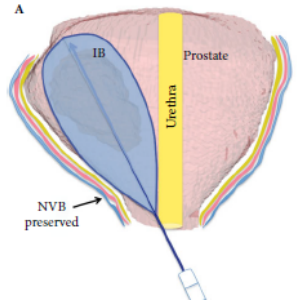
Primary focal cryoablation for *low-, intermediate and high-risk* PCa : outcomes of *180 patients* in median of 33 months follow up

Osamu Ukimura, MD, PhD

Methods

Subject

- 180 patients in Primary Focal Hemi-gland ablation (in 2002-2016)
- Free hand technique under TRUS with 2 freezing-thawing cycles



Abreu et al.
BJU Int 2014

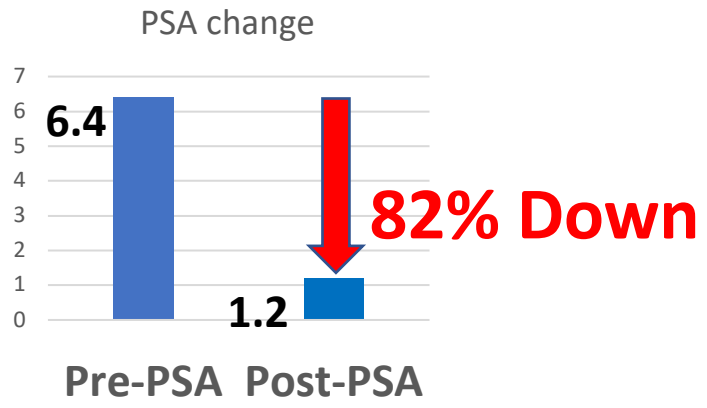
Follow up

- 3,6,12 months and annually thereafter, DRE, PSA and Imaging
- Follow up biopsy was offered 12 and 24 months

Results of PSA change

Table 2 Results of PSA change		PCa risk by D'Amico criteria		
	All	Low	Intermediate	High
No. patients (%)	180	31 (17%)	121 (67%)	28 (16%)
PSA, ng/ml (IQR)	6.4 (4.3-9.3)	5.6 (4.7-6.4)	6.7 (4.4-9.8)	7.1 (3.5-12)
Time to PSA nadir, month, median (IQR)	4 (3-7.8)	5 (3-10)	3 (3-7)	3.5 (3-7.8)
PSA decreased %, median (IQR)*	82 (63-92)	76 (52-87)	83 (62-92)	86 (65-94)
No. PSA decreased>70% (%)	118 (66%)	19 (61%)	79 (65%)	20 (71%)

Pre-PSA (6.4) decreased to 1.2



Results of follow up biopsy

Table 3 Results of follow up biopsy		PCa risk by D'Amico criteria		
	All	Low	Intermediate	High
No. patients (%)	180	31 (17%)	121 (67%)	28 (16%)
No. patients with follow up biopsy (%)	104 (58%)	25 (86%)	63 (52%)	16 (57%)
Total No. follow up biopsy	176	47	101	28
Follow up biopsy outcomes N (%)				
Any Gleason Treated lobe	16 (9%)	1 (3%)	10 (8%)	5 (18%)
Untreated lobe	37 (21%)	8 (26%)	24 (20%)	5 (18%)
Gleason ≥ 7 Treated lobe	15 (8%)	1 (3%)	10 (8%)	4 (14%)
Untreated lobe	17 (9%)	1 (3%)	14 (12%)	2 (7%)

Functional outcomes (Potency) after focal cryoablation of the prostate

Parameter	N (%)
Potency	N=180
No. Potent men **pre** PFC	111 (62%)
Maintain potency **post** PFC	84 (76%)
Use of pharmaceutiscs	25 (23%)

Functional outcomes (Continence) after focal cryoablation of the prostate

Parameter	N (%)
Continence	**N=180**
No. Continent men **pre** cryoablation	177 (98%)
Retained continence **post** cryoablation	172 (97%)
AUA-Symptom Score	
Pre AUA SS, median (IQR) 145pts	7 (3-12)
Post ASA SS, median (IQR) 117pts	5 (3-8)
Difference from pre to post AUA SS, median (IQR) 109pts	2 (-1 to 5)

Morbidity of Focal Therapy in the Treatment of Localized Prostate Cancer

Eric Barret[a,*], *Youness Ahallal*[a], *Rafael Sanchez-Salas*[a], *Marc Galiano*[a], *Jean-Marc Cosset*[a], *Pierre Validire*[b], *Petr Macek*[a], *Matthieu Durand*[a], *Dominique Prapotnich*[a], *François Rozet*[a], *Xavier Cathelineau*[a]

[a] *Urology Service, Department of Surgery, Institut Mutualiste Montsouris, Paris, France;* [b] *Department of Pathology, Institut Mutualiste Montsouris, Paris, France*

106 Focal therapy patients

- Cryotherapy 50 (47%)
  - (Galil Medical, Inc., USA)
- VTP 23 (22%)
  - (Steba Biotech, France)
- HIFU 21 (20%)
  - (EDAP TMS, France).
- Brachytherapy 12 (11%)
  - (‘‘free’’ iodine 125 seeds)

Euro Urol 63(2013) 618-622

Morbidity of Focal Therapy in the Treatment of Localized Prostate Cancer

Eric Barret[a,*], *Youness Ahallal*[a], *Rafael Sanchez-Salas*[a], *Marc Galiano*[a], *Jean-Marc Cosset*[a], *Pierre Validire*[b], *Petr Macek*[a], *Matthieu Durand*[a], *Dominique Prapotnich*[a], *François Rozet*[a], *Xavier Cathelineau*[a]

[a] *Urology Service, Department of Surgery, Institut Mutualiste Montsouris, Paris, France;* [b] *Department of Pathology, Institut Mutualiste Montsouris, Paris, France*

- 13% treatment related complications
  - 9 patients urinary retention (grade 1)
    - 5 HIFU
    - 4 Cryotherapy
  - 1 patient pelvic pain (grade 1)
    - Cryotherapy
  - 1 patient gross hematuria (grade 2)
    - Cryotherapy
  - 1 patient Rectal fistula (grade 3b)
    - Cryotherapy
    - Temporary diverting colostomy
  - 1 patient urethral stricture (grade 3b)
    - Cryotherapy

Euro Urol 63(2013) 618-622

Cryotherapy Complications?

- Rectal fistulas near 0% in modern cryo series
- Urethral strictures near 0% when urethral warmer used properly

- Babaian RJ et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol 2008;180:1993–2004.
- Jones JS, et al. Whole gland primary prostate cryoablation: initial results from the cryo on-line data registry. J Urol 2008; 180:554–8.
- Pisters LL, et al. Salvage prostate cryoablation: initial results from the cryo on- line data registry. J Urol 2008;180:559–64.
- Miller DC, Pisters LL, Belldegrun AS. Cryotherapy for prostate cancer, Chapter 101. In: Wein AJ, Ka-voussi LR, Novick AC, et al, editors. Campbell- Walsh Urology, 9th edition. Saunders, 2007.

Refining Focal Therapy

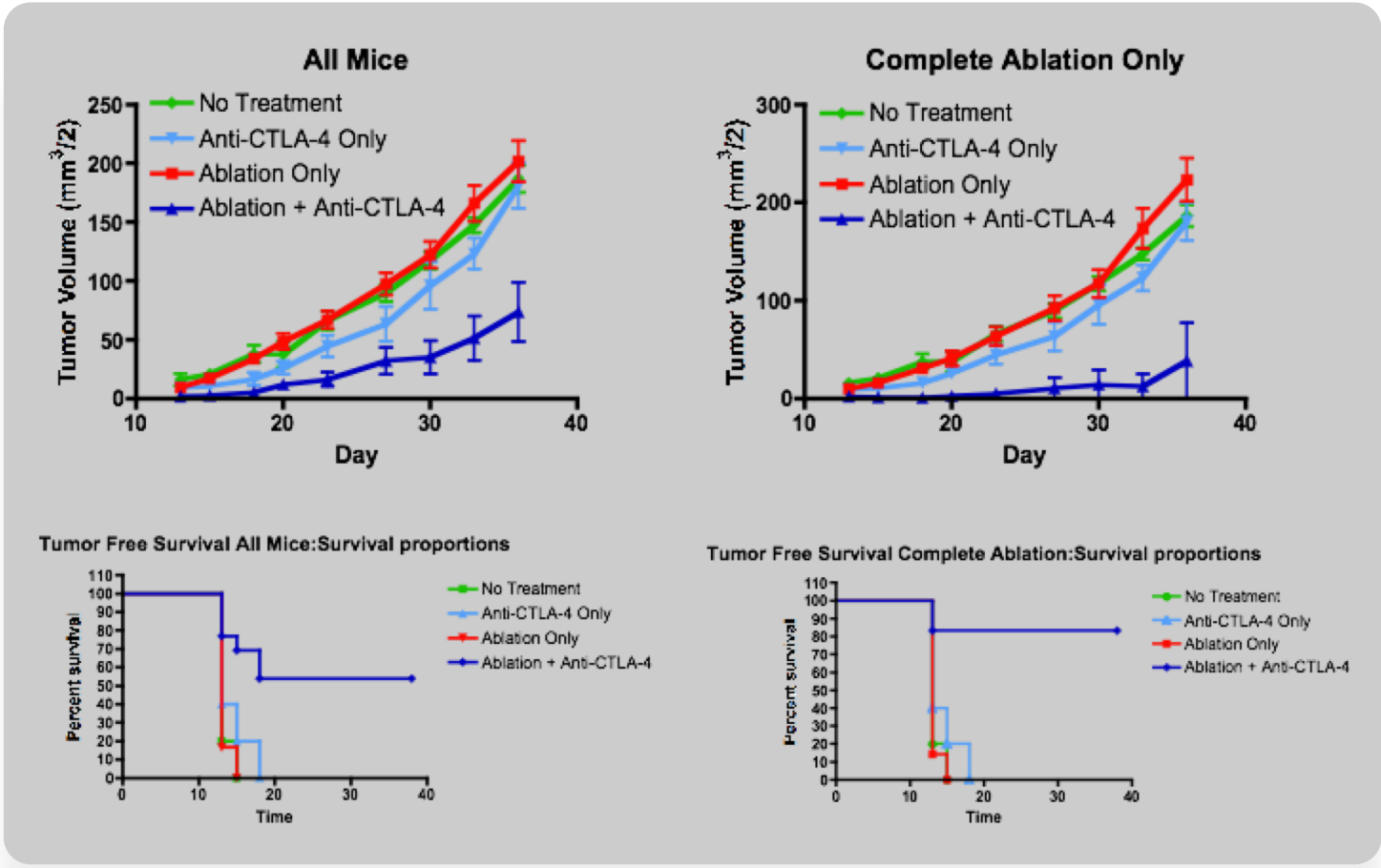
- Repeat focal therapy
  - Independent mutations
  - Metachronous tumors
  - Chronic disease management

- Functional Outcomes
  - How much can be ablated before there is an impact on QOL?
  - Does location matter?
    - Apex vs. Base
  - Does ablative energy source influence QOL?
    - Cold vs. Heat vs. Vascular

Focal Therapy as Part of Multi-Modal Strategy

- Locally Advanced or Metastatic disease
- Treatment Induced Immuno Therapy
  - Check point Blockade (anti-CTLA-4)
  - Auto-immunization (APC activation)
- Limit local morbidity while treating distant disease

Treatment Induced Immuno-Therapy



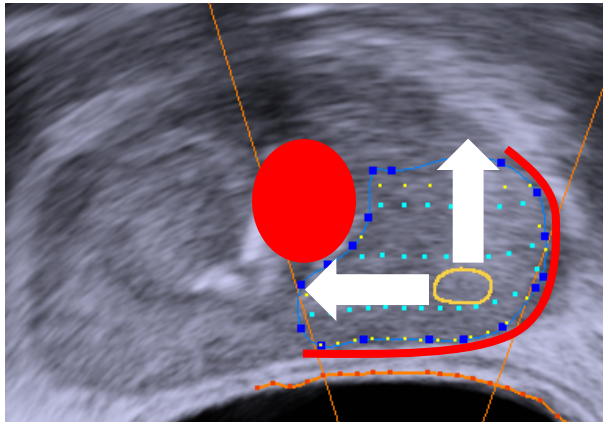
Waitz R, et al.; Cancer Res 72(2) 2012

Patient Selection For Focal Therapy @ M.D. Anderson Cancer Center

- Remain under clinical protocol
- WELL informed of intentions, rationale and limited data
- Multiparametric Contrast Enhanced Endorectal MRI
  - Decrease risk of undersampling
- 3-Dimensional biopsy
  - Commitment to post-treatment biopsy

Conclusion

- MRI underestimates the size and extent of prostate tumors
- Higher Gleason score and tumor size > more safety distance!
- Apex to base axis > more safety distance!
- Treatment device makes a difference




Thank You!