Focal therapy for prostate cancer: seriously or seriously?

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Disclosures

- Speaking honorarium from Elekta in 2014

Outline

- What is the rationale for focal therapy?
- Who is a candidate?
- How do you identify candidates?
- What treatment modality should be used?
- What volume do you treat?
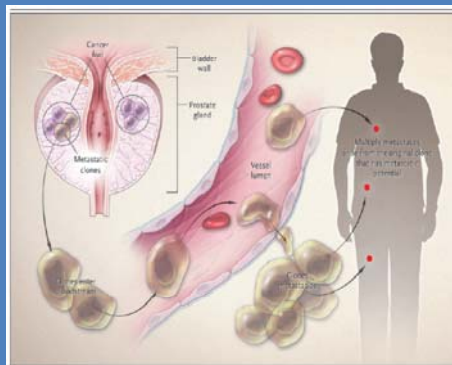- Is there data to support doing this?

What's wrong with whole gland therapy?

- Alternative to **active surveillance** argument
  - Focal is compromise b/w whole gland and AS
    - Problem: focal is still overtreatment
- Alternative to **definitive treatment** argument
  - The whole gland is not the target
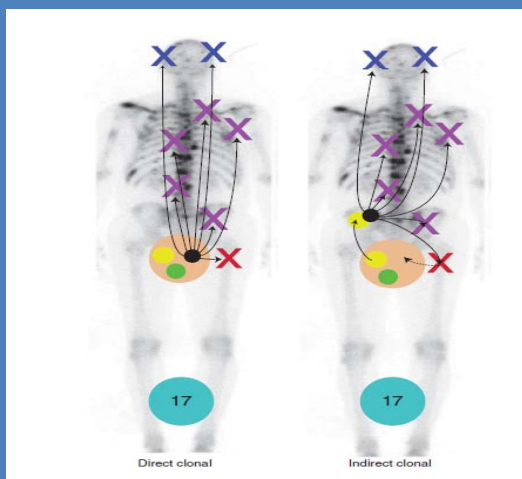
Index Lesion Hypothesis

- Disease progression is driven by **dominant lesion**
- "Active surveillance" of small **insignificant** satellite lesions

Ahmed H. NEJM. 2009.

Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer

Wennuan Liu[1,9], Sari Laitinen[2,9], Sofia Khan[3], Mauno Vihinen[3], Jeanne Kowalski[4], Guoqiang Yu[5], Li Chen[5], Charles M Ewing[6], Mario A Eisenberger[7], Michael A Carducci[7], William G Nelson[7], Srinivasan Yegnasubramanian[7], Jun Luo[6,7], Yue Wang[5], Jianfeng Xu[1], William B Isaacs[6,7], Tapio Visakorpi[2] & G Steven Bova[6–8]
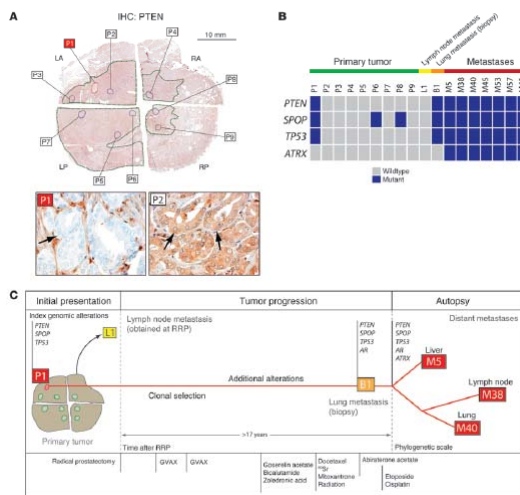
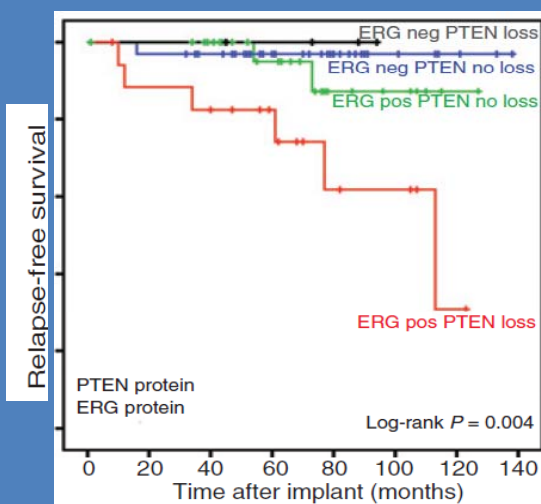Tracking the clonal origin of lethal prostate cancer

Michael C. Haffner,[1] Timothy Mosbruger,[1] David M. Esopi,[1] Helen Fedor,[2] Christopher M. Heaphy,[2] David A. Walker,[1] Nkosi Adejola,[1] Meltem Gürel,[1] Jessica Hicks,[2] Alan K. Meeker,[1,2,3] Marc K. Halushka,[2] Jonathan W. Simons,[4] William B. Isaacs,[1,2,3] Angelo M. De Marzo,[1,2,3] William G. Nelson,[1,2,3] and Srinivasan Yegnasubramanian[1]

J Clin Invest. 2013;123(11):4918–4922. doi:10.1172/JCI70354.

Recurrent Prostate Cancer Genomic Alterations Predict Response to Brachytherapy Treatment

Jacqueline Fontugne[1], Daniel Lee[1,2], Chiara Cantaloni[5], Christopher E. Barbieri[1,2], Orazio Caffo[6], Esther Hanspeter[9], Guido Mazzoleni[9], Paolo Dalla Palma[7], Mark A. Rubin[1,2,3], Giovanni Fellin[8], Juan Miguel Mosquera[1,3], Mattia Barbareschi[7], and Francesca Demichelis[4,5]

Cancer Epidemiol Biomarkers Prev; 23(4); 1–7.

Definition of clinically significant

	Gleason grade	Maximum cancer core length	Reference standard
Epstein et al. [4]	≥3+4	≥3 mm	TRUS biopsy
Stamey et al. [5]	≥3+3	≥3 mm	Cystoprostatectomy specimen
Harnden et al. [6]	≥3+4	≥3 mm	Systematic review biopsy and radical prostatectomy
Goto et al. [7]	≥3+4	≥2 mm	TRUS biopsy
UCL definition 2 [8]	≥3+4	≥4 mm	TPM
UCL definition 1 [8]	≥4+3	≥6 mm	TPM

TPM, transperineal prostate mapping; TRUS, trans-rectal ultrasound; UCL, University College London.

Wolters Kluwer Health   OvidSP

Who is a candidate?

Focal Therapy in Prostate Cancer: International Multidisciplinary Consensus on Trial Design

TABLE 3 Consensus findings on patient selection for focal therapy

1. Life expectancy >10 years
2. PSA ≤15 ng/mL
3. Multi-parametric (T1W/T2W, diffusion-weighting, dynamic contrast enhancement ± spectroscopy) magnetic resonance imaging prior to biopsy
4. Bilateral template-guided prostate mapping biopsy with 5 mm sampling frame
5. Unilateral disease; lesion size ≤ 0.5 mL (approximately equates to maximum cancer length of 10 mm) with or without clinically insignificant disease on the contralateral side (cancer core length ≤ 3 mm)
6. Gleason score of index lesion 6–7 (3 + 4)
7. Tumour stage ≤ T2b
8. Prostate size ≤ 60 mL

Langley S et al. BJUI. 2012.

Focal Therapy in Prostate Cancer: International Multidisciplinary Consensus on Trial Design

Table 2 – Inclusion and exclusion criteria for focal therapy trials

Inclusion criteria	
Serum PSA	PSA <15 ng/ml
	PSA >15 ng/ml should be counselled with caution
Clinical stage	T1c–T2a
Pathology	Gleason score 3 + 3
	Gleason score 3 + 4
Life expectancy	>10 yr [35]
Prostate volume	Any; except in case of HIFU: <40 ml
Exclusion criteria	

Previous treatment:
Previous treatment of the primary cancer within the prostate
Previous hormone treatment for prostate cancer within 6 months before trial
Previous radiation to pelvis
Active urinary tract infection
Radiologic imaging:
PI-RADS score <3; clinically significant cancer is equivocal [26]
Extracapsular extension or seminal vesicle invasion
Lymph node or bone metastasis

HIFU = high-intensity focused ultrasound; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.
These criteria are the minimal requirements for including and excluding candidates in focal therapy trials.
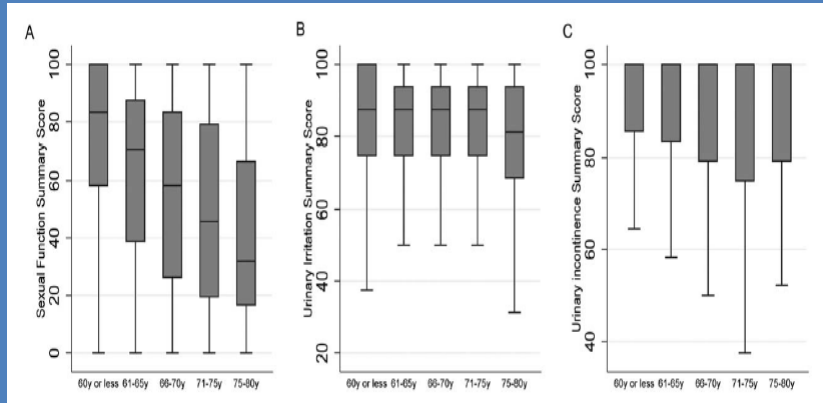
Van den Bos W et al. European Urology. 2014.

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Contemporary Prevalence of Pretreatment Urinary, Sexual, Hormonal, and Bowel Dysfunction

Defining the Population at Risk for Harms of Prostate Cancer Treatment

Matthew J. Resnick, MD[1,2]; Daniel A. Barocas, MD, MPH[1]; Alicia K. Morgans, MD[3]; Sharon E. Phillips, MSPH[4]; Vivien W. Chen, MPH, PhD[5]; Matthew R. Cooperberg, MD, MPH[6]; Michael Goodman, MD, MPH[7]; Sheldon Greenfield, MD[8]; Ann S. Hamilton, PhD[9]; Karen E. Hoffman, MD, MHSc, MPH[10]; Sherri H. Kaplan, MPH, MS, PhD[11]; Lisa E. Paddock, MPH, PhD[12]; Antoinette M. Stroup, PhD[13]; Xiao-Cheng Wu, MD, MPH[5]; Tatsuki Koyama, PhD[4]; and David F. Penson, MD, MPH[1,2]
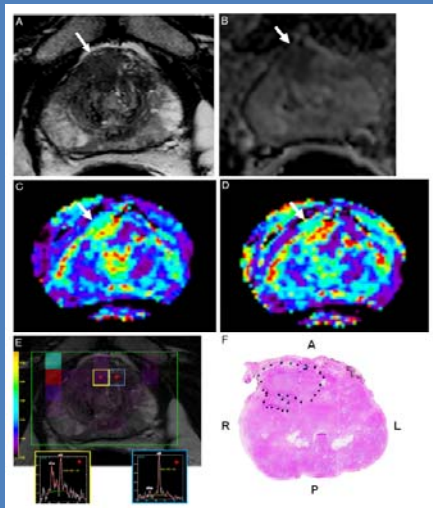
Cancer   April 15, 2014

How do you identify the index lesion short of doing a prostatectomy?

- Template mapping biopsies
- Multi-parametric MRI

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The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer: recommendations from a consensus panel
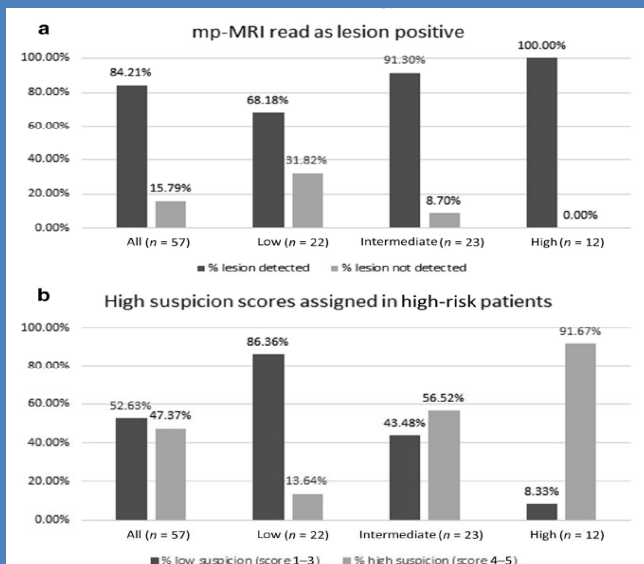

Template-guided saturation biopsies are no longer necessary when a high quality state of the art mpMRI is available; however, suspicious lesions should always be confirmed by (targeted) biopsy.

- 90% sensitivity/specificity for finding disease > 0.5 mL and GS ≥ 7

Turkbey B et al. J Urol 2011.
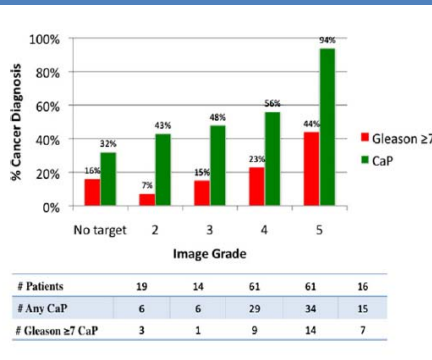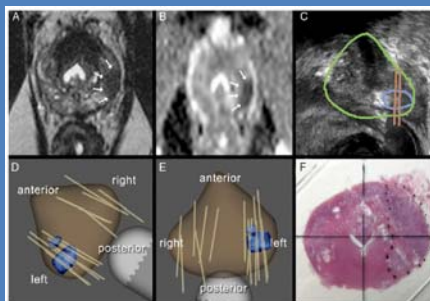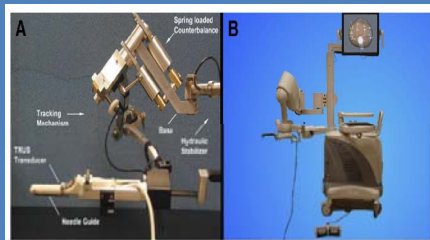Villers A et al. J Urol 2006.

Muller B et al. BJUI. 2014.

Importance of Lesion Score

Anderson E et al. Brachytherapy. 2014.

U/S-MRI Fusion

Sonn G. Journal of Urology. 2012.

What treatment modality?

FT: Energy Modalities
Moderator: **Thomas Polascik** (Durham, USA)

Laser / **TBA**
HIFU   EDAP / **Sebastian Crouzet** (Lyon, France)
HIFU   Sonacare / **Hashim Ahmed** (London, UK)
Cryo / **John Ward** (Houston USA)
Electroporation / **Jean de la Rosette** (Amsterdam, Netherlands)
Vascular Photodynamic / **Jonathan Coleman** (New York, USA)
Histotripsy /   **William Roberts** (Ann Arbor, USA)
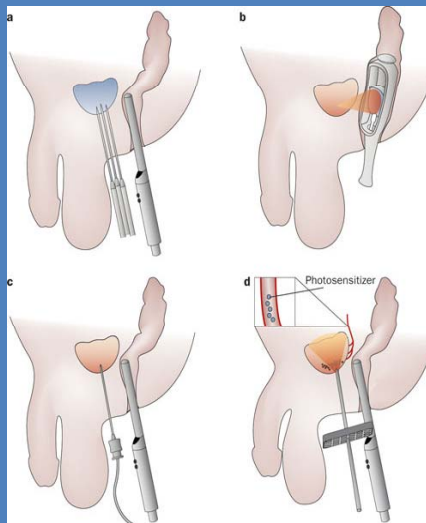
Brachytherapy??

Treatment Techniques
Achieving the Trifecta

Cryotherapy
Impotence 80%
Incontinence 5%
Pelvic/rectal pain 1-11%
Fistula 1%

HIFU
Impotence 44%
Obstruction 17%
Urethral stricture 12%
Incontinence 8%

Laser
Limited clinical data

PDT
Limited long term data
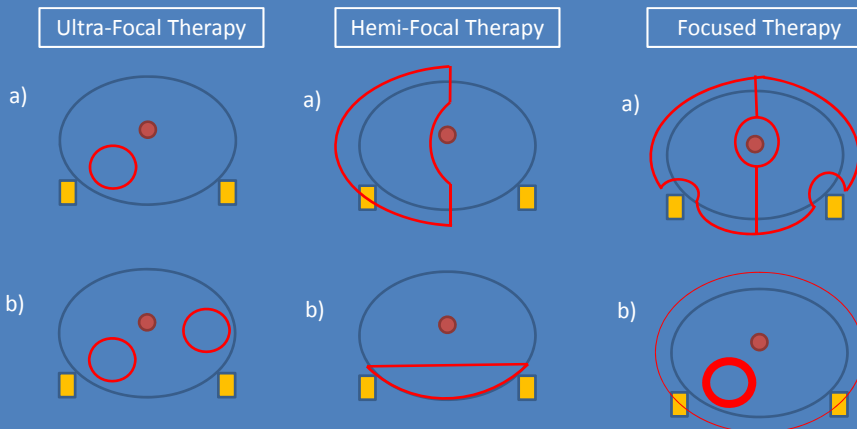
Not included is
electroporation

Lindner U et al. Nature Reviews Urology. 2010.

Stakes of treatment

- HDR brachytherapy
  - > 90% PSA control (low/int risk)
  - 10% GU (Late)
  - < 5% GI (Late)
  - ~50% ED

What volume do you treat?

| Ultra-Focal Therapy | Hemi-Focal Therapy | Focused Therapy |

a)   a)   a)

b)   b)   b)

Langley S et al. BJU Int. 2012.

Distribution of prostate cancer based on prostatectomy specimens

	# of patients	Disease able to be treated with HG approach	Disease able to be treated with UF approach
GS 3+3	16	37%	0%
GS 3+4	71	37%	11%
GS 4+3	25	20%	24%
GS ≥ 8	25	16%	12%

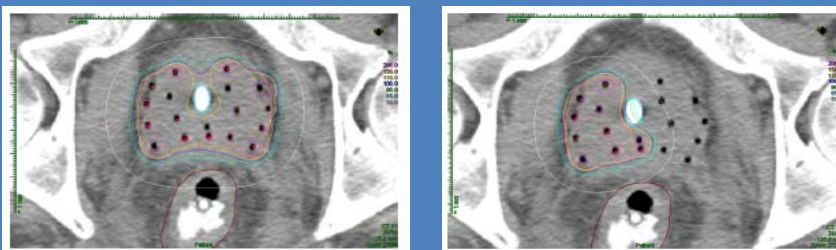Sifuentes J et al. Manuscript in preparation.

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Prostate Cancer Tumour Features on Template Prostate-mapping Biopsies: Implications for Focal Therapy

Paras B. Singh [a], Chukwuemeka Anele [b], Emma Dalton [b], Omar Barbouti [b], Daniel Stevens [c], Pratik Gurung [a], Manit Arya [d,e], Charles Jameson [f], Alex Freeman [f], Mark Emberton [a,d], Hashim U. Ahmed [a,d,]*

European Urology. 2013.

Whole Gland vs Hemi-Gland

Radiation Dose	Rectum		Bladder		Urethra	
	WG	HG	WG	HG	WG	HG
$D_{0.1cc}$ (%)	76	71	84	82	107	98
D_{1cc} (%)	68	59	73	64	103	83
D_{2cc} (%)	64	53	68	56	95	69
	9%		12%		26%	

Kamrava M et al. Brachytherapy. 2013.

Managing "Spill" Dose

| HG Right | + | HG Left | = | Overdose |

Target	%
D_{90}	155
V_{100}	100
V_{150}	93

| HG Left | + | Partial Right | = | Acceptable |

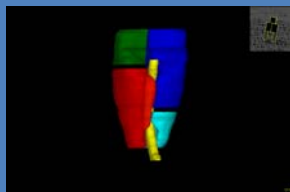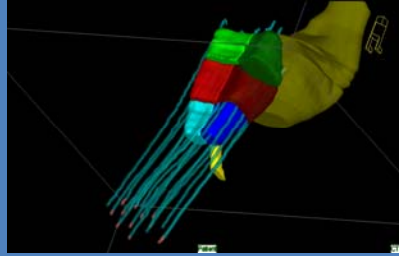| Target	%
D_{90}	108
V_{100}	98
V_{150}	34

Kamrava M et al. Brachytherapy. 2013.

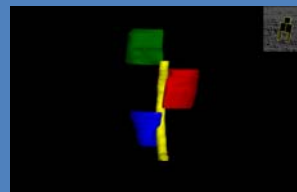# Example of actual HG implant

What's ideal subvolume to treat?
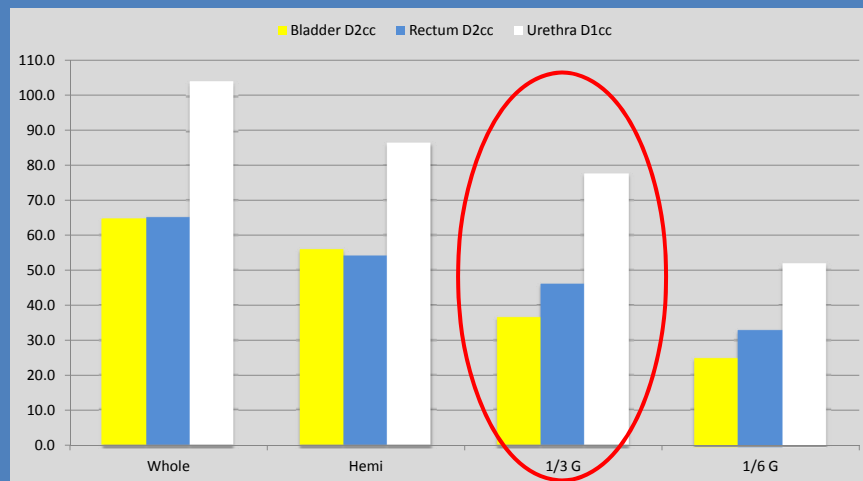

1/3 Gland   1/6 Gland

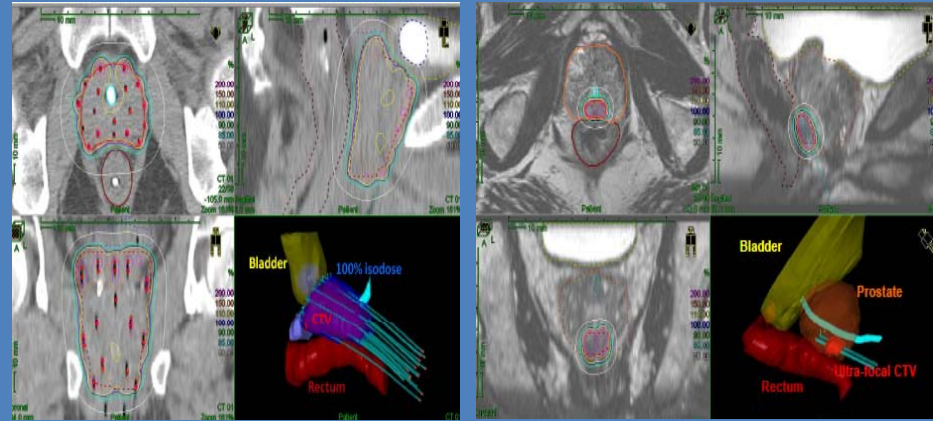Banerjee R et al. Manuscript in preparation.

Organ at Risk Doses for WG vs. HG vs. < HG

Banerjee R et al. Manuscript in preparation.

Ultrafocal

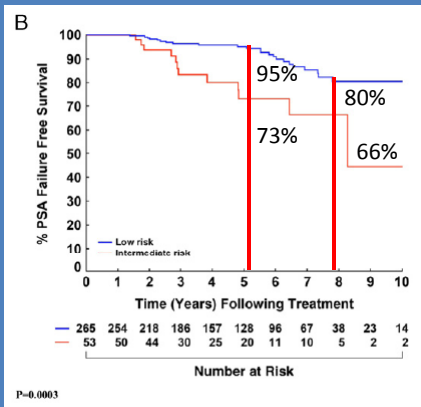Park S et al. Manuscript in preparation.

PZ Brachytherapy

Table 1. *Patient baseline characteristics*

No. Gleason (%):		
3 + 3 = 6	280	(88)
3 + 4 = 7	38	(12)
Median ng/ml PSA (IQR)	5.0	(3.8–6.9)
No. ng/ml PSA (%):		
4 or Less	95	(30)
Greater than 4–10	208	(65)
Greater than 10–14.9	15	(5)
No. risk (%):		
Low	265	(83)
Intermediate	53	(17)
No. more than 50% of cores pos (%)	45	(14)
No. supplemental EBRT (%)	61	(19)
No. nonwhite race (%)	23	(7)
Median cc vol (IQR)	38	(28–52)
Median pt age (IQR)		63.3 (59.2–68.7)

318 pts, median f/u 5.1 yrs, 83% low risk

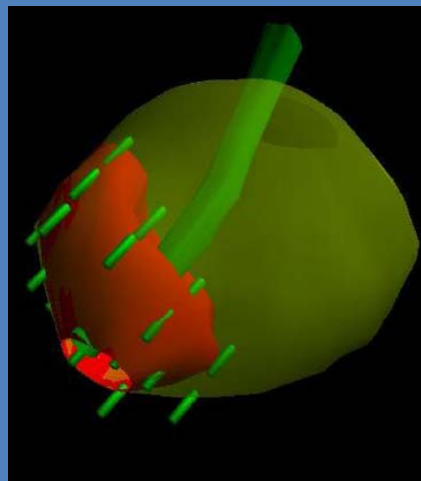Nguyen PL et al. Journal of Urology. 2012.

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PSAV > 0.75 ng/ml per year

Table 3. *Comparison of patients who met nadir+2 criteria*

	PSAV Greater Than 0.75 ng/ml/yr	PSAV Less Than 0.75 ng/ml/yr	p Value
No. pts	26	10	
No. MRI suspicious for local recurrence (%)	22 (85)	2 (20)	<0.001
No. biopsy pos for local recurrence (%)	16 (62)	1 (10)	0.008
Median mos PSADT	11.0	25.1	
No. initially intermediate risk (%)	12 (46)	1 (10)	0.06

Nguyen PL et al. Journal of Urology. 2012.

Focal LDR Brachytherapy

- 21 patients
- 34% of the prostate treated w/ I-125 145 Gy
- At 1 year PSA decline of ~60% (6.9->2.6)
- At 6 months improvement in erectile function and borderline reduction in urinary toxicity compared with whole gland treatment

Cosset JM et al. Brachytherapy. 2013.

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]

Table 2 – Preliminary oncologic and functional results

Energy modality	PSA, ng/ml, median (IQR)				IPSS, median (IQR)		IIEF-5, median (IQR)	
	Baseline	3 mo	6 mo	12 mo	Baseline	12 mo	Baseline	12 mo
Cryotherapy	6.2 (5.0–7.9)	2.9 (2.0–5.0)	2.8 (1.2–4.6)	2.5 (0.9–4.4)	9 (3–10)	5 (1–11)	19 (9–25)	14 (8–25)
Brachytherapy	6.2 (5.4–7.5)	3.3 (2.5–5.7)	3.2 (2.0–5.1)	2.8 (1.2–4.7)	3 (1–7)	7 (2–12)	21 (10–25)	14 (8–24)
VTP	5.7 (4.8–6.7)	3.0 (2.2–4.9)	2.8 (1.1–4.4)	3.2 (2.1–4.7)	6 (2–9)	6 (3–10)	23 (17–25)	13 (7–25)
HIFU	6.0 (5.1–8.1)	2.7 (1.8–4.7)	3.1 (2.1–5.3)	3.1 (2.4–4.3)	3 (1–7)	6 (2–11)	20 (15–25)	14 (8–25)

PSA = prostate-specific antigen; IQR = interquartile range; IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function; VTP = vascular-targeted photodynamic therapy; HIFU = high-intensity focused ultrasonography.

Conclusions

- Index lesion concept is a hypothesis
- Ongoing trials will determine it's validity both from an oncologic and toxicity standpoint
- Ideal focal modality is not known
- Radiation oncology (**especially brachytherapy**) needs to be actively involved in this emerging area

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