

Focal Therapy for Prostate Cancer

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UBC Urology Grand Rounds, Oct 1, 2008

Outline

- Introduction
- Rationale for focal therapy
- Targeted modalities
 - HIFU
 - Cryotherapy
 - Up & coming
 - Photodynamic therapy, Radiation
- Conclusions

Introduction

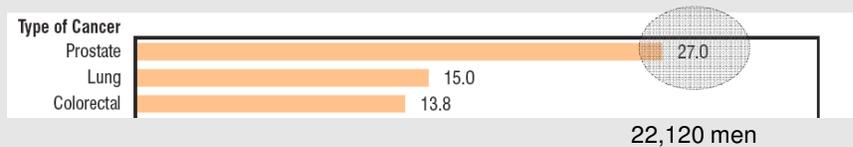
- Urologic oncology has undergone significant changes in terms of the indications and options for surgical intervention
 - Active surveillance of small renal masses
 - Partial nephrectomy
 - Cytoreductive nephrectomy
 - Significant reduction in RPLNDs

- What is changing for prostate cancer?
 - Robotic assisted radical prostatectomy
 - Imaging modalities for PCa
 - Targeted focal therapy

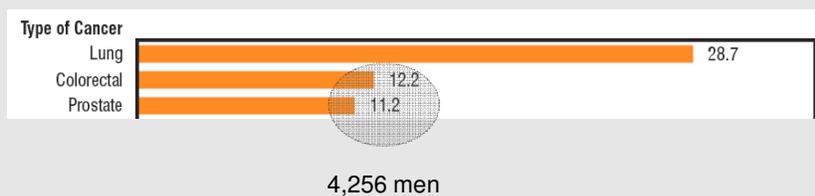
Changes in PCa Over Time

Introduction

- Incidence of prostate cancer among males:



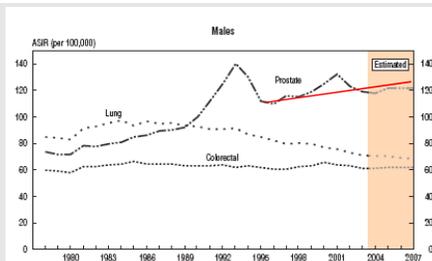
- Mortality from prostate cancer among males:



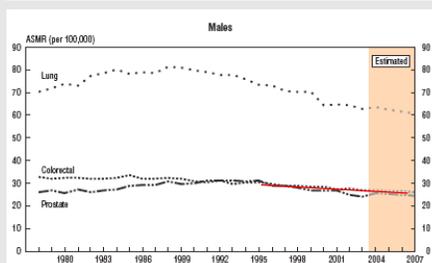
Introduction

- Prostate cancer

- Incidence over time:

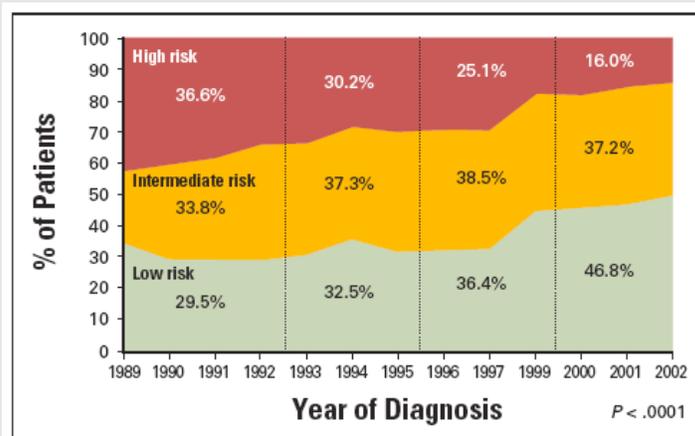


- Mortality over time



Introduction

- During past 10 years there has been a significant shift in the presentation of prostate cancer



CAPSURE, Cooperberg

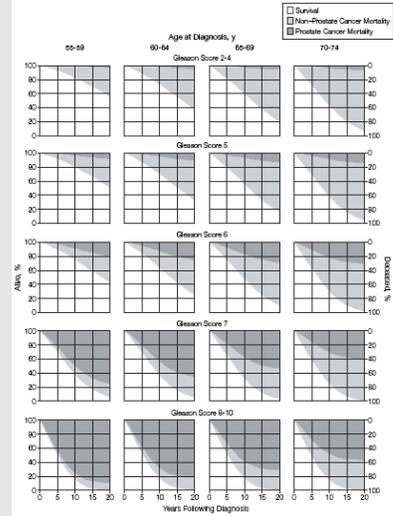
Introduction

- Stameys data
 - 1,300 RRP patients and specimens from 1983-2003
- Over the past 20yrs:
 - Decrease in mean age at Dx 64 to 59yrs
 - Decrease in mean PSA 25 to 8
 - Decrease in mean index tumor volume from 5.3 to 2.4cc

Stamey, JU 2004

Introduction

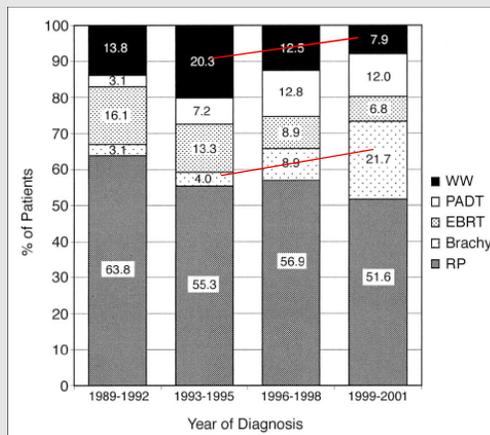
- Natural history of prostate cancer
 - Higher Gleason = higher PCa specific mortality
 - Younger age = higher PCa specific mortality
 - Older age and low Gleason disease = higher non PCa specific mortality
- Greatest variability in the men with Gleason 7 disease



Albertsen, JAMA 2005

Introduction

- There has been a significant increase in patients opting for curative treatment of PCA
 - More Brachy
 - Less RRP
 - Less WW
- BC Data: 1990-2000
 - Incidence rising in <65yr men
 - Met PCa declined to 3.5%
 - Increase in T1/2
 - Decrease in PSA (15 to 10)
 - Curative surgery: 30% to 50%



Cooperberg, JCO 2004
Pickles, Can J Urol, 2002

Does all PCa need Treatment?

Introduction

- Screening and over detection further complicate PCa

Screening for prostate cancer:
estimating the magnitude
of over-detection

Maurice McGregor,* MD; James A. Hanley,** PhD;
Jean-François Boivin,** MD, DSc;
Richard George McLean,** MB, BS

- PCa in Quebec (CMAJ 1998)
 - Used the Quebec mortality rate for PCa and North American studies looking at the rate of detection of PCa
 - Final conclusion was that 16-22 men out of 100 benefit from RRP in terms of overall survival
- Overdetection also demonstrated by:
 - Incidence to mortality ratio
 - US: 8.6:1
 - UK: 3:1
 - Autopsy series have demonstrated that 30-40% of those >50yrs have histologic evidence of PCa

Eggerer, JU 2007

What is the Impact of Our Current Treatment?

Introduction

- How does our open surgery do?

POTENCY, CONTINENCE AND COMPLICATION RATES IN 1,870 CONSECUTIVE RADICAL RETROPUBIC PROSTATECTOMIES

WILLIAM J. CATALONA,* GUSTAVO F. CARVALHAL, DOUGLAS E. MAGER AND DEBORAH S. SMITH

- Represents a tertiary care series from 1983-1997
- Retrospective review based on followup history and physical
 - No objective measure of erections/incontinence

Introduction

Population

TABLE 2. Distribution of patient characteristics for 858 men included in analysis of potency

Mean age \pm SD (range)	62 \pm 7	(42-77)
No. race (%):		
White	821	(96)
Black	20	(2)
Other	17	(2)
No. preop. PSA (%):*		
Less than 2.6	69	(9)
2.6-4.0	56	(8)
4.1-9.9	429	(57)
Greater than 9.9	193	(26)
No. clinical stage (%):		
T1a or T1b	57	(7)
T1c	260	(30)
T2	533	(62)
T3	8	(1)
No. pathological stage (%):		
pT1 or pT2	599	(70)
pT3a or pT3b	206	(24)
pT3c or N1	53	(6)
No. type surgical procedure (%):		
Bilat. nerve sparing	798	(93)
Unilat. nerve sparing	60	(7)

Patients previously potent with at least 18 months of followup who underwent nerve sparing procedures without adjuvant radiotherapy at the time of

Introduction

Outcomes

TABLE 3. Percentage of 858 patients who recovered erections after nerve sparing radical prostatectomy stratified by age and type of surgery

Age	No./Total No. (%)		
	Bilat. Nerve Sparing	Unilat. Nerve Sparing	Total
40-49	42/46 (91)	2 (50)	43/48 (90)
50-59	220/269 (82)	3/9 (33)	223/278 (80)
60-69	229/375 (61)	20/39 (51)	249/414 (60)
70 or Greater	52/108 (48)	4/10 (40)	56/118 (47)
Totals	543/798 (68)	28/60 (47)	571/858 (66.5)

TABLE 4. Percentage of 1,325 patients with return of continence after radical retropubic prostatectomy stratified by age

Age	No. Postop. Continence/Total No. (%)
40-49	49/53 (92)
50-59	346/358 (97)
60-69	584/632 (92)
70 or Greater	244/282 (87)
Total	1,223/1,325 (92)

Patients previously continent with at least 18 months of followup.

TABLE 5. Percentage of 1,870 patients with postoperative complications excluding impotency and incontinence

	No. Pts.	% (95% CI)
Anastomotic stricture	71	4 (2.9-4.7)
Thromboembolic	39	2 (1.4-2.7)
Inguinal hernia	25	1 (0.8-1.8)
Miscellaneous*	21	1 (0.6-1.6)
Infectious	15	0.8 (0.4-1.2)
Incisional hernia	11	0.6 (0.2-0.9)
Lymphatic	7	0.4 (0.1-0.6)
Neurological	5	0.3 (0.03-0.5)
Myocardial infarction	2	0.1 (0.0-0.2)
Total	196	10 (9-11.8)
Death	0	0 (nonapplicable)

Introduction

- What about brachytherapy?

Long-Term Urinary, Sexual, and Rectal Morbidity in Patients Treated with Iodine-125 Prostate Brachytherapy Followed Up for a Minimum of 5 Years

Nelson N. Stone and Richard G. Stock

- Median 7 year followup for 325 men treated with I¹²⁵ Brachytherapy

Introduction

- Population

Table 1. Presenting and treatment disease characteristics

Variable	Patients (n)
PSA (ng/mL)	
≤4	38 (11.7)
>4–10	212 (65.2)
>10	75 (23.1)
Gleason score	
2–4	64 (19.7)
5–6	255 (78.5)
7–8	6 (1.8)
Clinical stage	
T1c	132 (41.2)
T2a	100 (30.8)
T2b	77 (23.7)
T2c	14 (4.3)
Race	
White	271 (83.4)
African American	34 (10.5)
Hispanic	16 (4.9)
Asian	3 (0.9)
Indian	1 (0.3)
HT	
No	250 (76.9)
Yes	75 (23.1)

Introduction

Outcomes

- Rectal toxicity in 24%
- Incontinence 1.2%
- Worsening of urinary symptoms until 12-18mon
- Potency in 60% of men with preop erectile function (with PDE5I PRN)

Table 2. Comparison of preimplant and postimplant urinary symptoms as measured by AUA symptom score

Time	n	Preimplant Score	SD	P Value (Compared with Baseline)
Baseline	325	7.1	6.3	
6 mo	156	12.5	7.4	<0.001
1 yr	145	9.1	6.5	<0.001
2 yr	165	9.5	7.0	0.012
3 yr	161	8.1	6.6	0.381
4 yr	164	7.3	6.0	0.199
5 yr	176	7.3	6	0.615
Last follow-up	213	7.1	5.8	0.610

AUA = American Urological Association. Numbers represent mean on scale of 0–35; postimplant scores at average of 7 years after implantation.

Table 4. Relationship between age and postimplant potency preservation in patients with initial potency score of 2 or 3 (Spearman rho $r = 0.375$, $P < 0.001$)

Age (yr)	Erectile Function Score (n)			Total
	0	1	2	
40–50	0	0	1 (12.5)	7 (87.5)
51–60	3 (6.3)	6 (12.5)	12 (25.5)	21 (56.3)
61–70	20 (16.1)	29 (23.4)	29 (23.4)	78 (37.1)
>70	16 (16.5)	17 (30.4)	11 (19.6)	44 (21.4)
Total	39 (16.5)	52 (22)	53 (22.5)	144 (39)

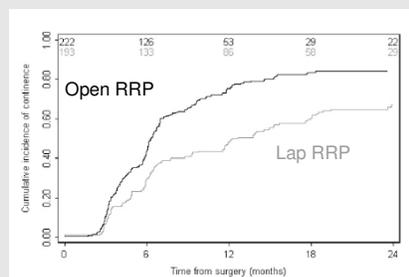
Scores from mean of 7.2 year after implantation. Data in parentheses are percentages.

MSEFS Score: 0=no erections, 3=normal erection sufficient for penetration

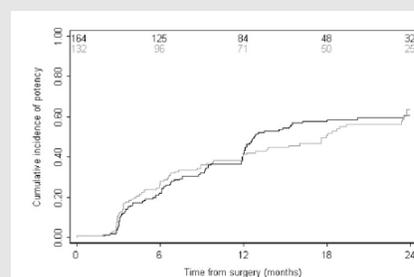
Introduction

- What about the new era of MIS prostatectomy?

Continence



Potency



Touijer, JU 2008

Introduction

- Is the Da Vinci Robot the answer to reducing complications?

Table 2. Unadjusted Rates of Complications, Length of Stay, and Anastomotic Strictures for Patients Undergoing Minimally Invasive Versus Open Radical Prostatectomy

Parameter	Minimally Invasive Radical Prostatectomy (n = 608)		Open Radical Prostatectomy (n = 2,094)		P
	No.	%	No.	%	
Perioperative complication					
Overall	181	29.8	763	36.4	.002
Cardiac	26	4.3	139	6.6	.03
Respiratory	41	6.7	244	11.7	<.001
Vascular	32	5.3	137	6.5	.25
Wound or bleeding	10	1.6	75	3.6	.02
Genitourinary	27	4.4	168	8.0	.003
Miscellaneous medical	67	11.0	342	16.3	.001
Miscellaneous surgical	40	6.6	167	8.0	.25
Length of stay, days					
Mean		1.42		4.35	
Standard deviation		2.04		5.84	<.001
Anastomotic stricture					
No.	52	15.2	205	12.0	.111
Salvage therapy					
No.	148	27.8	177	9.1	<.001
No.	533		1,943		

Hu, JCO 2008

Why not do more Active Surveillance?

Introduction

- Active surveillance excludes a high proportion of men
 - PSA >10
 - PSADT <3-4yrs
 - Tumor in >50% of a core
 - >Half cores positive
 - Gleason 7 or greater
- Active surveillance is often viewed as “putting off the inevitable”
 - Studies have demonstrated a crossover rate of 20-30% over 3-5yrs
 - 22% crossover rate
 - 15% due to PSA
 - 4% due to Gleason
 - 3% clinically)
 - 12% opted for radical treatment despite no progression
 - *Klotz 2005 JCO*
- It requires intensive surveillance
 - PSA q3mon, biopsy q1yr, then q3yr

Introduction

- Natural history of prostate is well defined for the young man with high risk disease
 - Should be offered definitive, well proven therapy
- Outcomes of low and intermediate risk patients less clear
- More low risk patients are being diagnosed now than 20 years ago
- More patients are opting for treatment
- Over treatment of prostate cancer does occur
- Only alternative to radical therapy for PCa is active surveillance
 - Active surveillance protocols have failed to gain widespread adoption for low risk tumors
- Current surgical therapies are associated with significant morbidity related to continence and erectile function

Rational for Focal Therapy

Introduction

- Focal therapy:
 - Targeting a specific area of cancer
- Other cancers, such as breast, have benefited from a “focal approach” with significant gain in QOL and no loss of oncologic control
- Focal therapy hypothesis for PCa
 - Targeted minimally invasive therapy is suitable for low/intermediate risk men and will result in lower morbidity than current therapy, and acceptable oncologic outcomes

Why Radical therapy?

- Prostate cancer is multifocal
 - 60-90% of men undergoing radical therapy have bilateral disease
 - 56-90% of men have multifocal tumors
- Field effect changes around the primary prostate cancer
 - Normal tissue surrounding the primary neoplasm has altered gene expression and precancerous genetic changes
- PCa is usually infiltrative
 - Accurate localisation of tumor and margins difficult
- Imaging techniques are inadequate to localise prostate cancer
- Focal therapies traditionally not possible due to
 - Absence of demarcation between treated and normal
 - Urethral/rectal anatomy

Can we predict unifocal disease? NO!

- Data from SEARCH database on RRP patients from 1988-2006
 - Excludes ADT or RT
 - Excluded high risk men
 - PSA >10
 - Gleason 7-10
 - cT2b
 - >2 cores positive
 - Bilateral disease on biopsy
 - 261 men

TABLE 1. Patient characteristics by final pathological findings after radical prostatectomy

Characteristic	Bilat	Unilat	p Value
No. pts	168	93	
Mean ± SD age	60.6 ± 6.4	60.5 ± 6.9	0.976
No. ethnicity (%):			0.047
White	84 (50.0)	59 (63.4)	
Black	73 (43.5)	26 (28.0)	
Other	11 (6.6)	8 (8.6)	
Median PSA (ng/ml)	5.3	6.0	0.071
Mean ± SD BMI (kg/m ²)	28.3 ± 5.3	28.3 ± 5.1	0.942
No. 1 core pos (%)	118 (70.2)	68 (73.1)	0.622
No. clinical stage (%):			0.796
T1c	124 (73.8)	70 (75.3)	
T2a	44 (26.1)	23 (24.7)	
No. biopsy Gleason sum (%):			0.487
4	9 (5.4)	7 (7.5)	
5	19 (11.3)	9 (9.7)	
6	140 (83.3)	76 (81.7)	

Scales, JU 2007

Can we predict unifocal disease? NO!

- Results
 - 35% men with unilateral disease on standard biopsy actually had unilateral disease on RRP specimen
 - pT2c disease not predicted by
 - PSA
 - Gleason
 - Clinical stage
 - 1 or 2 cores positive

Can we predict unifocal disease? NO!

- Saturation biopsies in the office have been positive in 30-40% men with previous negative extended core biopsies
- 60% of men on active surveillance protocol have negative repeat 6 core biopsy despite known cancer in first biopsy

Can we predict unifocal disease? NO!

- If we look at all comers to RRP
 - The pathologic specimen demonstrates unilateral disease:
 - 13% (using whole mount sectioning done) 2000-2001
 - 17% (using 3mm step sectioning done) 1992-1996
 - 38% 2001-2003
- Sanwick Urol 1998
 - 24% men with unilateral disease on biopsy had + margin benign side
- Connolly SJUN 2004
 - 85% incidence of bilateral disease with unilateral positive biopsy

Can we predict unifocal disease? NO, but it doesn't matter!

- The other side
 - Up to 1/3 of patients may have unifocal cancer
 - 80% of the multifocal tumors are $<0.5\text{cm}^3$, suggesting clinical insignificance
 - Looking at 1832 RRP specimens by wholemount
 - Mean volume of 5 largest cancers: 2.3, 0.39, 0.17, 0.09, 0.04cm^3
 - Those with ECE, 92% arose from primary tumor
 - Those with low risk features: 99% of nonindex tumors were same Gleason or lower, and no ECE
 - When you exclude small "insignificant" tumors up to 64-80% of patients would have a single significant tumor
 - The "index lesion" hypothesis suggests that tumors $>0.5\text{cc}$ and Gleason >6 drive PCa
- However,
 - Evidence on genetic analysis of metastatic deposits demonstrate chromo alterations different from the primary tumor
 - Suggests nondominant tumor does have pathogenic potential
 - No evidence that satellite lesions are truly clinically insignificant

Jones, Curr Tr Opt Onco, 2007

Can we predict unifocal disease? NO, but it doesn't matter!

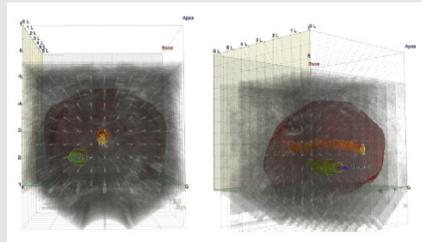
- The nondominant tumors can be controlled by another intervention
- Hypothesis
 - Neoadjuvant whole gland low dose XRT
 - Long term 5 α Reductase inhibitors to prevent new neoplastic transformation/growth

Can we predict unifocal disease? Maybe...

- Transition zone PSA density and F/T PSA
 - Djavan B Urol 1999
- Orientation of positive biopsy
 - Epstein JU 1999
- Best bet is to use a combination of factors
 - Nomogram based on stage, Gleason, PSA, length of core +, prostate size
 - (Kattan JU 2003)

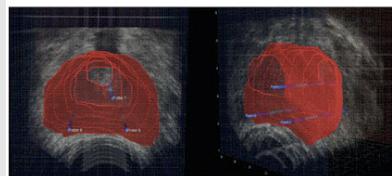
Can we predict unifocal disease? Maybe...

- Second option
 - TRUS guided saturation biopsies
 - Transperineal biopsies with brachy template and US guidance
 - Systematic sampling of gland every 5mm
 - 20-40 biopsies for a 20-40cc gland
 - Gives accurate coordinates for tumor
 - Respiratory movement stabilized with either a needle or mock beads
 - Accuracy predicted to be 95% using computer models
 - Risks
 - Large prostates (>60g)
 - 5αReductase I
 - Transrectal approach
 - Increased infection?
 - AUR?
 - Affect ease of surgery?
 - Requires GA/spinal anesthesia



Prostatic Imaging

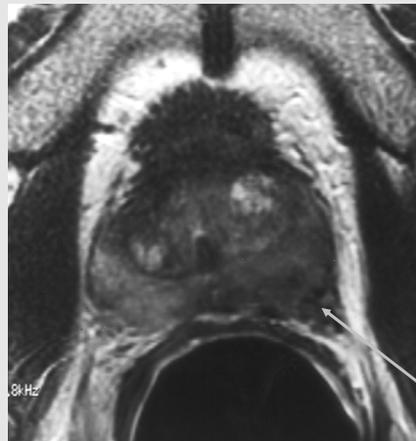
- TRUS by itself is unreliable to detect tumors
 - Combined with color/power doppler
 - Sens 43-87%, spec 17-92%
 - Wide range due to
 - Equipment variation
 - Probe frequency
 - Operator experience
 - Lack of standard definition of abnormal
 - Small tumors often missed
 - Prostatitis/BPH can look like PCa
 - Upcoming advances
 - US contrast agents show blood flow better
 - Use of preUS dutasteride to reduce blood flow in normal tissue



Prostatic Imaging

- MRI
 - PCa nodules
 - 50-76% detection rate on T2 imaging
 - 5-35% false positive
 - Confounded by
 - Benign conditions: prostatitis, BPH, blood from previous biopsy
 - Limited ability to look at transitional zone
 - Lack of natural contrast between normal and infiltrative PCa
 - Natural heterogeneity between normal and abnormal tissue
 - 85% sensitivity for PCa >1cm with MRI (referenced to whole mount path), versus 5% for those <5mm
 - Benefit in evaluating post treatment area of necrosis
 - TRUS is unreliable due to bubbles and cavitation
 - MRI with gad can detect size and position of lesion, and see rectal wall necrosis

Prostatic Imaging

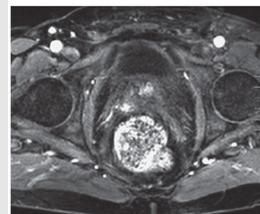


Prostatic Imaging

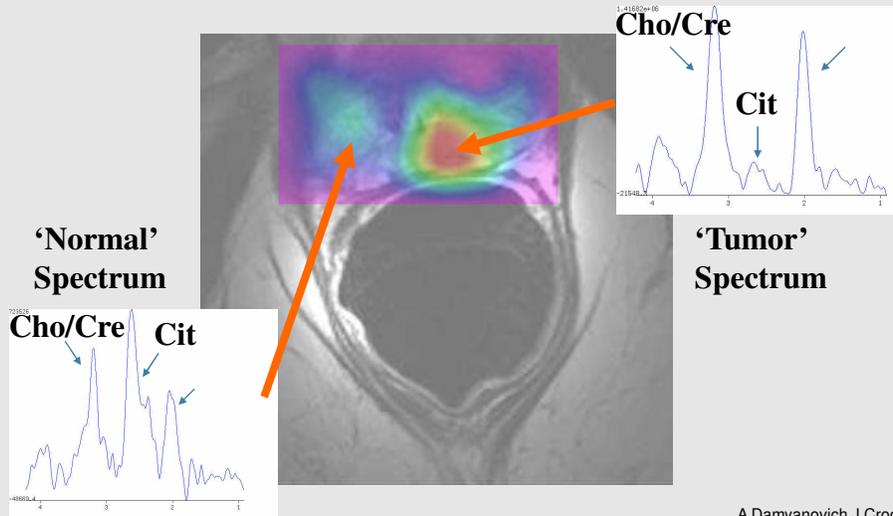
- MRI Advances
 - Resolution is improving with
 - 3T MRI (don't need endorectal coil)
 - Dynamic contrast enhancement
 - MR spectroscopy imaging
 - Accuracy ranges from 40-90%
 - Limitations
 - Expensive
 - Interpretation limited by biopsy induced hemorrhage
 - Numerous variables:
 - Size definition of significant tumor
 - MRI modality used
 - Use of endorectal coils
 - Gold standard: TRUS vs pathology
 - Stage and grade of lesion

Prostatic Imaging

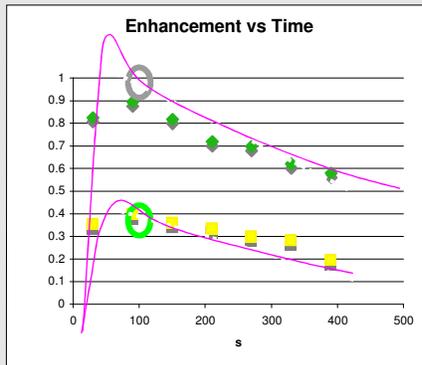
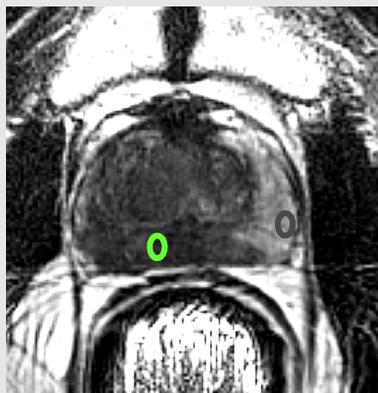
- ^1H MR spectroscopic imaging based on metabolic info
 - Better for transitional zone tumors, and patients who have undergone therapy
 - Based on increase in choline and decrease in citrate within PCa tissue
 - Advantages
 - Can see metabolic changes with a resolution of 0.25cc with standard 1.5T magnet
 - Disadvantages
 - Limited spatial resolution
 - Can't see central gland well
 - Still misses up to 37% of tumor foci
- Dynamic contrast enhanced MRI
 - Takes advantage of different enhancement patterns between benign and malignant
 - Tumor in peripheral zone enhance 3-5min earlier than normal tissue
 - Best results so far
 - Lack of standardization



Prostatic Imaging

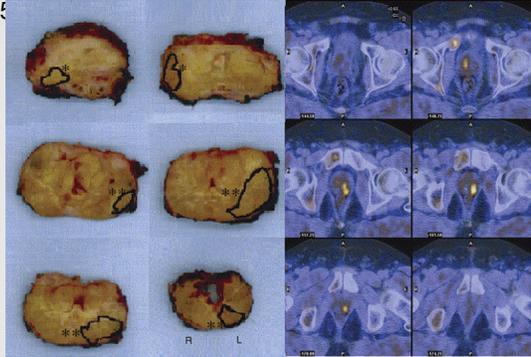


Prostatic Imaging



Prostatic Imaging

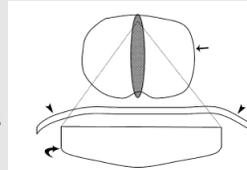
- In the future
 - PET
 - Initial results with ^{18}F -FDG disappointing
 - 83% sensitivity for localization of nodules $>5\text{mm}$ and 4% for $<5\text{mm}$
 - Sensitivity for ECE 22%
 - Sensitivity similar to TRUS Biopsy
 - US with power doppler
 - Dual PET/CT



**Modality:
HIFU**

HIFU

- High Intensity Focus US
 - Uses focused US waves from parabolic transducer
 - Characterized by its frequency, geometry, and physical dimensions
 - Generates heat >80C
 - Two mechanisms induce coagulative necrosis
 - Thermal effect: (above 60C), and protein denaturation
 - Cavitation and mechanical tissue disruption occurs (less predictable)
 - Due to oscillation of microbubbles in the sonicated tissue, collapse and dispersion of energy
 - Creates an oval area of necrosis with a sharp margin with normal tissue
 - This focal zone is refocused as often as necessary to treat target area
 - Real time feedback of thermal effects
 - See hyperechoic area on US
 - Extent is not always accurate
 - MRI clearly shows lesion
- Approved by Health Canada and many European countries



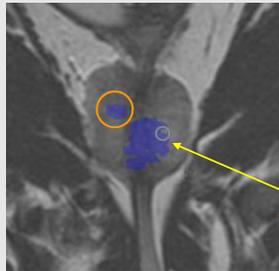
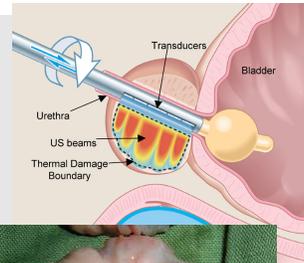
HIFU

- Two devices are available
 - Sonablate (Focus Surgery, USA)
 - Uses single probe (4MHz) for both imaging and therapeutics
 - Single preset mode with power adjustments by physician based on US image
 - Requires physician to monitor and adjust probe during treatment
 - Ablaterm (EDAP-TMS, France)
 - Imaging (7.5MHz) and therapeutic (3MHz) transducers in one endorectal probe
 - Uses a special bed
 - Has 3 preset modes

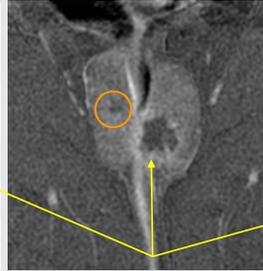


HIFU

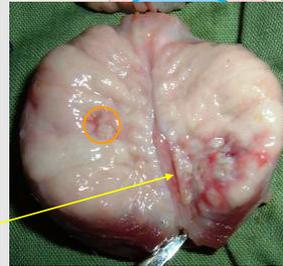
- New device: ExAblate 2100P
 - MRI guided HIFU
 - Real time temperature feedback
 - Proof of concept completed in dog model
 - Phase 1 trials underway



Accumulated thermal dose following FUS treatment shown on T2w MR coronal image



Contrast enhanced T1w subtraction image showing the lesion



Macro pathology image following the procedure showing the ablated areas

HIFU

- HIFU technology and its application to PCa has evolved rapidly
 - Routine preop TURP if obstructive symptoms
 - Prophylactic Abx
 - Leaving a margin around prostatic apex
 - Rectal cooling
 - Higher frequency transducers

HIFU

▪ Limitations of HIFU

- Limited penetration of transducer
 - Maximum prostate size is 40g (limited by AP diameter of the prostate)
 - Can be partially overcome with TURP
- Can't treat prostates with significant calcifications (>5mm)
- Difficult to treat anterior portion of prostate
- Difficult to monitor treatment effect directly
- Exclude patients with rectal walls >6mm or abnormal rectal anatomy

HIFU

▪ Risks (derived from series with whole gland treatment)

Author	Urinary Retention (%)	Stress Incontinence (%) (grade 1/2/3)	Bladder Outlet Obstruction (%)	Urinary Tract Infection (%)	Impotence (%)	Fistulas (%)	Sloughing (%)	Perineal Pain (%)
Poissonnier et al ¹³	-	13	12	2	-	0	9	3
Vallancien et al ¹⁴	6	3	0	10	32	0	-	0
Lee et al ¹²	0.3	16 (16/0/0)	0	-	-	0	14	-
Blana et al ¹⁴	-	-	19.7	0.4	49.8	0.5	-	0.9
Chaussey and Thuroff ¹¹	-	15.6* (9.1/6.3/0) vs 6.9 (4.6/2.3/0)	-	47.9 vs 11.4	35.9	0	-	-
Thuroff et al ¹⁵	8.6	13.1 (10.6/2.5/0)	3.6	13.8	-	1.2 (0.5**)	-	-
Uchida et al ¹⁶	0.6	0.6 (grade 1)	22	6	20	1	-	-

* HIFU vs HIFU + TURP.
** Since the addition of the cooling system.

HIFU

- For whole gland treatment
 - Positive biopsy rate 7-34%
 - Many patients require more than 1 treatment session to convert to negative biopsy
 - Patients with longer followup treated with prototype machines

Table 1 - Biochemical and biopsy disease-free survival after HIFU therapy

Series	No. of patients	Median or mean follow-up (mo)	Outcome (PSA and/or biopsy)
Uchida et al. [11]	63	22	75% PSA-free (ASTRO criteria) for the full series, depending on risk factors such as PSA, Gleason score, and T-stage; 13% positive biopsy rate
Vallencien et al. ^a [14]	30	20	Mean PSA 0.9 ng/ml; no progression-free data provided; 27% positive biopsies
Blana et al. [12]	146	22	87% had PSA < 1 ng/ml, 71.5% <0.4 ng/ml, and 54% <0.2 ng/ml; 7% positive biopsies
Thüroff et al. [18]	402	11 ^b	Median PSA: 0.6 ng/ml; mean: 1.8 ng/ml; no progression-free data provided; 13% positive biopsies
Gelet et al. [19]	102	19	3 consecutive increases in PSA and a velocity of >0.75 ng/ml/yr or a positive biopsy of 66%; 25% positive biopsy rate
Chaussy and Thüroff ^a [13]	271	19	ASTRO criteria: 80-84%; positive biopsies in 29-34%, 12-18% after <1 HIFU treatment

HIFU

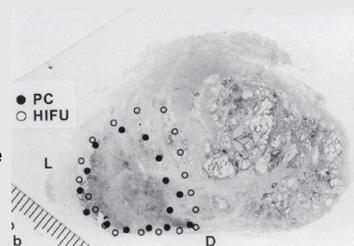
[CANCER RESEARCH 55, 3346-3351, August 1, 1995]

Effect of High-Intensity Focused Ultrasound on Human Prostate Cancer *in Vivo*

Stephan Madersbacher, Markus Pedevilla, Lorri Vingers, Martin Susani, and Michael Marberger¹

Departments of Urology [S. M., M. P., L. V., M. M.] and Pathology [M. S.], University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria

- 19 patients
 - HIFU used to create a central target lesion of the prostate, and evaluate correlate between targeting with TRUS and actual pathological lesion
- 10 patients
 - T2a/b
 - Visible lesion on TRUS that correlated with single core of biopsy proven "focal" prostate cancer
 - 3 patients had complete destruction of PCa focus
 - 7 had incomplete destruction (average 53%) because of unexpected tumor distribution



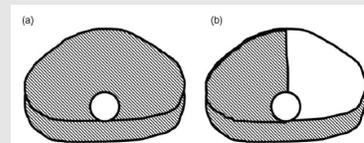
HIFU

Focal Therapy with High-intensity-focused Ultrasound in the Treatment of Localized Prostate Cancer

Satoru Muto, Takashi Yoshii, Keisuke Saito, Yutaka Kamiyama, Hisamitsu Ide and Shigeo Horie

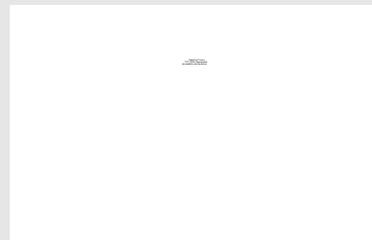
Department of Urology, Teikyo University School of Medicine, Tokyo, Japan

- Sonablate 500 to treat Low, Intermediate, and High risk patients with either whole gland HIFU or focal HIFU (29 patients)
- Based on >12 core biopsy and pelvic MRI
- For 29 patients treated with focal HIFU:
 - 76% had negative biopsies at 6 and 12mon and falling PSA
 - Less urinary symptoms and shorter catheter duration



HIFU

- Phase II RCT in University College London, UK
 - 45-80yrs
 - Gleason Grade 6/7
 - cT2
 - PSA <15
 - Maximum volume 40cc
- All patients receive ms-MRI and transperineal 5mm template biopsy
- Able to treat all malignant areas and preserve 50% prostatic tissue and 1 NVB



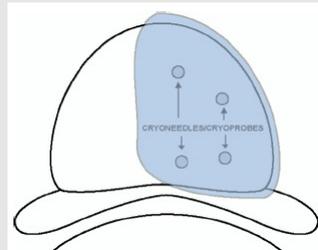
Modality: Cryotherapy

Cryotherapy

- Third generation probes (2000)
 - Gas rather than liquid cooling allowing smaller diameter probes (17G)
 - Use of urethral warming catheter
 - Transperineal brachy template (allows multiple cryoprobes and overlapping ice balls to better conform to prostate)
 - TRUS guided, thermosensistor controlled
- Mechanism
 - Direct cellular damage: ice crystal formation and osmotic derangement
 - Indirect cellular damage: vascular damage leading to malperfusion and ischemia

Cryotherapy

- Extent of destruction dependent on
 - Cooling rate
 - Lowest temperature
 - Time it is maintained
 - Number of cycles
- Iceball edge is visualized with US, and has a temperature of 0 to -2C
 - Therefore need to extend iceball 3-4mm beyond tumor margin



Cryotherapy

- Cryotherapy results for whole gland therapy
- Majority of long term followup based on second generation machines (liquid nitrogen, larger needles)
 - Third generation: gas cooling, thermocouplers to monitor temp, 2 freeze cycles, urethral warmers

Table 2 – Biochemical and biopsy disease-free survival after cryotherapy

Series	Type of machine	No. of patients	Median follow-up (mo)	Outcome (PSA and/or biopsy)
Cohen et al. [20]	Second generation	239	Minimum 21	PSA < 1 ng/ml: 69-77% and < 0.4 ng/ml: 40-60%; positive biopsies: 31% (one treatment), 18% (after retreatment)
Long et al. [21]	Second generation	975	24	PSA < 1 ng/ml: 63% and < 0.5 ng/ml: 52%; positive biopsies: 18%
Aus et al. [22]	Second generation	54	58	Projected 5-yr data: PSA < 1 ng/ml and negative biopsy: 39%
Prepelica et al. [23]	Third generation ^a	65 (high-risk patients ^b)	35	Projected 6-yr data: ASTRO: 81.7% PSA < 4 ng/ml: 50% and < 1 ng/ml: 35%
Bahn et al. [24]	Second and third generation ^a	590	68	Projected 7-yr data: ASTRO: 89.5%, PSA < 1 ng/ml: 76% and < 0.5 ng/ml: 62%; positive biopsies: 13%
Han et al. [25]	Third generation	122	12	PSA < 0.4 ng/ml: 75%
Cytron et al. [26]	Third generation	31	13	PSA < 1 ng/ml: 68% and < 0.5 ng/ml: 81%

ASTRO: American Society for Therapeutic Radiology and Oncology; PSA: prostate-specific antigen.

^a Gas-driven system but with thicker probes than used today.

^b PSA > 10 ng/ml or Gleason > 7.

Cryotherapy

- Side effects of third generation probes for whole gland therapy

Complication	Second generation cryotherapy	Third generation cryotherapy
Stress incontinence	2-27%	4.4%
Fistula	0-2.4%	0%
Stricture	1-9%	?
UTI	0-10%	0-6%
Impotence	47-93%	80-87%

UTI: urinary tract infection.

- Impotence rates have limited it's widespread acceptance and use for whole gland therapy
- Urethral warming responsible for significant decrease in urethral sloughing, UTI, and stricture

Cryotherapy

FOCAL "NERVE-SPARING" CRYOSURGERY FOR TREATMENT OF PRIMARY PROSTATE CANCER: A NEW APPROACH TO PRESERVING POTENCY

GARY ONIK, PERINCHERY NARAYAN, DAVID VAUGHAN, MARTIN DINEEN, AND RICHARD BRUNELLE

- 11 patients
- Unilateral disease, confirmed with repeat 8 core biopsy of "normal" side
- Cryotherapy used to focus on one lobe/NVB of the prostate, sparing the second lobe/NVB

TABLE I. Patient characteristics

Age (yr)	Follow-up (mo)	Gleason Score	Preoperative PSA* (ng/mL)	Positive Cores (n)	Stage	Preoperative TURP
62	72	5	10.5	1	T1c	No
64	62	8	12.9	1	T2a	Yes
58	61	5	4	1	T2a	No
67	41	6	4.5	1	T1c	No
72	29	6	10.8	1	T1c	Yes
56	24	6	5.5	1	T2a	No
67	21	7	1.5	1	T2a	No
55	12	7	16.5	3 of 4 cores, right	T2b	No
64	6	3	6	1	T1c	No

Onik, Urol 2002

Cryotherapy

TABLE I. *Continued*

Preoperative Hormones	Area Frozen	Postoperative PSA [†] (ng/mL)	PSA Stable	Biopsy Status	Change/Potency	Return to Function (mo)
No	Bilateral	0.1	Yes	Negative	Impotent	
Yes	Bilateral	0.5	Yes	Negative	Potent with Viagra	12
Yes	Bilateral	0.75	Yes	Negative	Potent	6
No	Hemi-cryosurgery	0.7	Yes	No biopsy	Potent	4
Yes	Hemi-cryosurgery	4.8	Yes	Negative	Impotent	
No	Hemi-cryosurgery	1.8	Yes	Negative	Potent	3
No	Hemi-cryosurgery	0.5	Yes	Negative	Potent	6
Yes	Hemi-cryosurgery	0.1	Yes	No biopsy, Jehovah Witness	Potent	9
No	Tumor + 1.5-cm margin	4	Yes	No biopsy, too soon	Potent	1 wk

Cryotherapy

- Updated in 2007
 - All patients now undergoing 3D transperineal saturation biopsy every 5mm
 - 6mon Neoadjuvant hormone therapy (to decrease gland size), stopped after treatment
 - Cryotherapy with 3rd generation probe was used to target the positive biopsy
 - NVB spared unless biopsy + cancer within 1cm of NVB
 - Hydrodissection used to prevent rectourethral fistulas
 - Followup: ASTRO criteria, biopsy at 1yr

Cryotherapy

- 55 patients with at least 1yr of followup (mean 3.6yrs)
- Risk group
 - Low 26
 - Med 20
 - High 9
- 95% had stable PSA at most recent followup
 - All had negative biopsies at 12mon
- 5% of patients with unstable PSA, and were found on rebiopsy to have cancer in untreated side
 - 2/4 of these patients did not receive the transperineal saturation biopsy
 - In keeping with computer model predicted failure
- Morbidity
 - 85% potency
 - 100% continence (no pads)

Cryotherapy

- Advantages
 - Includes patients traditionally excluded by brachytherapy (mod-high risk)
 - Good preservation of potency, with return to function in 3-6mons
 - 7/9 patients (only 1 NVB spared)
 - Potency makes sense hypothetically
 - RRP impotence related to NVB preservation, edema/scarring of nerves, hemodynamic changes postop, atrophic changes in penis
 - Ability to repeat the procedure

Cryotherapy

- Other series
 - Bahn J Endo Urol 2006
 - 27 men treated with focal cryotherapy
 - Workup with color doppler and regular TRUS biopsies
 - 24/25 negative biopsy rate
 - Potency: 48% + 40% with PDE5I (total 88%)
 - Lambert Urol 2007
 - 25 men treated with focal cryotherapy (unilateral ablation and NVB destruction)
 - Gleason 6 or 7, T1c, tumor volume estimated <10%, no neoadjuvant therapy
 - Followup 28mon
 - Complications
 - 71% potent (1/3 with PDE5I)
 - No fistulas, retention, incontinence
 - 3/25 found to have recurrent cancer (2 on contralateral side) and all treated with repeat cryotherapy

Cryotherapy

- Comparison of complications rates reported from 2000-2006

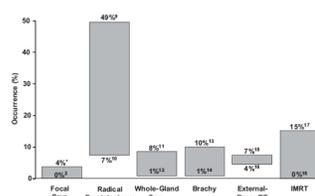


Figure 2. Comparison of published incontinence rates that appear in the literature from 2000 to 2006 for focal cryoablation (Cryo), radical prostatectomy, whole-gland Cryo, brachytherapy (Brachy), external-beam radiation therapy (RT), and intensity-modulated radiation therapy (IMRT). *Indicates results for the current series.

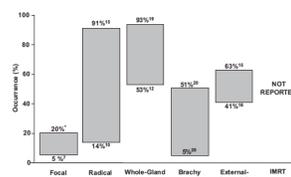
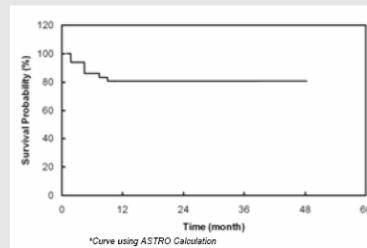
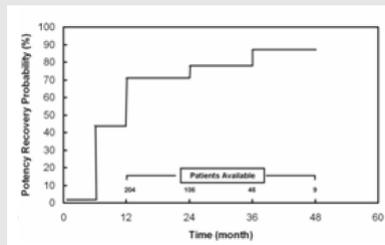


Figure 3. Comparison of published impotence rates that appear in the literature from 2000 to 2006 for focal cryoablation (Cryo), radical prostatectomy, whole-gland Cryo, brachytherapy (Brachy), external-beam radiation therapy (RT), and intensity-modulated radiation therapy (IMRT). *Indicates results for the current series.

Ellis, Urol 2007

Cryotherapy

- Largest “series” from the Cryo-Online Database registry study
- 341 men undergoing some form of focal cryotherapy
 - Mean age 68yrs
 - Majority T1c, mean PSA 6.8
 - Mean followup 16mons
 - Potency 50% at 6mon, >74% at 36mon
 - Incontinence 1.6% at 12mon



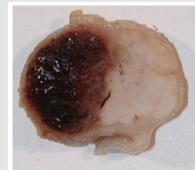
**Modality:
Radiation and Photodynamic Therapy**

Radiation

- Radiation
 - Intensity modulated RT
 - Can be focused on one lobe of prostate
 - Feasibility of treating whole prostate with 70Gy and then a boost to 90Gy for the dominant lesion
 - Brachytherapy
 - High dose rate implants with MR spectroscopy imaging or Prostatecint guided placement
 - Allow dose to be raised to 150-190% of standard dose with high dose rate ¹⁹²I
 - Advantages
 - Established biologic basis
 - Known to be tumoricidal
 - Familiar to Rad Onc/Urologists
 - Unknowns
 - Radiation scatter effects
 - Long term tumor control rates
 - Ability to retreat

PDT

- Photodynamic therapy
 - Systemically or locally administered photosensitizer is activated by specific wavelength of light, results in active free radicals that have an ablative effect on tissue
 - Photosensitizer (porphyrin derivative) is given, accumulates in tissue
 - Foscan (MTHP-C)
 - Initial results poor: high oncologic failure rate, and 50% ED/urethral injury
 - Tookad (WST09) (vascular targeted photodynamic [VTP] therapy) based on chlorophyll
 - Used in canine model successfully
 - Investigated as an option for salvage after radiation: good results, minimal toxicity
 - Unknowns
 - Dosimetry of light fluorescence
 - Photosensitizer maximum tolerated dose
 - O₂ distribution within the prostate



Conclusions

Challenges ahead

- This is still an experimental approach, and needs to be developed with proper RCTs and Ethics Board review
- Long term followup is the key for PCa data
 - Oncologic outcomes have to be the first consideration
- Patient selection is not yet clear
 - Use active surveillance criteria?
 - Low and intermediate risk patients suitable?
 - Pretreatment workup
 - Optimal imaging modality
 - 3D transperineal saturation biopsies the best modality currently available
- Optimal modality
 - HIFU? Cryotherapy?, technologies are improving and evolving faster than the published data can keep up
 - Do all foci of PCa need treatment, or is the "index lesion" hypothesis correct
 - Hemiblation versus true focal therapy
- Followup of patients
 - No clear/validated definitions in terms PSA recurrence or need/schedule to rebiopsy
 - Reduction in morbidity is intuitive and promising, but as of yet unproven
- Is post treatment failure safely salvaged with RRP/RT?

Outcomes that should be followed

- Extensive post-treatment biopsy
- Imaging to characterize treatment effect and correlate with outcome
- Morbidity
- QOL

Scott E. Eggener, Peter T. Scardino,^{*} Peter R. Carroll, Michael J. Zelefsky, Oliver Sartor, Hedvig Hricak, Thomas M. Wheeler, Samson W. Fine, John Trachtenberg, Mark A. Rubin, Mak Otori, Kentaro Kuroiwa, Michel Rossignol and Lucien Abenham for the International Task Force on Prostate Cancer and the Focal Lesion Paradigm[†]

Proposed Clinical, Biopsy and Imaging Criteria for Focal Therapy Patient Selection

Clinical

Clinical stage T1 or T2a⁴⁵
 PSA less than 10 ng/ml⁴⁶
 PSA density less than 0.15 ng/ml/cc⁴⁷
 PSA velocity less than 2 ng/ml yearly in the year prior to diagnosis⁴⁶

Biopsy

Minimum of 12 cores⁵⁶
 No Gleason grade 4 or 5⁴⁵
 Maximum percentage of cancer in each core (eg 20%)⁴⁸
 Maximum length of cancer in each core (eg 7 mm)⁴⁹
 Maximum percentage of total cores with cancer (eg 33%)⁵⁰

Imaging

Single lesion with a maximum size (eg 12 mm)
 Maximum length of capsular contact (eg 10 mm)
 No evidence of extraprostatic extension or seminal vesicle invasion

Proposed algorithm

