

# Current Findings on High Intensity Focused Ultrasound (HIFU)

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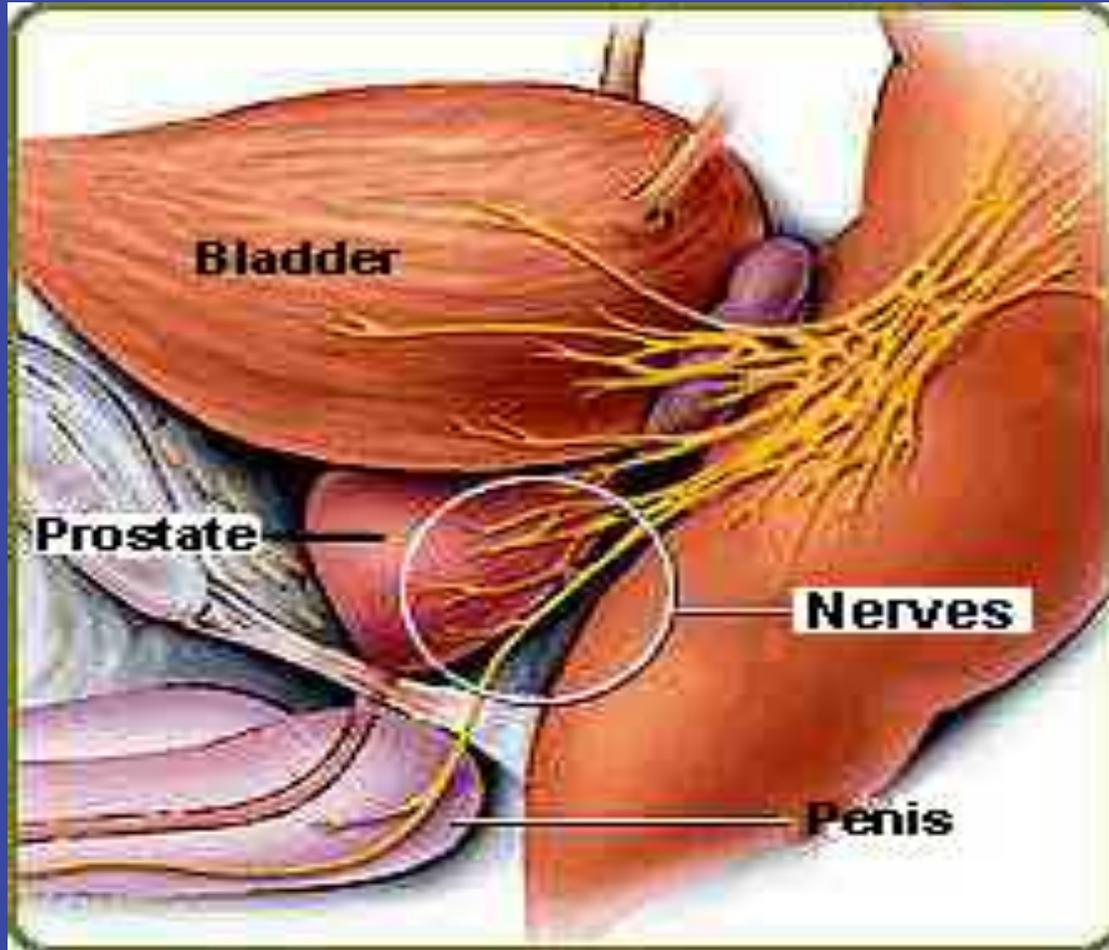
Love Chair in Prostate Cancer Prevention

Princess Margaret Hospital

Toronto, Canada



# Prostate: Rough Neighborhood



# Treatment Options

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- Radical prostatectomy (open or robotic)
- External beam radiation (IMRT)
- Seeds implantation (brachytherapy)
- Combination beam and seed implant
- Cryotherapy (total or focal)
- HIFU



# TRADITIONAL RADICAL THERAPIES ARE NOT PERFECT

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After **RP** for cT1-2 disease, reported recurrence rates (PSA, local or systemic) are

- 20-31% at 5 years
- 32-53% at 10 years

- After **RT**, reported recurrence rates (PSA, local or systemic) are
  - 34% at 5 years in patients with cT1-2 disease
  - 46-66% at 10 years in patients with cT2c-4 disease



# FIVE YEAR OUTCOME COMPARISONS

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## Biochemical Disease Free Survival

	<b>RP</b>	<b>CRYO</b>	<b>Brachy</b>	<b>3DCRT</b>	<b>XRT</b>	<b>HIFU</b>
<b>Low</b>	76-98%	60-92%	78-89%	76-87%	81-86%	75-81%
<b>Moderate</b>	60-76%	61-89%	66-82%	51-58%	26-60%	

BDFS definitions do vary but are comparable

Katz and Rewcastle 2003



# The Perfect Prostate Cancer Treatment

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- It does not exist
- “Best” treatment is one that balances cancer control with quality of Life



**Cancer (PSA) control**

**Quality of Life**



# Goal of Prostate Cancer Treatment

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## The Trifecta or Home Run



- Cancer (PSA) Control: patient does not die from prostate cancer
- Continent with normal urinary function
- Potent with preservation of erectile function



# Optimal Outcomes after RP

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- Statistical analysis to predict probability of “optimal outcome” (Trifecta) after RP based on MSK data base
- 647 patients evaluable, July 1998 – July 2003. Mean age 58 Stage: T1c or T2a : 78.8%
- Optimal Outcome = **PSA** at 0.2 , **Dry** without pads, **Potent**: normal erections with or without PDE5
- Population: mean age 58, nerve sparing RP (Bilateral in 93.4%)
- Trifecta probability:
- 1 year: 30%, 2 years: 42%, 3 years: 47% , 4 years : 53%

Saranchuk, Kattan, Elkin, Touijer, Scardino. Achieving Optimal Outcomes after Radical Prostatectomy J Clinical Oncology 23: No 18, 4146-4151.



# What Temperature Does HIFU Achieve in Target Tissue ?

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- A)  $-30^{\circ}$  to  $-40^{\circ}$  C
- B)  $50^{\circ}$  -  $69^{\circ}$  C
- C)  $70^{\circ}$  -  $89^{\circ}$  C
- D)  $90^{\circ}$  -  $99^{\circ}$  C
- E)  $100^{\circ}$  -  $109^{\circ}$  C



# What is HIFU?

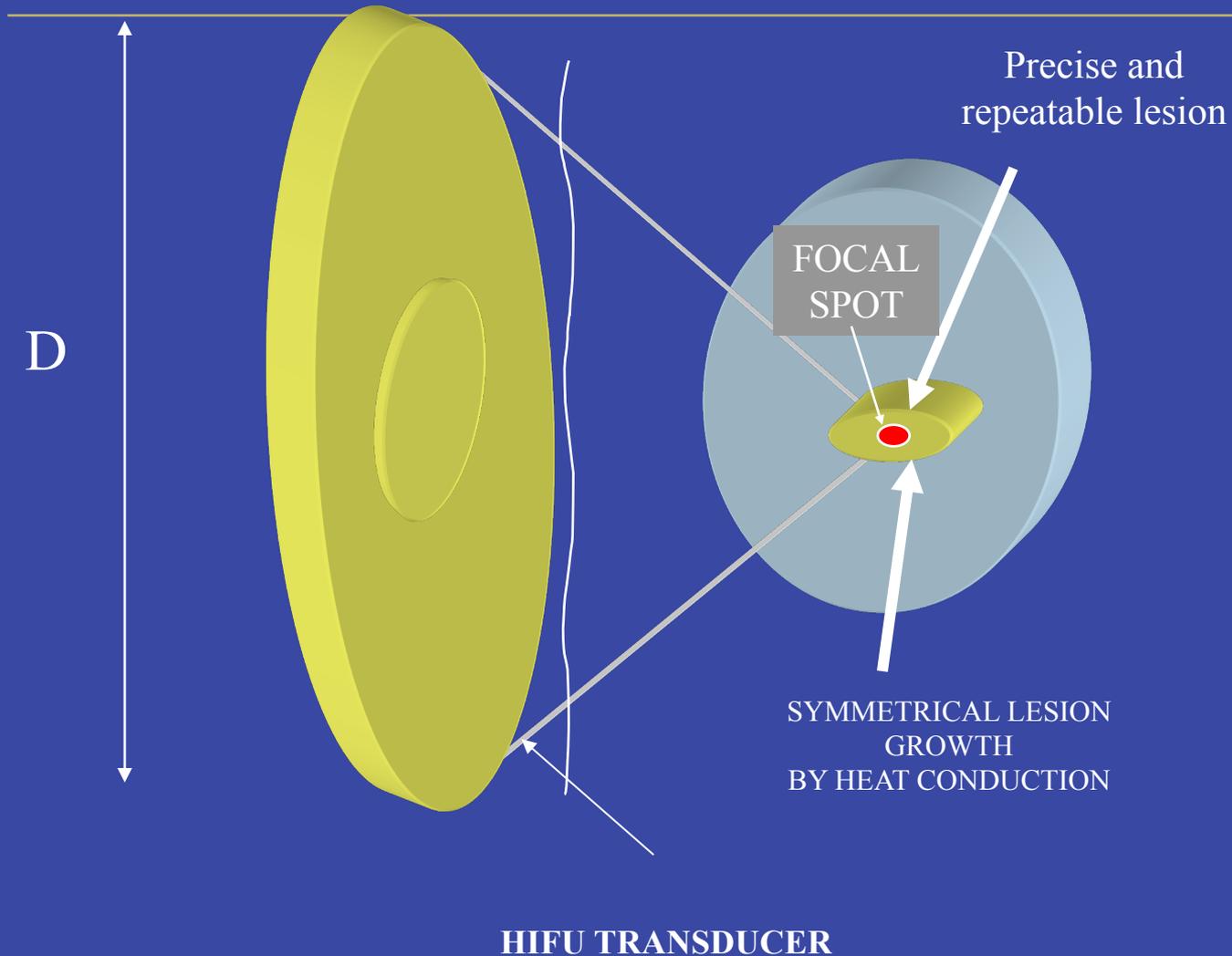
## Basic Science and Physics

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- Non-Invasive acoustic ablation technique that uses intersecting, precision- focused ultrasound waves
- Raises the temperature of the target tissue to 90-99 degrees Celsius
- Destroys the targeted tissues at the focal intersection
- Rapid heat dissipation past focal point

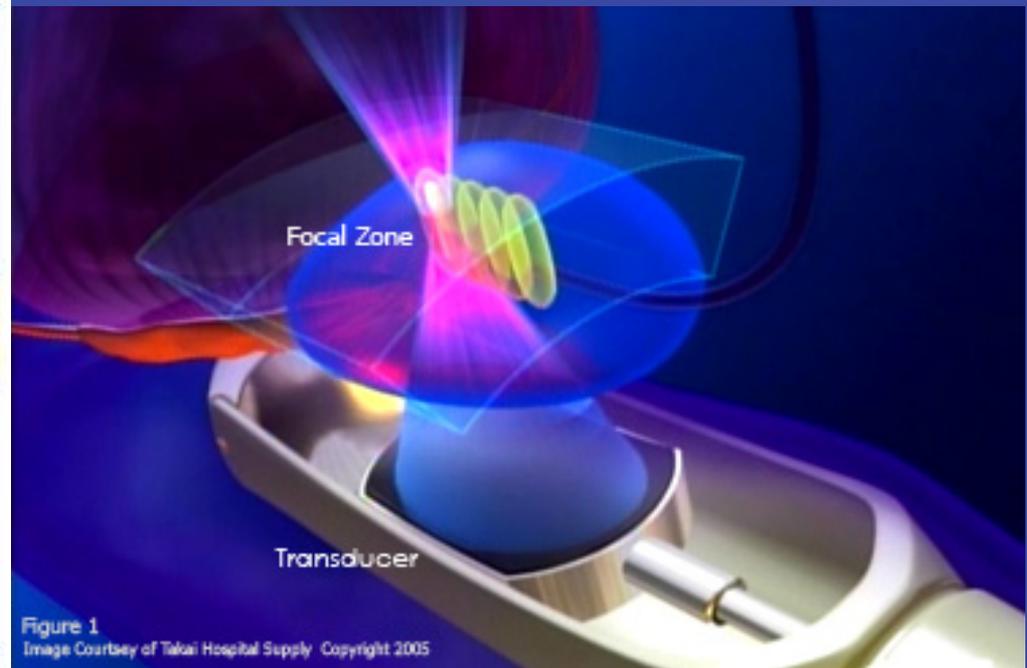
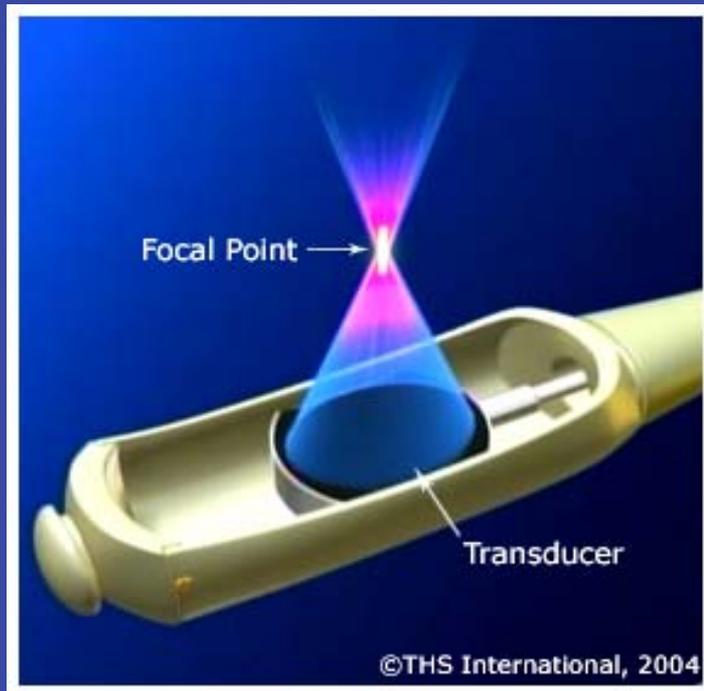


# Physics of HIFU

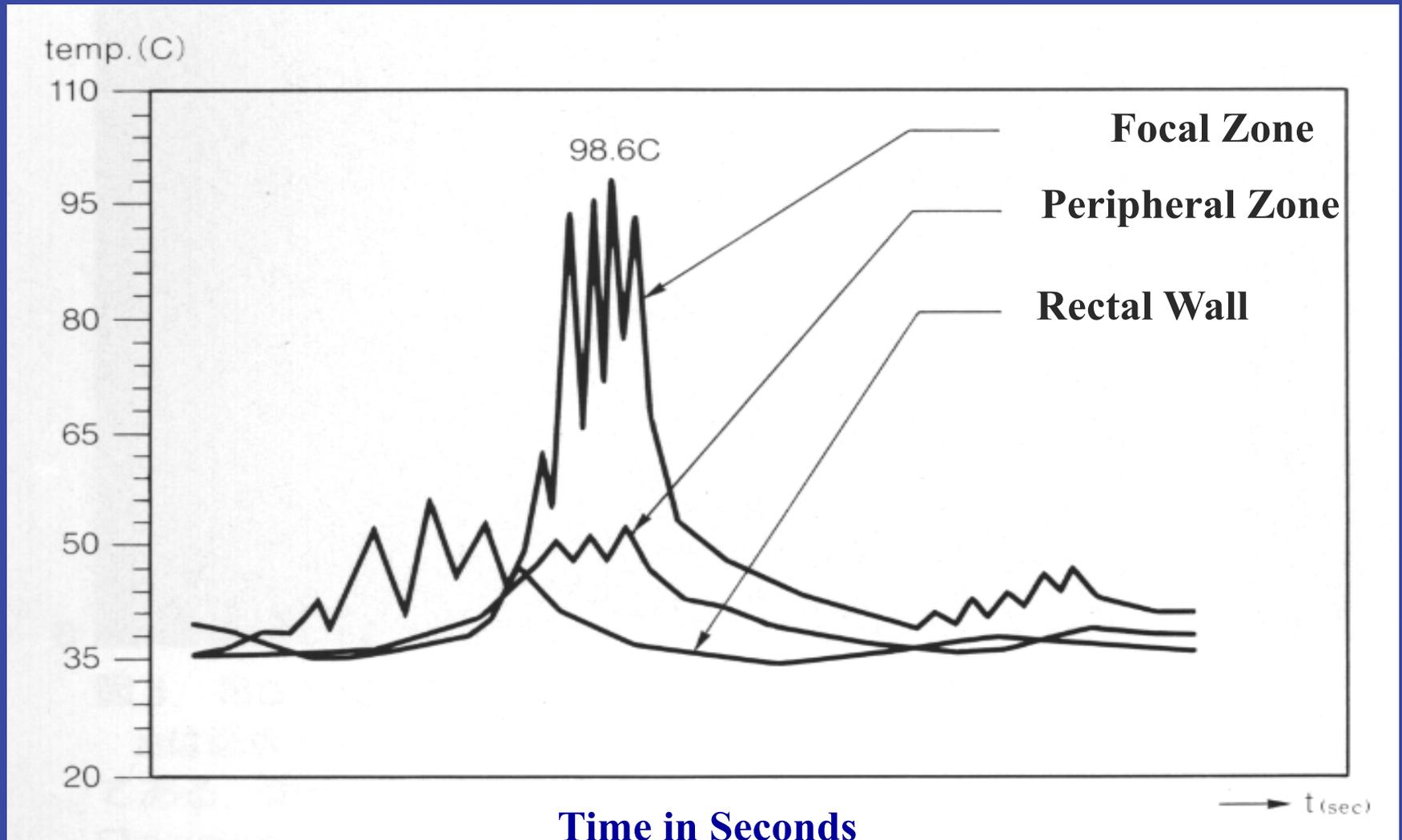


# Sonablate<sup>®</sup> 500 System

## 3mm x 3mm x 12mm lesion



# Time –Temperature Plot



# TWO SYSTEMS APPROVED

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# SONOBLATE vs ABLATHERM

HIFU Device for Prostate Disease	Sonablate® 500	Ablatherm®
<b>TURP* Required?</b> *	NO. Can treat up to a 50cc prostate without invasive surgery prior to HIFU	YES. Requires a transurethral resection of the prostate (TURP) with prostates larger than 24cc
<b>Image Quality</b>	Real-time and reference images give immediate feedback for <i>maximum</i> performance. Images are in 3D for better detail and easier planning	No 3D imaging available. Does not use reference images during treatment.
<b>Nerve Detection</b>	During treatment planning, blood flow around nerves is identified with color overlay on real-time images thus protecting nerves responsible for preserving potency	Not capable of identifying or monitoring blood flow through neurovascular bundles possibly resulting in a higher statistical incidence of erectile dysfunction
<b>The Probe</b>	Small probe may be positioned for optimal outcomes and controlled by physician for maximum patient comfort	A larger diameter probe* is fixed on the treatment table and not directly controlled by the physician
<b>Power Adjustment</b>	Features dynamic power adjustment to compensate for tissue response to the sound waves	Three pre-set power levels which can not be adjusted to tissue response
<b>Precision</b>	12mm lesions are so precise in the focal zone that the physician can pinpoint an area without damaging surrounding tissue	19-24mm lesions could miss some prostatic tissue and increase the chance for recurrence.
<b>Safety Features</b>	Reflexivity Index Measure alerts physician to patient movement Rectal wall monitoring Sonachill system circulates chilled water to protect delicate tissue outside the focal zone Energy display provides immediate feedback on effectiveness of treatment	External motion detection Refrigerated / temperature controlled gel to keep rectal wall temperature down No energy display to provide immediate feedback during HIFU on effectiveness.

# WHICH OF THE FOLLOWING IS NOT A MAJOR IMPEDIMENT TO HIFU DELIVERY?

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- A) Pubic arch interference
- B) Large prostate volume
- C) Brachytherapy seeds
- D) Extensive dystrophic calcification
- E) Severe anal stenosis



# Patient Selection

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- Localized primary prostate cancer: ( T1 – T3)
- Localized radiation recurrent prostate cancer
- Focal Rx
- SIZE: up to 40-50cc volume can be treated with Sonablate 500
- **IDEAL SIZE: less than 40 cc, prostate height less than 4 cm : use medical therapy to downsize**



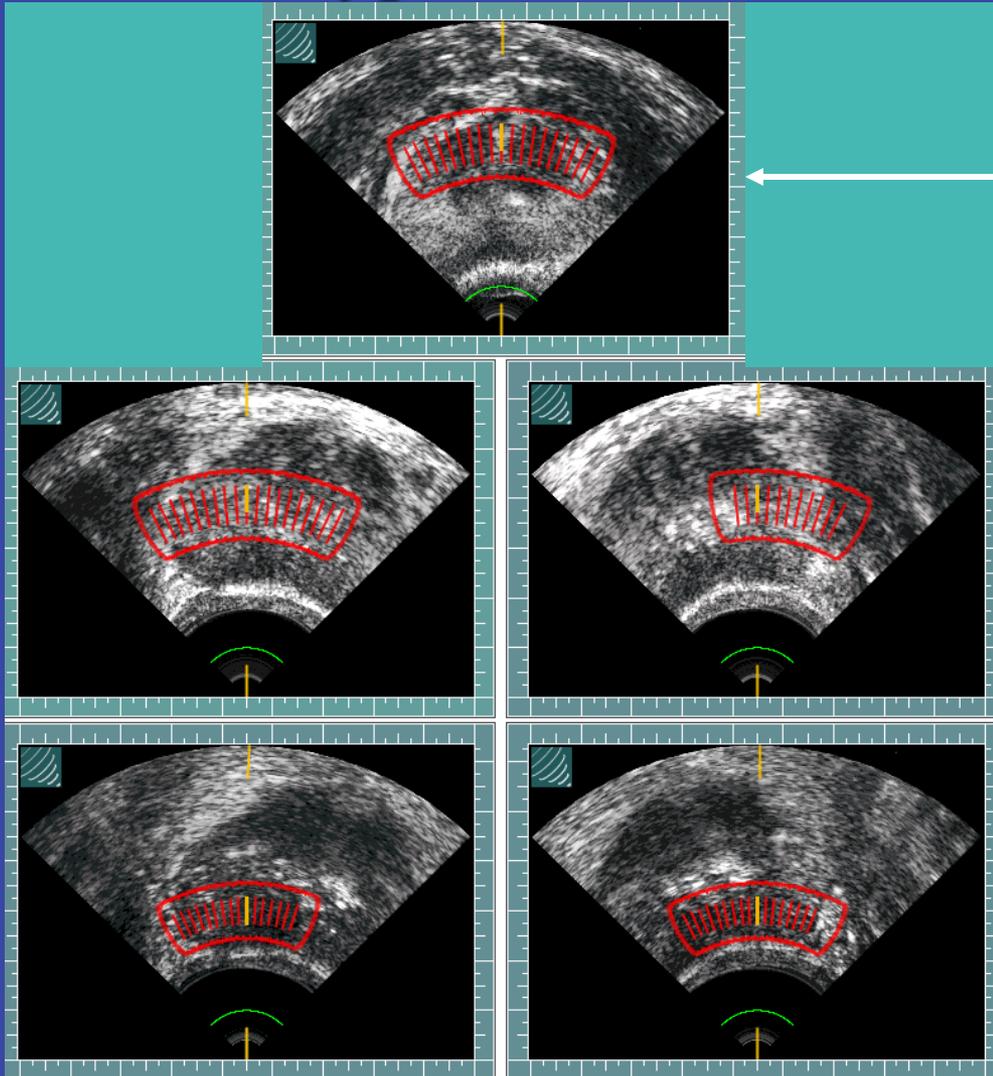
# Patient Selection

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- Minimal calcifications within the prostate:  
confluent calcifications  $> 1$  cm relative  
contraindication
- Patients on anticoagulation therapy: able to tolerate  
temporary reversal of anticoagulation
- Rectum can accommodate 2 fingers dilatation



# Typical Treatment Sequence



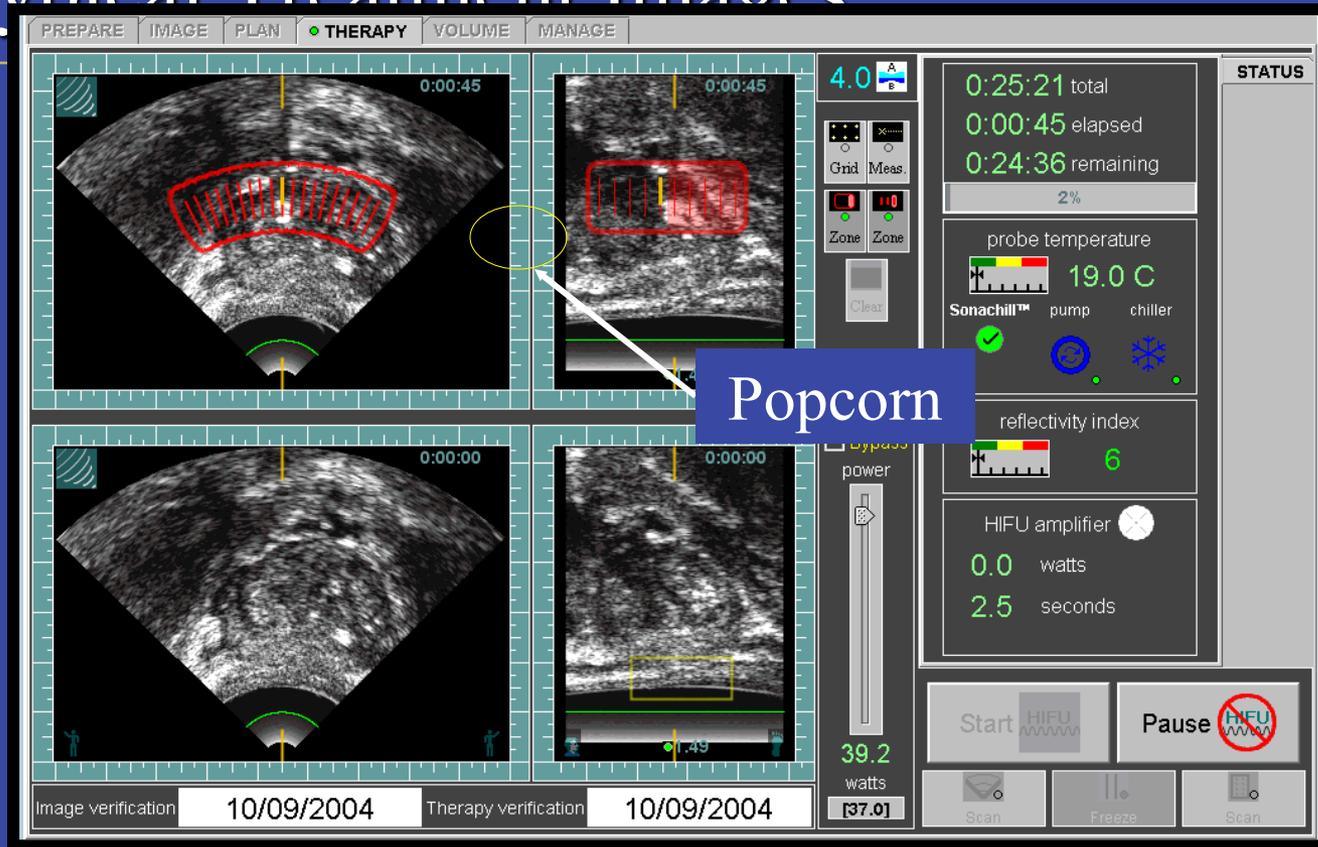
1<sup>st</sup> Treatment --- Anterior  
Region

Use 4.0 cm focal length  
probe

Mid-region of the  
prostate: Use 3.0 cm or  
4.0 cm

Posterior region of the  
prostate must be treated  
with 3.0 cm focal length  
probe

# Typical Treatment Images



Start Treatment from the anterior region.  
Adjust power levels to generate “Popcorn” echoes in the therapy box. Continue to adjust power to keep the “Popcorn” contained inside the therapy box.

# Post HIFU Care

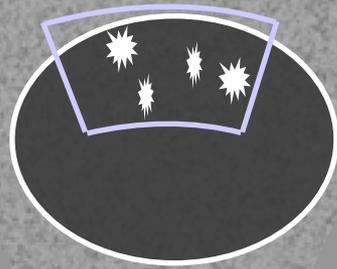
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- SP tube for 14 – 21 days( size)
- Focal: foley cath only
- Monitor for UTI
- Alpha blocker for 2 – 3 months
- Avoid early instrumentation if possible
- Reassure patients that LUTS will subside
- Stricture rate: 5-10% usually can be managed with office dilation
- PSA at 3 months

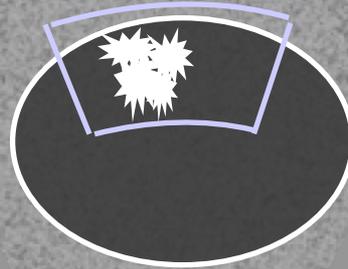


# 'Uchida Grading'

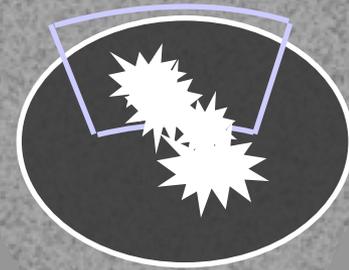
(Current recommended practice:  
not evidence-based)



Grade 1



Grade 2



Grade 3

## Principle:

1. Titrate up power to achieve Grade 1
2. Avoid Grade 3
3. Use Grade 2 as indicator that Grade 3 imminent & 'Power down'

# Visually Directed HIFU

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- During treatment: power level is constantly adjusted to achieve Uchida Grade I or Grade II changes within the treatment zone.
- Uchida GR III changes: uncontrolled cavitation (popcorn) occurring in the near field outside of the treatment zone:  
REQUIRES reduced energy



# HIFU Results and Data

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**Illing, Leslie, Kennedy, Calleary, Ogden, Emberton, Visually directed high intensity focused ultrasound for organ confined prostate cancer: a proposed standard for the conduct of therapy, BJU, Oct. 2006.**

- Study population: 34 men Stage T1 – T2, hormone naïve, PSA<15, size <40cc
- 9 men treated using algorithm based HIFU, 25 treated with visually directed HIFU
- Results: **algorithm based group**; Mean PSA nadir at 3 m:1.51
- Results: **visually directed HIFU group**: Mean PSA nadir at 3 m: 0.15
- 84% of men had Nadir PSA of 0.2ng/ml or lower
- 33% of men had negligible PSA levels





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What proportion of patients treated w  
whole gland HIFU require re-treatment?

- A) None
- B) 3-7%
- C) 10-20%
- D) 35-45%
- E) 50-75%



# HIFU Clinical Results and Data

# of SB Treatments worldwide	# of SB Centers in world	# of SB500 Users	# of HIFU cases by all USHIFU physicians
12,500	Nearly 140	Nearly 325	Nearly 2600

## Efficacy

KEY FINDING	Length of Follow-Up	Percentage	Physician	Presentation/Study
Negative Biopsy Rate	1 year	91%	Sumitomo, Hayakawa, Nagakura	One Year outcomes following HIFU Japan Endourology & ESWI Conference 2005
Biochemical Disease-Free Rate	6 years	97% (low risk group: pre-HIFU PSA <10)	Uchida, Shoi ,Nagata	HIFU for Localized Prostate Cancer 6 year Experience Japan Endourology & ESWI Conference 2004
Nadir PSA after Visually directed HIFU	3 months	84% (PSA of 0.2ng/ml or lower)	Emberton, Illing, Dawkins, Ogden	British Journal of Urology, Oct 2006
Recurrence Rate	---	5%	<i>HIFU in Americas experience</i>	



# HIFU Results and Data

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Uchida, British Journal of Urology (2006)

- 63 Patients, Mean FU: 23 months(3 – 63 months), all patients had biopsy at 6 months
- 3 year biochemical disease free rate (ASTRO) in all patients was 75% after 3 years:
  - Low Risk: 84%, Mod risk: 69% High Risk: 51%
- Negative Biopsy in 87% of patients
- Incontinence rate 1% Fistula : 1 patient (pre cooling). Stricture: 24 % (office dilatation )



# HIFU Results and Data

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- Sumitomo, Japan Endourology and ESWL Conference (2005)
- 71 Patients with median follow-up of 1 year
- Negative biopsy rate of 91%
- Complete recovery rates for intermediate and low risk averaged 90%
- High risk patients under 20ng/ml PSA levels were 82% disease free



## Treatment of localized prostate cancer by HIFU; results of the first French prospective study on patients not previously treated: Minimum of five years of follow-up-Ablatherm

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--Conort P, Rischmann P, Bensadoun H, Pfister C, Chevalier D, Saussine C, Vallancien G, Gelet A

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Results: Evaluated 117 patients, mean age 69 years, PSA 8.4 +/- 3.4ng/ml

- 36 patients required 2 sessions
- 24 failed, 13 radiotherapies (no major complication), 10 hormone, 1 prostatectomy
- 75% were considered successful (with more than 5 years of follow-up)
- HIFU, with a retreatment rate of 39%, can successfully treat more than 50% of patients without any major side-effects
- Adjuvant treatment was required for 22% with good tolerance and success



Transrectal HIFU using the Sonablate®500 for the treatment of prostate cancer;  
The Perugia-Turin experience

Mearini L, D'urso L, Collura D, Zucchi A, Formiconi A, Muto M, Porena M

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- Results: 163 men were evaluated (median age: 72 years, median baseline PSA: 7.3ng/ml, Gleason ranged from 3-10, median prostate volume: 32.4ml, median treatment time: 189 minutes, median FU: 23.8 months)
  - Disease stage:
    - T1- 72 patients
    - T2- 69 patients
    - T3a- 22 patients



- Post HIFU Treatment:

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- Median nadir value: 0.18ng/ml
  - Median PSA: 3 months-0.3ng/ml, 6 months-0.54ng/ml
  - Negative biopsy at 6 months: 73.4%
  - bNED: 71.9% overall, 87.2% for low and intermediate risk groups
  - At multivariate analysis, only baseline PSA is an independent predictor of a positive biopsy

- Conclusions:

- Using HIFU (Sonablate®500), it has been found that outcome is positively associated with a lower baseline PSA, lower PSA nadir, lower Gleason score and lower tumour stage.



# FAILURE: GOAL IS PSA <0.2

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- PSA < 0.2
  - 11% positive biopsy
  - OR of failure 1.0
- PSA 0.2-1.0
  - 46% positive biopsy
  - OR of failure 7.6
- PSA >1.0
  - 48% positive biopsy
  - OR of failure 8.2



# Can-Am HIFU /Low risk- Whole Gland

Elterman et al Can J Urol 2012

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- 65 patients with 78 month follow up
  - PSA Results
    - Pre PSA 5.8 (1.9- 10.8)
    - Post PSA .18 (0-1.5)
  - Stricture 3/65 pts
  - ED (54)—6/54 (11%)
  - Incontinence:6 pts
  - Rectal Fistula: 1
- As a result I personally abandoned HIFU for whole gland ablation



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# BIOLOGICAL BASIS OF FOCAL THERAPY

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## PRO

- Dominant nodule
- Genomic subtyping
- BOVA 2009
  - Monoclonal origin for most if not all M+ PCA
  - Nature Medicine 2009

## CON

- Multifocal disease
- Avg 5.1 tumors per prostate @ RP



# Enabling Technology: MRI for tumor localization

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*MRI June 2007*

*Confirms large anterior tumour*



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# THERAPEUTIC GOALS

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- Subtotal ablation
- Hemiablation
- Target ablation
- Zonal wipe out
  - Imaging negative
- Back to very low risk



available at [www.sciencedirect.com](http://www.sciencedirect.com)  
journal homepage: [www.europeanurology.com](http://www.europeanurology.com)



European Association of Urology



## Platinum Priority – Prostate Cancer

*Editorial by Herbert Lepor on pp. 221–222 of this issue*

# Focal High-intensity Focused Ultrasound Targeted Hemiblation for Unilateral Prostate Cancer: A Prospective Evaluation of Oncologic and Functional Outcomes

*Ernesto R. Cordeiro Feijoo, Arjun Sivaraman, Eric Barret<sup>\*</sup>, Rafael Sanchez-Salas, Marc Galiano, Francois Rozet, Dominique Prapotnich, Nathalie Cathala, Annick Mombet, Xavier Cathelineau*

*Department of Urology, Institut Montsouris, Université Paris-Descartes, Paris, France*

### Article info

#### *Article history:*

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#### *Associate Editor:*

Ciscom Navas

### Abstract

**Background:** In selected patients with unilateral, organ-confined prostate cancer (PCa), hemiblation of the affected lobe might be feasible to achieve acceptable cancer control with fewer complications.

**Objectives:** To assess the oncologic and functional outcomes of focal high-intensity focused ultrasound (HIFU) hemiblation in unilateral organ-confined PCa.

**Table 2 – Contemporary outcomes on high-intensity focused ultrasound focal ablation for prostate cancer**

Study	Patients, <i>n</i>	Mean preprocedural PSA	Mean prostate volume	Gleason score	Cancer localization	Mean follow-up	Biopsy recurrence	Continence, %	Potency
Ahmed et al (2011) [13]	20	7.3	NA	≤4+3	MRI and transperineal template-guided mapping biopsy	12 mo	11% at 6 mo	90	95%
El Fegoun et al (2011) [15]	12	7.3	37	≤4+3	TRUS biopsy	10 yr	8% at 1 yr	100	NA
Ahmed et al (2012) [14]	41	6.6		≤4+3	MRI and transperineal template-guided mapping biopsy	12 mo	23% at 6 mo	100	89%
Barret et al (2013) [16]	21	6	43	3+3	Transperineal template-guided mapping biopsy	12 mo	NA	100	Mean IIEF decreased from 20 to 19
Present study (2015)	67	6.1	36	≤3+4	MRI and TRUS biopsy	12 mo	16.4% at 1 yr	100	Mean IIEF decreased from 17.9 to 15.4

IIEF = International Index of Erectile Function; MRI = magnetic resonance imaging; NA = not available; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

# Hemiablation EDAP

Velthoven et al PCan& Pdis 2016

- 50 pts with unilateral disease on biopsy/MRI
- 8 yr follow up
- Mean PSAn 1.6 ng/ml
- bNED 28% (Pheonix)
- Continenence 94%
- Potent 83%
- Only 8 pts biopsied
  - 2 out of field
  - 1 in field
  - 2 both



# PERSONAL RESULTS: 79 Focal Only

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- At least 1 year follow up with biopsy (N=66)
- Successful zonal ablation: 60/66
- Positive cores out of zone: 13% (n=8/66)
- Potency: 58/62—93.5%
- Ejaculatory Issues: 16%
- Rectal Fistula: 1
- Osteo Pubis: 1



# Salvage HIFU therapy for locally recurrent prostate cancer after EBRT

Seo SI, Jeon SS, Jo MK, Lee HM., Choi HY

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- **Objectives:** To evaluate the efficacy and safety of salvage therapy using HIFU for locally recurrent prostate cancer after EBRT
- **Results:** Evaluated 30 patients with locally recurrent prostate cancer after primary treatment who underwent salvage HIFU
  - 56.7% had no evidence of biochemical recurrence (median follow-up of 12 months)



- PSA nadir level after salvage HIFU therapy was the only significant predictor on multivariate analysis.
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- Complications:

- Urethral stricture (3 patients)
- Transient urinary retention (5 patients)
- Incontinence (3 patients)
- Transurethral resection of necrotic tissue debris (3 patients)

- Conclusions:

- This preliminary experience has demonstrated that salvage HIFU is an effective treatment option for locally recurrent prostate cancer after EBRT
- Morbidity related to salvage HIFU therapy was lower than other types of salvage therapy



# FDA STUDY Post EBRT

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- Feliciano: New York
  - Mean age was 69. Pre-treatment PSA ranged from 1.3 to 13.1 ng/ml. Pre-treatment Gleason scores ranged from 6(N=4) to 7(N=7). Pre-treatment prostate mass ranged from 16g to 46g
    - Ten of the 11 patients (91%) were found to have a negative biopsy at 180 days post treatment.
    - Nine out of 11 (82%) patients achieved a PSA nadir  $\leq$  0.5ng/mL by the 180 days post-treatment.
    - Overall treatment success, negative biopsy and nadir of  $\leq$ 0.50ng/mL, was 82% (9/11).



# New FDA Post Radiation Failures

## P.I. Herb Lepore

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- 202 patients that have failed external beam radiation
- Gleason score 6 & 7
- 2 year follow-up with quarterly PSA
- 6 month and one year biopsy
- FDA submission : 111 pts - 63% neg bx rate at one year



# Conclusions

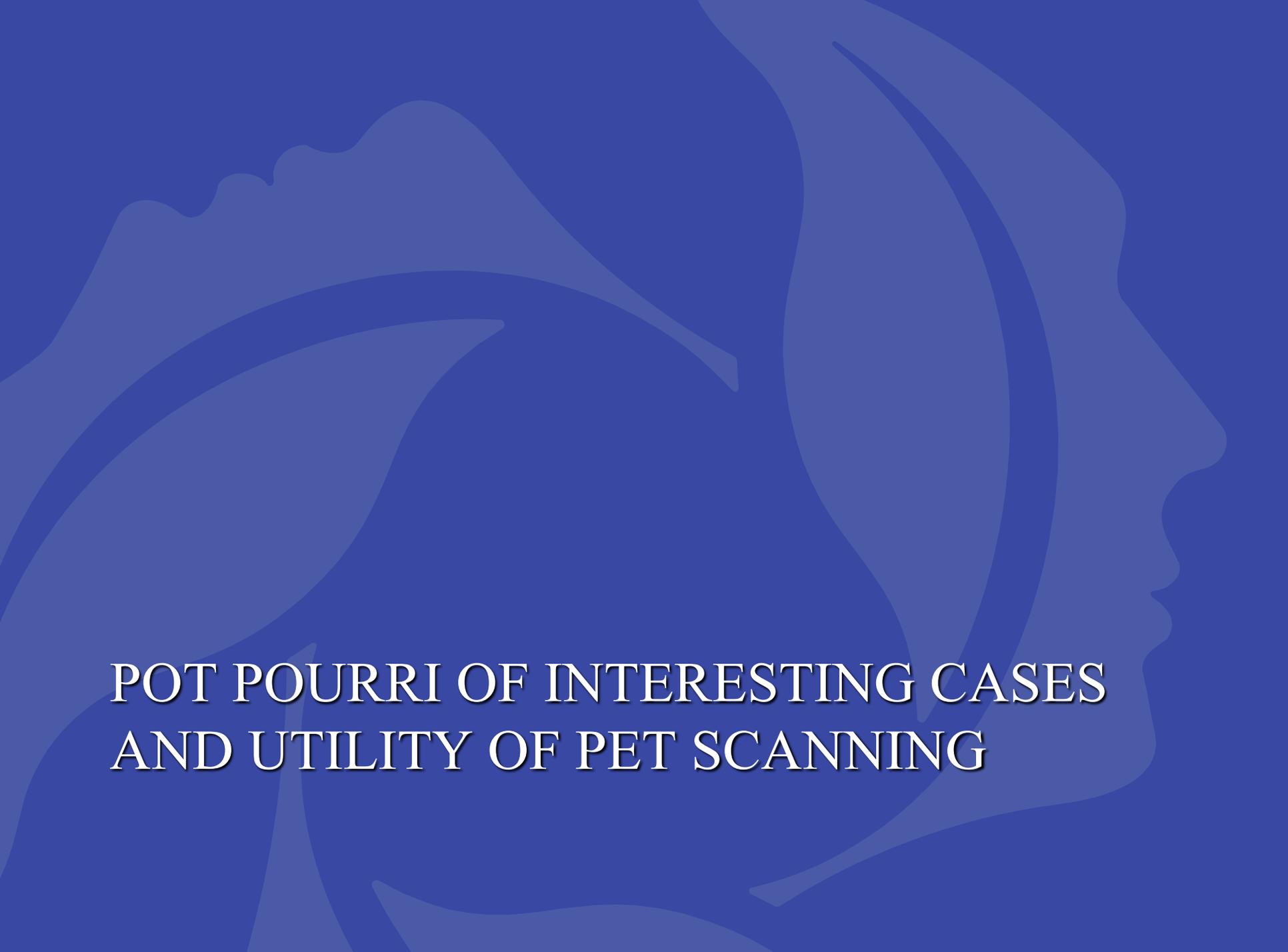
- Not all Patients are cured regardless of primary “curative” PrCa option
- All men are concerned re: morbidity and quality of life post treatment as well as cure rate
- HIFU seems to be a non-invasive, out-patient alternative therapy to localized prostate cancer that affords minimum morbidity
- Further long-term follow up data is needed and forthcoming
- Best indications are for focal therapy and XRT failures

# INTERESTING TIMES

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- What We Know
  - FDA approved
  - Fairly safe
  - Minimal impact on urinary /sexual fxn
  - Rare fistula
- What We Don't Know
  - Cancer control/re-treatment rates
  - Salvage therapy—how much harder?
  - Benefit to patient





POT POURRI OF INTERESTING CASES  
AND UTILITY OF PET SCANNING

# MR LF- 73 yr old lawyer

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- November 2015 seen by myself
- Initially diagnosed in 2004—
  - PSA 2.74
  - Gleason 6 2/8 cores
- 2004- December RRP



# PATHOLOGY- pT3B RO Nx

## SPECIMEN(S) RECEIVED

1. Prostate: Prostatectomy, Radical .

## DIAGNOSIS

1. Prostate and seminal vesicles - radical prostatectomy:
- a) Tumour type: Adenocarcinoma, usual acinar type
  - b) Gleason' s grade and score:
    - i) Primary pattern: 3/5
    - ii) Secondary pattern: 4/5
    - iii) Score: 7/10 (3+4)
  - c) Zones involved by tumour: Peripheral
  - d) Amount of tumour: Approximately 4% of gland surface area examined histologically
  - e) Distribution of tumour: Multifocal and bilateral
  - f) High-grade prostatic intraepithelial neoplasia: Present
  - g) Surgical margins: All are negative for malignancy (apical, bladder neck and peripheral)
  - h) Perineural invasion: Present
  - i) Vascular/lymphatic invasion: Not identified
  - j) Seminal vesicles: Involved by tumour (right)
  - k) Extra-prostatic soft tissue: Tumour confined to prostate with no extension into extra-prostatic soft tissue

Date/Time	PSA
29Jan99 1527	1.9
10Jun99 1114	1.1
24Feb00 1125	0.99
22Feb01 1214	0.76
06Mar03 1552	1.39
03Jun04 1605	2.54
13Sep04 1316	2.74
17Jan05 1113	< 0.05
27Sep05 1638	< 0.05
06Apr06 1005	< 0.05
16Oct06 1054	< 0.05
16Mar09 0956	0.09
05Jun09 0935	0.11
08Jan10 0949	< 0.05

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**LOSS TO FOLLOW**

# BACK TO PRINCESS MARGARET

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- When PSA hit 0.4 ng/ml- started on Eligard  
Has been on/off therapy (IAS)
- Current PSA 0.74 ng/ml and T was low normal
- CT/Bone Scans negative for mets
- Complained of “horrible” ADT side effects
  - Myalgias
  - Depression
- What to do?



# DECIDED TO WAIT FOR PSA TO HIT 2.4

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- Choline PET- Mayo Clinic
- Uptake in residual seminal vesical
- Nodes clear
- What next??



# BIOPSY REMNANT SEMINAL VESICAL

Surgical Pathology		Complete
<ul style="list-style-type: none"><li>Specimen Type: Tissue</li><li>Collection Date: Apr 27 2016 08:00:00 EDT</li><li>Specimen Collected By: GAMMA-DYNACARE MEDICAL LABORATORIES</li></ul>		
Final Diagnosis	1. BIOPSY, SEMINAL VESICLE, RIGHT BASE - SEMINAL VESICLE TYPE TISSUE INVOLVED BY PROSTATIC ADENOCARCINOMA; GLEASON SCORE 7/10 (PRIMARY 4, SECONDARY 3); INVOLVING 4/5 CORES; APPROXIMATELY 30-40% TISSUE INVOLVEMENT; PERINEURAL INVASION PRESENT. 2. BIOPSY, SEMINAL VESICLE, RIGHT TIP - SEMINAL VESICLE TYPE TISSUE, NEGATIVE FOR MALIGNANCY.	Complete
<ul style="list-style-type: none"><li>Observation Sub-ID: 1</li></ul>		

- Current PSA is 3.4 ng/ml



# MAY 2016

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- HIFU To remnant SV
- Post treatment PSA  
0.03 ng/ml

Most recent reading 0.04

November 2017

