HIFU: Ready for Prime Time?

Perinchery Narayan, M.D.
Chief Medical Officer, HIFU Solution LLC
Director North Florida Research Institute
North Florida Urology Associates
Paradigm Shifts in Prostate Cancer

- Paradigm shifts are profound changes that occur once in several decades in management of disease.
- “Revolution” in scientific thinking
- PSA revolutionized prostate cancer diagnosis and treatment in the late 80s and 90s
- 100s of papers published for and against PSA
- However, PSA took hold & clinicians enthusiastically embraced it
- Along with PSA, several other developments occurred
- There was an increase in diagnosis of prostate cancer and we changed the way we do biopsies
- PSA landmark discovery of 20th Century - American Association of Cancer Research
- Revolutionized diagnosis of prostate cancer and has shifted stage at diagnosis from T2, T3 to T1c
- Prior to PSA 5 year survival (66%)
- Currently 5 year survival (99.9%)
Prostate cancer mortality has reduced 53% in the last 25 years
(American Cancer Society, 2017)
The PSA Controversy - Randomized Trials

- Widespread use of PSA is driven by assumption that PSA screening reduces death rates
- Best data that PSA reduces death rate is from clinical trials
- Two randomized clinical trials have been done
- The European Trial (ERSPC): PSA reduces death rate by 21% at 13 years of f/u.
- Overdiagnosis: 27 men diagnosed to prevent 1 death.
- The PLCO trial (USA): Found no evidence of improved death rate. However, results of this trial invalidated by recent data.

ERSPC Lancet 2014
JE Shoag, S Mittal, New York Presbytery, Jim HU Weill Cornell University

- “90% of controls in the PLCO trial had at least 1 PSA test before or during the trial.”
- “Men in control group had more testing than intervention arm.”
- “The contamination in the PLCO trial makes it unreliable to determine role of PSA on prostate cancer death rate.”
PSA Reduces Death Rate

As of now, there is only 1 randomized trial of screening PSA vs. no PSA - The ERSPC trial
182,388 men - 900 cancer deaths - 13 year F/U
PSA testing every 2-4 years vs. standard care no PSA
Men aged 55-69 years at start of trial
PSA screening arm shows 21% reduction in prostate cancer death at 13 years
27 men need diagnoses to prevent 1 death
With further F/U, 5 men needed to diagnose to prevent 1 death

Schröder et al. Lancet Volume 384, No. 9959, p2027–2035, 6 December 2014
Paradigm Shifts in Prostate Cancer - Increasing Costs

- Last 10 years, a second set of paradigm shifts have occurred
- This has been driven by tremendous increase in prostate cancer diagnosis and side effects of treatment
- The number of men over age 65 is expected to more than double from 40 million in 2010 to 88 million in 2050
- Medicare is under siege to cut costs
- There is an increasing uproar of complaints from many quarters that prostate cancer treatment is causing significant harms with escalating costs
Surgery and Radical Radiation is Not Preferred Anymore

- The sledgehammer approach of “war on cancer” and radical prostatectomy and radiation for every diagnosed cancer is causing escalating costs and morbidity.
- Short term morbidity of surgery is 20% & occasional deaths from cardiac, respiratory, DVT, blood transfusion and others.
- Long term morbidity is consistently 70-80% ED and 10-17% incontinence.
- Long term studies started over 10 years ago have shown that watchful waiting and active surveillance result in 95-98% survival at 10-15 years - Pivot, ProtecT trials.
USPSTF and Harms of Abandoning PSA Screening

- Because of the recognition of the harms of surgery and overdiagnosis by PSA, USPSTF declared in 2012 that PSA is not recommended for routine screening in men over 50
- 2 Studies in JAMA 2016 found that since USPSTF recommendations, PSA screening has declined by 16%
- Barocas in 2015 reported a drop of 28% in intermediate risk cancer and a drop of 23% in high risk cancer diagnosis after USPSTF
- In June 2016, researchers at Northwestern University in Chicago found annual incidence of metastatic incidence increased 72% in 2013 as compared to 2004

How to Reduce Overdiagnosis and Overtreatment

- Smart screening techniques of PSA recommended by NCCN, ASCO, and ACS can reduce overdiagnosis
- The 4K Test- improves PSA specificity for aggressive cancer
- mp-MRI- detects aggressive cancer, reduces overdiagnosis
- Use of 4K Test and mpMRI can reduce biopsy rate by 1/3 without missing significant cancers
- HIFU Therapy- a useful compromise between AS and radical treatment- has less side effects
Another Reason For Minimally Invasive Therapy

Prostate Cancer Deaths are Increasing in Older Men

- Men over 75 screened less due to wrong perception of life expectancy
- Men 75 or older form 16% of male population but 26% of prostate cancer, 48% of metastatic disease, and 53% of deaths
- Geriatric specialists - health status more important than age, healthy man at 75 will live 10 yrs and should be treated
- Older men, however, cannot have surgery. HIFU may be a better option than radiation due to less side effects

Paradigm Shifts in Prostate Cancer Minimally Invasive-HIFU

- The US FDA approval of high intensity focused ultrasound (HIFU) in October 2015 is starting to have a major impact in use of minimally invasive therapy for prostate cancer
- HIFU: the first treatment available in office with low side effects and can be used for focal Rx hemi-ablation, or whole gland treatment
- HIFU is also causing a re-assessment in other therapies such as focal cryotherapy and newer treatments such as focal radiation, IRE, and others
62 year old male with PSA 6.57
These findings only on MRI, ultrasound often normal

DWI IMAGE

ADC Map

Coronal T2
67 year old male with negative TRUS biopsy PSA 7.0 showing anterior cancer
67 year old male with negative TRUS biopsy PSA 7.0 showing anterior cancer

DCE w/o color

DCE w/ color
HIFU: a technical solution to a clinical problem

- There is an unmet need for the newly diagnosed patient who, in absence of HIFU, is faced with deciding between surveillance and radical therapy
  - Whole gland HIFU is a less radical approach with similar oncologic outcomes but less morbidity
  - Hemiablation HIFU errs on the side of safety without burning any bridges for future intervention
Principles of HIFU - Focused High Intensity US

- As acoustic wave moves through tissue, it is absorbed and converted to heat
- With focused beams, lower temperature heat can pass through normal tissue avoiding rectal damage
- Beam is cigar shaped
- Tissue damage is a function of temperature and time of exposure
- Temperature achieved is 80-90°C
- Higher temperatures avoided to prevent boiling and microexplosions
Principles of HIFU (Cont’d)

- Ultrasound beams focused on precisely defined portion of tissue
- Robotic arm moves ultrasound beam a few mm at a time to treat a portion or entire prostate
- Anesthesia only required to prevent patient movement
- Imaging transducer will track the treatment areas as they are being treated
Creation of Lesion Involves Two Main Effects:

1. **Thermal effect** related to tissue temperature
2. **Cavitation effect** caused by air bubbles which absorb acoustic energy and increases tissue heating. Temperature rises to between 80-90°C
HIFU Tissue Effects

Time Frame of Tissue Destruction

Immediate:
- Coagulation
- Necrosis

After 7 Days:
- Inflammatory Response

After 14 Days:
- Induction of Fibrosis
HIFU Technical Considerations

Two devices FDA Approved for Ablation of Prostate Tissue
October 2015

Ablatherm Robotic HIFU

Sonablate 450
FDA Clearance: HIFU Intended Use

510(k) Intended use: The Ablatherm® Integrated Imaging device is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostate tissue.

“A good analogy is the scalpel. A scalpel is a tool to cut tissue but is not approved to treat specific diseases (e.g., prostate cancer or aortic aneurysm).”

Jonathan Jarrow, MD
FDA Clinical Reviewer of Ablatherm

John Baxley, MS
FDA Lead and Engineering Reviewer of Ablatherm
Unique Attributes of Ablatherm HIFU

Three dimensional robotic motion
• 3 translations and 2 rotations
• Image recognition software detects rectal wall and fine tunes the probe position

Integrated ultrasound transducers avoid compromise
• 7.5 MHz imaging
• 3 MHz ablation

Patented Ablasonic™ fluid for consistent fluid transmission
25cc/hour ablation speed
Ablatherm Safety Features

Treatment module:
Patient’s bed and Technology carrier

Control module:
Treatment strategy planning and monitoring

Endorectal applicator:
Therapy transducer (3MHz)
Imaging transducer (7.5MHz)
Clinical Versatility of HIFU

Ablatherm HIFU has proven long term clinical data on more than 50,000 treatments with different approaches and patients populations:

**Whole Gland Ablation**
From Low Risk to locally advanced disease

**Focal / Partial Ablation**
For targeted disease in primary care
For targeted recurrence in salvage approach

**Salvage Curative Option**
From whole gland salvage to focal salvage
Long-term Clinical Results - First-line Treatment

Over 85 peer-reviewed publications with Ablatherm® HIFU
Unique Safety of Ablatherm HIFU

Automatic safety features
- Rectal wall temperature monitoring
- Rectal wall detection
- Patient movement detection

<table>
<thead>
<tr>
<th></th>
<th>Ablatherm HIFU</th>
<th>Sonablate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole gland ablation:</td>
<td>2.4-3.1%^{1,2}</td>
<td>3-12%^{3,4}</td>
</tr>
<tr>
<td>Incontinence (pad rate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Radiation:</td>
<td>0.4%^{5}</td>
<td>4-4.8%^{6,7,8}</td>
</tr>
<tr>
<td>Fistula</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ablatherm Robotic HIFU Equals Safety

## Results of Surgery for Prostate Cancer

- Radical Prostatectomy - gold standard for localized prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>Risk Group</th>
<th>n</th>
<th>10 Year Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boorjian 2008 RP</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Low</td>
<td>3283</td>
<td>100%</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Intermediate</td>
<td>2795</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1513</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Stephenson 2008 RP</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Low</td>
<td>5200</td>
<td>99%</td>
</tr>
<tr>
<td>MSK CCF U Mich</td>
<td>Intermediate</td>
<td>4184</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1962</td>
<td>92%</td>
</tr>
</tbody>
</table>

- Radiotherapy is also commonly used with similar oncologic outcomes<sup>3</sup>

# Results of Whole Gland HIFU for Prostate Cancer

- HIFU efficacy similar to RRP

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>n</th>
<th>10 Year Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ganzer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>229</td>
<td>100%</td>
</tr>
<tr>
<td>Moderate</td>
<td>211</td>
<td>96.22%</td>
</tr>
<tr>
<td><strong>Thuroff</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All localized (72% mod or high)</td>
<td>704</td>
<td>99%</td>
</tr>
<tr>
<td><strong>Crouzet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>357</td>
<td>99%</td>
</tr>
<tr>
<td>Moderate</td>
<td>452</td>
<td>98%</td>
</tr>
<tr>
<td>High</td>
<td>174</td>
<td>92%</td>
</tr>
</tbody>
</table>

## Prostate Cancer Treatment

- 10 year Cancer Specific Survival after HIFU = RRP

<table>
<thead>
<tr>
<th></th>
<th>10 Year Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Prostatectomy</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low</td>
<td>99-100%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>96-97%</td>
</tr>
<tr>
<td>High</td>
<td>92-95%</td>
</tr>
</tbody>
</table>

Prostate Cancer Treatment Morbidity - ProtecT

- All treatments have morbidity including surveillance

Prostate Cancer Treatment Morbidity

- All treatments have morbidity including surveillance

<table>
<thead>
<tr>
<th></th>
<th>Active Surveillance (ProtecT)¹</th>
<th>Radiotherapy (ProtecT)¹</th>
<th>Radical Prostatectomy (ProtecT)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>62 years</td>
<td>62 years</td>
<td>62 years</td>
</tr>
<tr>
<td>Incontinence*</td>
<td>3%</td>
<td>4%</td>
<td>20%</td>
</tr>
<tr>
<td>Erectile dysfunction*</td>
<td>21%</td>
<td>66%</td>
<td>82%</td>
</tr>
</tbody>
</table>

*2 years after treatment initiation

<table>
<thead>
<tr>
<th></th>
<th>Active Surveillance (ProtecT)$^1$</th>
<th>Whole Gland HIFU (FDA IDE)$^2$</th>
<th>Radiotherapy (ProtecT)$^1$</th>
<th>RRP (ProtecT)$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>62 years</td>
<td>64 years</td>
<td>62 years</td>
<td>62 years</td>
</tr>
<tr>
<td>Incontinence*</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
<td>20%</td>
</tr>
<tr>
<td>ED*</td>
<td>21%</td>
<td>37%</td>
<td>66%</td>
<td>82%</td>
</tr>
</tbody>
</table>

*2 years after treatment initiation

HIFU maintains the efficacy of radical treatment with less morbidity

Further morbidity reduction with Hemiablation

Focal Ablation
Clinical Results – Partial / Focal Treatment

Institut Montsouris, Paris, European Uro 2015

- 71 pts Ablatherm Hemiablation
  Mean F/U: 21 months.
- 10 pts (14%) had postop side effects:
  - 4 UTIs & 4 urinary retentions
  - 2 retentions treated with TURP
- Mean IIEF decreased from 17.9 to 15.4
- 84% biopsy negative in treated lobe
Prospective Clinical Trial - Hemiablation

Focal High Intensity Focused Ultrasound of Unilateral Localized Prostate cancer: A Prospective Multicentric Hemiablation Study of 111 Patients

- 111 Ablatherm pts treated at 10 centers in France
- Hemiablation with Ablatherm
- 95% no significant cancer in the treated lobe (Gleason ≥ 7 OR CCL > 3mm OR > 2 cores positive)
- Freedom from radical treatment at 2 years: 89%
- 78% preservation of erectile function at 2 years
- 3% Incontinence (pads) at 2 years
<table>
<thead>
<tr>
<th></th>
<th>Active Surveillance (PIVOT)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Active Surveillance (ProtecT)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Hemi HIFU (AFU Trial)&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>67 years</td>
<td>62 years</td>
<td>65 years</td>
</tr>
<tr>
<td>De novo* Incontinence At 2 yrs</td>
<td>2% ('lots of problems' or 'large volume' or 'no control')</td>
<td>3% (pad use)</td>
<td>3% (pad use)</td>
</tr>
<tr>
<td>De novo ED* At 2 yrs</td>
<td>17% (inability to penetrate)</td>
<td>21% (sufficient for intercourse)</td>
<td>22% (maintain SHIM &gt;16)</td>
</tr>
</tbody>
</table>

*proportion of population not reporting condition at baseline reporting it at follow-up.

Minimal incremental morbidity with Hemiablation HIFU

---

<sup>1</sup> Wilt et al NEJM. 2012; <sup>2</sup> Donovan et al NEJM 2016; <sup>3</sup> Rischmann et al European Urology 2017
# Side Effects HIFU vs. Radiation & Surgery

- HEMI HIFU is essentially equivalent to Active Surveillance
- Whole gland HIFU has less side effects compared to RRP

## Table:

<table>
<thead>
<tr>
<th></th>
<th>Act. Surv. (ProtecT)¹</th>
<th>Hemi HIFU (AFU Trial)²</th>
<th>Whole Gland HIFU (FDA IDE)²</th>
<th>Radiotherapy (ProtecT)¹</th>
<th>RRP (ProtecT)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>62 years</td>
<td>65 years</td>
<td>64 years</td>
<td>62 years</td>
<td>62 years</td>
</tr>
<tr>
<td>Incontinence *</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*2 years after treatment initiation

Whole Gland HIFU maintains efficacy of radical treatment with less morbidity

Hemi HIFU: side effects = Act. Surv.; reduces need for radical treatment by 50%
HIFU: a technical solution to a clinical problem

There is an unmet need for the newly diagnosed patient who, in absence of HIFU, is faced with deciding between surveillance and radical therapy

- Whole gland HIFU is a less radical approach with similar oncologic outcomes but less morbidity
- Hemiablation HIFU provides more safety without burning any bridges for future intervention
HIFU - Take Home Points

- HIFU is a non-invasive procedure that treats prostate cancer - avoids 2 most common life altering side effects seen with surgery and radiation - urinary incontinence and erectile dysfunction
- Small size & precision of HIFU beam allows dramatic decrease in side effects; no incisions needed
- Truly outpatient procedure performed in doctor’s office
- Treatment takes 1.5 - 3 hours (Hemi vs. Whole Gland)
- Normal activity resumes within few days
- Minimal to no pain
- No radiation exposure
- Other treatments not contraindicated later
- Excellent results - over 10 years experience
- Approved in > 41 countries, > 50,000 patients treated
Erectile dysfunction avoided by HIFU
Incontinence avoided by HIFU

I DONT HAVE STRESS INCONTINENCE

YOUR JUST THAT FUNNY