Focal Therapy for Prostate Cancer

Julio Pow-Sang MD
Moffitt Cancer Center
Patient Selection for Focal Therapy

1. Risk stratify first

2. Determine if
   - unifocal,
   - unilateral
   - Index \(\), clinically significant lesion

3. Which technology to use?
   - Cryosurgery
   - HIFU
   - Laser
   - RFA
Risk Stratification NCCN

- Unifocal
- Unilateral
- Index lesion
The Variability of Prostate Cancer

The Disease

• Variable presentation
• Multiple treatments

Organ variability

• Large prostate
• Median lobe of variable configuration
• Prostatitis changes
• Accessory pudendal artery (ies)
• Narrow pelvis
• Pubic notch

The patient and co-morbidities

• Age (functional more than chronological)
• Diseases precluding surgery or XRT
Management Options For Localized Prostate Cancer

- Active Surveillance
- Surgery
- Radiation Therapy
- Cryosurgery
- HIFU
- Focal Therapy
Radical Prostatectomy Milestones

1982
Walsh: Anat. RPP

1987
Gomez: Bladd. neck presv.

1993
Koch: Collaborative pathways

1994
Poore: Pres. PPLs

1998
Hollabaugh: Continence preserving RRP

1999
Kim: Nerve interpos.

2000
Guillonnea/Vallencianne/Abbou: LRP

Robotic

Marshall, LaFontaine: Minilap. RRP
### Radical Prostatectomy

#### Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Schuessler: 1st LRP</td>
</tr>
<tr>
<td>1997</td>
<td>Raboy: Initial experience with LERP</td>
</tr>
<tr>
<td>1998</td>
<td>Guillonneau &amp; Vallencien: 1st LRP with refined technique</td>
</tr>
<tr>
<td>2000</td>
<td>Abbou: 1st 20 cases of LRP</td>
</tr>
<tr>
<td>2001</td>
<td>Abbou: 1st Robotic LRP</td>
</tr>
<tr>
<td>2003</td>
<td>Van Velthoven: Single not running suture starting at 6 o’clock</td>
</tr>
<tr>
<td>2002</td>
<td>Menon: Robotics and Vattikuti Urology Institute</td>
</tr>
</tbody>
</table>

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Schuessler, Schulam, Clayman, Kavoussi: Initial experience 9 patients

Raboy: Initial experience with LERP
Radiation Therapy

External Radiation
- 3DCRT
- IMRT
- SBRT
- Proton Therapy

Implant Radiation
- LDR Brachytherapy
- HDR Brachytherapy
Active Surveillance - Toronto

- 450 men
- Median f/u 6.8 years (1 to 13)
- 10 year prostate cancer actuarial survival 97.2%
- 30% reclassified
- 50% PSA failure in treated group
- PSA doubling < 3 years 8.5 times risk of PSA failure

*Klotz JCO 2010 28:126*
Active Surveillance – Johns Hopkins

- 769 men
- Mean f/u 2.2 years (0.01-15)
- Free of intervention
  - 2 Years: 81%
  - 5 Years: 59%
  - 10 years: 41%

Tosoian JCO 2011 29:2185
Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

- Decreased cancer specific mortality with treatment
- More apparent in clinically significant cancers and in younger men

PIVOT

- 52 centers
- 13,022 screened
- 5,023 men eligible
- 731 men agreed to participate Mean age 67 years
- ~ One-third African-American
- Risk:
  - 43% Low
  - 36% Intermediate
  - 20% High

All cause mortality
  ARR: 2.9%
  HR: 0.88 (95% CI 0.71-1.08) p=0.22

Pr. Ca. mortality
  ARR: 2.7%
  HR: 0.63 (95% CI 0.36-1.09) p=0.09

High risk (PSA>10ng/ml)
  ARR: 7.2%
  HR: 0.36 (95% CI 0.15-0.89) P=0.03

Wilt AUA 2011
Patient Selection

- Clinically significant cancer
- Curable cancer
- Based on life expectancy, not age
- Co-morbidities
- Patient’s choice
Risk Stratification NCCN

- Unifocal
- Unilateral
- Index lesion
The Index Lesion and the Origin of Prostate Cancer

Hashim Uddin Ahmed, M.R.C.S., B.M., B.Ch.
ORIGINAL ARTICLE

Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy

M Karavitakis¹,², M Winkler³, P Abel¹,³, N Livni⁴, I Beckley³ and HU Ahmed⁵
Natural history of small index lesions suspicious for prostate cancer on multiparametric MRI: recommendations for interval imaging follow-up
## MRI Suspicion Score

<table>
<thead>
<tr>
<th>Lesion-based findings on MRI sequences</th>
<th>( T2W ) MRI</th>
<th>ADC map of ( DW-MRI )</th>
<th>( DCE ) MRI</th>
<th>MR spectroscopy</th>
<th>MP-MRI suspicion score</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>Negative</td>
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<td>+</td>
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<td>Low</td>
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<td>Low</td>
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<td>Moderate</td>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>High</td>
</tr>
</tbody>
</table>

Rais-Bahrami Diag Interv Radiol 2014 20:293
Prostate Surgery
Disruptive Technologies

~75,000 years
~500 years
~150 years
15 years
20 years
Principles of Cryotherapy Effect

Cell damage correlates with:

- Lethal temp - 40°C
- Duration of freeze >5 minutes
- “Hold” lethal temp. 2 minutes
- Freeze-thaw cycles 2

Six-month Biopsy
Cryoablation Options

- Primary Total Gland
- Partial Gland (Focal, Partial, \( \frac{3}{4} \))
- Salvage
TARGETED CRYOABLATION OF THE PROSTATE

COMPONENTS

- Transrectal Ultrasound Guided
- Cryoprobes
- Temperature probes
- Urethral warmer
- Planning software
Focal Cryosurgery-Patient Candidates

No evidence of cancer in the contra-lateral side

Assessment:
- Saturation biopsy/-Multiparametric MRI

Extent:
- Focal
- Partial
- Hemi
# Primary Cryosurgery
## Oncologic and Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-Up (months)</th>
<th>Definition</th>
<th>BDFS</th>
<th>Rectal Injury</th>
<th>Incontinence</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhar COLD Registry JU 2009</td>
<td>3209</td>
<td>18</td>
<td>ASTRO (3 cons ↑)</td>
<td>80% (L) 78% (M) 77% (H)</td>
<td>0.3%</td>
<td>5%</td>
<td>33% (12 mo)</td>
</tr>
<tr>
<td>Cohen Urol 2008</td>
<td>370</td>
<td>147±33</td>
<td>Phoenix (Nadir + 2)</td>
<td>80% (L) 74% (M) 46% (H)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ellis Urol 2007</td>
<td>416</td>
<td>20.4±14.7</td>
<td>ASTRO (3 cons ↑)</td>
<td>84% (L) 82% (M) 69% (H)</td>
<td>0.0%</td>
<td>4.0%</td>
<td>51% (48 mo)</td>
</tr>
</tbody>
</table>
Cryosurgery
Long Term Biochemical DFS

- 370 men
- 1991-1996
- Median f/u: 12.55 years
- 10 year BDFS:
  - Low 80.56%
  - Intermediate 74.16%
  - High 45.54%
- 10-year Bx-: 76.96%

L: 17%  I: 39%  H: 43%

Cohen Urology, 2008 71:515
Randomized Trial of External Beam Radiation Therapy versus Cryoablation in Patients with Localized Prostate Cancer

- 122 men per arm (Intended: 240/arm)
- Median f/u 100 months
- At 36 months cryo versus:
  - XRT: 68Gy-70Gy early 2000s
    73.5Gy late 2002
  - Dz progression: 23.9% v 23.7%
  - PSA-failure: 17.1% v 13.2%
  - Trend reversed at 84 months
    27% v 31.7%
  - Bx + : 7.7% v 28.9%

* Wide Confidence Intervals!
## Salvage Cryosurgery
### Oncologic and Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-Up (months)</th>
<th>Definition</th>
<th>BDFS</th>
<th>Rectal Injury</th>
<th>Incontinence</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhar COLD Registry JU 2009</td>
<td>445</td>
<td>15</td>
<td>ASTRO (3 cons ↑)</td>
<td>72%</td>
<td>1%</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>Hamoui JU 2008</td>
<td>110</td>
<td>95</td>
<td>ASTRO II (Nadir + 2)</td>
<td>N/A</td>
<td>41%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ismail JU 2008</td>
<td>100</td>
<td>33.5</td>
<td>ASTRO (3 cons ↑)</td>
<td>73% (L)</td>
<td>1%</td>
<td>13%</td>
<td>14%</td>
</tr>
</tbody>
</table>
# Focal Cryosurgery
## Oncologic and Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-Up (months)</th>
<th>Definition</th>
<th>BDFS</th>
<th>Rectal Injury</th>
<th>Incon-tinence</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhar COLD Registry JU 2009</td>
<td>795</td>
<td>12</td>
<td>ASTRO (3 cons ↑)</td>
<td>81.5%</td>
<td>0.4%</td>
<td>2.8% (12 mo)</td>
<td>65% (12 mo)</td>
</tr>
<tr>
<td>Ellis Urol 2007</td>
<td>60</td>
<td>15.2±7.4</td>
<td>ASTRO (3 cons ↑)</td>
<td>80%</td>
<td>0.0%</td>
<td>3.6% (6 mo)</td>
<td>71% (12 mo)</td>
</tr>
<tr>
<td>Onik Urol 2007</td>
<td>55</td>
<td>43</td>
<td>ASTRO (3 cons ↑)</td>
<td>90%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>85%</td>
</tr>
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</table>
High Intensity Focused Ultrasound (HIFU)

- Acoustic focusing occurs at a point where multiple beams converge.
- Tissue effects are a function of:
  - Frequency (or wavelength) set at 4 MHz
  - Energy Intensity: Determined by input excitation voltage and duration of energy pulse that are easily adjustable.
HIFU-Indications

• Primary treatment
• Salvage after radiation therapy
• Focal therapy after HIFU
• Re-treatment
Ablatherm
Sonoblate 500
HIFU: Long-Term Results in Localized Prostate Cancer

- 140 patients with Ablatherm
- Mean follow-up 6.4 yr
- Bx negative rate: 86.4%
- Actuarial BCF–free survival rates (Phoenix)
  - 5 years 77%
  - 7 years 69%
- Actuarial DF survival rate
  - 5 years 66%
  - 7 years 59%

Blana, EuUrol 2007
Multicenter European Study

- 803 patients
  - Low: 40.2%
  - Intermediate: 46.3%
  - High: 13.5%
- Mean follow-up: 42 +/- 33 mo.
- Biopsy negative rate: 85%
- BCF survival (Phoenix)
  - 5 year: L: 83% I: 72% H: 68%
  - 7 year: L: 75% I: 63% H: 62%

Crouzet Eu.Urol.2010
6-Year Experience with HIFU
Stuttgart Definition

- 53 Patients with Ablatherm
- Mean f/u: 45.4 months
- BC failure (Stuttgart definition: Nadir+1.2 ng/ml)
  - 36 patients (62.2 %) biochemical failure

Ripert BJUI 2010
7-Year Outcomes with HIFU

- 126 patients using the Ablatherm
- TURP in 114 (89.1 %)
- BCR 59.5%
- median time to BCR was 13.8 months.
- 5-year BCR-free survival
  - Low 66.3%
  - Intermediate 40.2%
  - High 21.0%

Sung, The Prostate 2012
### 7-Year Outcomes with HIFU

#### TABLE IV. Complications Associated With High-Intensity Focused Ultrasound for Prostate Cancer

<table>
<thead>
<tr>
<th>Complication</th>
<th>% (n)</th>
<th>Grade (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During the first 3-month postoperative period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>7.9% (10)</td>
<td>GII (10)a</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Wound problem</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>0.8% (1)</td>
<td>GI (1)b</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>During the whole follow-up period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>19.1% (24)</td>
<td>GI (1), GII (23)</td>
</tr>
<tr>
<td>Obstruction (urethra, bladder neck)</td>
<td>15.9% (20)</td>
<td>GII (1), GII (5), GIII (14)c</td>
</tr>
<tr>
<td>UTI</td>
<td>3.2% (4)</td>
<td></td>
</tr>
<tr>
<td>Epididymitis</td>
<td>2.4% (3)</td>
<td>GII (3)</td>
</tr>
<tr>
<td>Incontinenced</td>
<td>30.9% (39)</td>
<td></td>
</tr>
<tr>
<td>At the final evaluation</td>
<td>6.3% (8)</td>
<td>GI (6), GII (1), GIII (1)c</td>
</tr>
<tr>
<td>Impotence</td>
<td>63.7%</td>
<td></td>
</tr>
</tbody>
</table>

*a Patients needed oral or intravenous injection of analgesics.
bPalpitation.
cGrade III requiring transurethral surgical intervention due to necrotic tissue or scarring.
dPatient presented with at least one episode of incontinence during follow-up period.
eGrade I requiring 0–1 pad per day; grade II more than one pad per day; grade III operative intervention.
Focal Therapy Trial with RFA

Evaluation of Bipolar RFA in focal therapy for prostate cancer

• Feasibility pilot study assessing 3 patients

• Primary objective:
  – Safety
  – Efficacy

• Secondary objective:
  – Quality of life
Methods

• Pre-Inclusion criteria:
  – Gleason 6 or less
  – PSA <10ng/mL
  – <5 adjacent biopsy cores positive
  – <50% cancer in each positive core

• After informed consent
  – 1.5 Tesla endorectal MRI
    • T2, DCE, DWE
  – Transperineal 16 region mapping biopsy
Methods

• **Inclusion criteria:**
  - Biopsy positive in 5 or less adjacent unilateral areas
  - Complete QOL instruments: EPIC-32, AUA symptom score, Sexual Health Inventory for Men (SHIM) score

• **Evaluation at 6 months with repeat:**
  - Endorectal MRI
  - Mapping biopsies
  - QOL survey
Procedure

- General anesthesia, lithotomy position
- Bipolar RFA probe inserted transperineally under ultrasound guidance
- Planning software using pre-acquired ultrasound images to guide placement of 8mm-16mm diameter bipolar probe
- Ablation for 200 seconds at a power of 8 to 20 W
Bipolar RFA Focal Therapy for Prostate Cancer

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GU Oncology Department
Moffitt Cancer Center
Procedure
Results

• 16/20 (80%) did not proceed with treatment:
  – 6 men had Gleason 7 on mapping biopsies
  – 5 men had negative mapping biopsies
  – 3 men had bilateral disease
  – 2 men elected alternative treatments

• 4/20 (20%) treated:
  – 1 with an 8mm probe and pull-back technique
  – 2 with a 12mm probe and pull-back technique
  – 1 with an 8mm and 12 mm probe single area
Results

• Mean operative time: 60 minutes (30-120)
• Mean f/u: 24 months (12-30 months)
• Immediate complications:
  – 1 patient with post-op gross hematuria that resolved spontaneously in 72 hours
• Six-month biopsy
  • 2/3: negative
• One patient declined biopsy
• QOL maintained
  – Potency
  – Continence
Follow-up

- Six-month biopsy in three patients: negative
- QOL maintained in all four patients:
  - Potency
  - Continence
Bipolar RFA Feasibility Study
Conclusions

- Procedure is feasible and safe
- Recruitment of patients to focal therapy trials is challenging, accrual rate 1 in 5
- The majority of potential candidates do not qualify upon further evaluation
- Potential for focal therapy with bipolar RFA is still at early stages of evaluation
Inclusion criteria:
- Biopsy positive in 5 or less adjacent unilateral areas
- Complete QOL instruments: EPIC-32, AUA symptom score, Sexual Health Inventory for Men (SHIM) score

Evaluation at 6 months with repeat:
- Endorectal MRI
- Mapping biopsies
- QOL survey
MCC #17753

• **Primary Objective:**
  – Negative 6-month biopsy at sites of focal ablation

• **Secondary Objective:**
  – Safety of the procedure and quality-of-life indicators from baseline to 6 months following treatment
  – To evaluate imaging characteristics of treated prostate cancer by bipolar RFA.

• **Tertiary Objective:**
  – To assess the potential health economic impact of focal RFA based on medical resource utilization data.
MCC #17753

• Estimate of negative biopsy rate at 6 months greater or equal to 90%

• Sample size of 20 patients to provide a two-sided 95% confidence interval of 68.3-98.8%

• If the negative biopsy rate at the 6-month visit is 95%, the 95% corresponding confidence interval is 75.1-99.9%
Focal Therapy for Prostate Cancer

• Challenges:
  – Patient selection?
  – Best modality?
• Optimal follow-up?
• Long term outcomes?
• Still, a feasible and reasonable option in well selected patients