Focal Therapy for prostate cancer

Cyril Natarajan
FOCAL THERAPY

• an investigational treatment approach situated between observational and whole gland management strategies.

• focal therapy aspires to provide long-term cancer control equivalent to that of more traditional therapies while simultaneously avoiding collateral damage to adjacent structures
LIMITATION

• Prostate cancers tend to be multifocal, unable to be completely characterized clinically, and not readily localized or visualized with current imaging techniques.

• 80% of Pca is multifocal and/or bilateral
  – Byar DP, Mostofi FK, Cancer 1972
PROBLEMS:

• Pretreatment prediction of unifocality or unilateral tumors is poor.
• true long-term impact of untreated non-index lesions is entirely unknown
• under staging and under grading occur in approximately 20% to 30% of patients, even with contemporary biopsy techniques and in the lowest risk patients.
• no dependable methods of monitoring the status of the cancer after focal therapy
• the perceived and intuitive quality of life advantages compared to whole gland therapy have not been proven.
MRI

• True likelihood of Pca at any site in the prostate is unknown
• Imaging or biopsy methods currently cannot reliably exclude multifocal disease (esp lesions < 1cm) or confirm unifocal disease
• No standardization re:
  • Lesion size criteria
  • Imaging source
  • Magnet strength
  • Endorectal coil
• Dynamic contrast-enhanced MRI
  • Sensitivity 73% (cf 57% for unenhanced)
  • Specificity 80%
    • Jager et al, Radiology, 1997
APPENDIX 1: PROPOSED RELATIVE INCLUSION CRITERIA FOR PATIENTS CONSIDERING FOCAL THERAPY\textsuperscript{72,73}

**Clinical**
Clinical stage T1 or T2a  
PSA <10 ng/ml  
PSA density <0.15 ng/ml/cc

**Biopsy**
Minimum 12 cores with consideration of a more extensive mapping biopsy  
No Gleason grade 4 or 5  
Total length of cancer <10 mm  
Maximum percentage of cancer in each core (eg 20%)  
Maximum length of cancer in each core (eg 7 mm)  
Maximum percentage of total cores with cancer (eg 33%)

**Imaging**
Single lesion with a maximum size (eg 15 mm)  
Maximum length of capsular contact (eg 10 mm)  
No definitive evidence of extraprostatic extension or seminal vesicle invasion
CSAP procedure

- Supercools lesions to < -40°C
- Liquid nitrogen based probes
  - Generally applied percutaneously; perineal approach
  - Intracellular ice formation
  - Microvascular damage
  - Ischaemia and necrosis
- Advantage
  - can visualize ice ball in real time
    - To assess adequacy of ‘kill zone’
    - Minimize injury to adjacent structures, eg rectum and external urinary sphincter
Can prostate cancer be stopped cold?

Same-day appointments available.
1.866.688.3009

Cleveland Clinic
Every life deserves world class care
<table>
<thead>
<tr>
<th>Journal</th>
<th>No. of patients</th>
<th>F/U</th>
<th>PSA Stability</th>
<th>Negative biopsy rates</th>
<th>Potency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onik et al, Urol Oncol, 2008</td>
<td>48</td>
<td>54 mo</td>
<td>94%</td>
<td>100%</td>
<td>90%</td>
<td>Largest series; Continence rate 100%; ‘male lumpectomy</td>
</tr>
<tr>
<td>Bahn et al, J Endourol, 2006</td>
<td>31</td>
<td>70 mo</td>
<td>92.8%</td>
<td>96.0%</td>
<td>88.9%</td>
<td>(with or w/out PDE5i’s) Salvage CSAP possible</td>
</tr>
<tr>
<td>CyroOnline Database registry study</td>
<td>795</td>
<td>36 mo</td>
<td>80%</td>
<td>75% (of those biopsied)</td>
<td>65%</td>
<td>4.5% of cohort had residual disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Actuarial BDFS (Kaplan-Meir)</td>
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</tbody>
</table>
HIFU

- Intersecting, precision-focused U/S waves
- Induction of hyperthermia (up to 90°C)
- Rapid desiccation and coagulative necrosis

**Advantages**
- Non-invasive
- Precise energy delivery with minimal collateral damage

**Disadvantages**
- Difficult to monitor destructive effect and ‘kill zone’ (no true ice ball equivalent)
HIFU

- Majority of data from Canada and Europe as no FDA approval as yet
- BDFR 56.3 – 92%
  - Mainly whole gland therapy for localised PCa
- For Focal Therapy
  - HPE from subsequent RP: 70% residual tumour
    - Madersbacher S et al, Can Res 1995
# CSAP and HIFU

<table>
<thead>
<tr>
<th></th>
<th>CSAP</th>
<th>HIFU</th>
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<tbody>
<tr>
<td>Outcomes</td>
<td>Most data: derived from studies on whole gland treatment</td>
<td>Most data: derived from studies on whole gland treatment</td>
</tr>
<tr>
<td></td>
<td>PSA stability 92.8%; -ve biopsy rates 96%; Salvage Tx possible</td>
<td>HPE from subsequent RP: 70% residual tumour; Studies lacking</td>
</tr>
<tr>
<td></td>
<td>Median F/U 70 months</td>
<td>(Madersbacher et al Can Res 1995)</td>
</tr>
<tr>
<td>Morbidity</td>
<td>Potency 88.9% with or w/out PDE5i (Bahn et al, J Endourol 2006)</td>
<td>AUR 1-9%</td>
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<tr>
<td></td>
<td></td>
<td>Urethral stricture 4-14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incontinence 1-15%</td>
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<tr>
<td></td>
<td></td>
<td>ED 13-53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectourethral fistulae 0-3%</td>
</tr>
<tr>
<td>FDA approved</td>
<td>Yes</td>
<td>No</td>
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</table>


## APPENDIX 2: OVERVIEW OF FOCAL THERAPY MODALITIES

<table>
<thead>
<tr>
<th></th>
<th>HIFU</th>
<th>Cryotherapy</th>
<th>Photodynamic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Hyperthermia induced coagulative necrosis</td>
<td>Hypothermia induced disruption of cellular membrane and vascular occlusion</td>
<td>Cellular damage from reactive oxygen species</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Transrectal</td>
<td>Transperineal</td>
<td>Transperineal</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Thermographic monitoring</td>
<td>Visible ice ball</td>
<td>Can repeat</td>
</tr>
<tr>
<td></td>
<td>Can repeat</td>
<td>Can repeat</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Most clinical experience as focal therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Challenging to treat anterior tumors</td>
<td>Challenging to treat anterior tumors</td>
<td>Challenging to treat anterior tumors</td>
</tr>
<tr>
<td></td>
<td>Limited clinical experience as focal therapy</td>
<td></td>
<td>Limited clinical experience as focal therapy</td>
</tr>
<tr>
<td><strong>Treatment monitoring</strong></td>
<td>MRI or ultrasound</td>
<td>Ultrasound</td>
<td>MRI or ultrasound</td>
</tr>
</tbody>
</table>
Summary: Minimal Invasive Procedures

- **HIFU (High-Intensity focused ultrasound)**
  - Retention almost 1 – 9%, ED 13 – 53%

- **CSAP (Cryosurgical ablation of Prostate)**
  - Established therapy (3rd generation now)
  - <40g
  - About 90% remain potent
  - FDA approved

- **RITA (Radio-frequency interstitial tumour ablation)**
  - Limited experience

- **PDT:**
  - photosensitizing drug that is activated in the prostate by low-power laser light, delivered using optical fibers. The fibers are placed within needles in the prostate, guided by transrectal ultrasound and a perineal template

- No long term data yet but results are inferior to radical prostatectomy
Other minimally invasive FT modalities

<table>
<thead>
<tr>
<th>Laser energy</th>
<th>Phase 1 trials: limited morbidity wrt potency and continence; Short-term efficacy sub-optimal</th>
</tr>
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<tbody>
<tr>
<td>Brachytherapy</td>
<td>Sub-total or focal; most studies report whole gland seed placement with concentration in tumor areas; MRI spectroscopy suggested to focus on malignant sites; No centre with studies</td>
</tr>
<tr>
<td>Focal EBRT</td>
<td>Cyberknife;</td>
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### 11.5 Summary of experimental therapeutic options to treat clinically localised PCa

<table>
<thead>
<tr>
<th>Conclusion</th>
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<tr>
<td>All other minimally invasive treatment options - such as HIFU microwave</td>
<td></td>
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<tr>
<td>and electrosurgery - are still experimental or investigational. For all</td>
<td></td>
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<tr>
<td>of these procedures, a longer follow-up is mandatory to assess their</td>
<td></td>
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<tr>
<td>true role in the management of PCa.</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
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<tbody>
<tr>
<td>In patients who are unfit for surgery, or with a life expectancy &lt; 10</td>
<td>C</td>
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<tr>
<td>years CSAP has evolved from an investigational therapy to a possible</td>
<td></td>
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<tr>
<td>alternative treatment for PCa.</td>
<td></td>
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<tr>
<td>Focal therapy of PCa is still in its infancy and cannot be</td>
<td>C</td>
</tr>
<tr>
<td>recommended as a therapeutic alternative outside clinical trials.</td>
<td></td>
</tr>
</tbody>
</table>
References

• Review article
  • Focal therapy in the management of localized prostate cancer

• Other reading
  • Novel approaches to improve prostate cancer diagnosis and management in early stage disease
    – Margerger M et al, BJUI supplements, 2012 109, Supp 2, 1- 7
  • Focal therapy for localised prostate cancer: Are we asking the right questions?
    – Murphy DG et al, BJUI comments; 2011, 109, 1 - 4
Thank you