Image Guide Prostate Cancer Therapy: Research, Development and Future Trends

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Duke University Medical Center
Durham, North Carolina
Image Guided Prostate Cancer Therapy

- Image
- Target
- Treat
- Assess
- Follow
• Prostate Ultrasound good for size estimate and needle/seed guidance and targeting treatment

• Computed Tomography does not provide additional information over US

• Magnetic Resonance Imaging reveals zonal anatomy, extracapsular anatomy and may be utilized in various settings (multi-parametric).

MRI is the champion of diagnostic imaging and can target tumors for treatment
• mpMRI with quality radiologic interpretive support approaches a 95% negative predictive value
• mpMRI distinguishes low grade from high grade neoplasms
• mpMRI provides size and staging information
• mpMRI may guide biopsy targeting
Avoidance of an unnecessary biopsy is a benefit as infectious risk of biopsy is increasingly a consideration.

mpMRI guided fusion biopsy is compatible with systematic biopsy.

mpMRI allows for longitudinal follow-up of lesions.

mpMRI permits targeting of therapy.
Image Guided Prostate Cancer Therapy

- External Beam Radiotherapy (Image Guided Intensity Modulated Radiation Therapy)(IGIMRT)
- Transperineal US Guided Brachytherapy
- Transperineal US Guided Cryotherapy
- Transrectal US Guided Focused Ultrasound (HIFU)
- Transrectal MRI Guided Focused Ultrasound
- Transurethral MRI Guided Focused Ultrasound
- Transperineal MRI Guided Laser Ablation
- Transperineal MRI Guided Photodynamic Therapy
Transrectal US Guided Focused Ultrasound (HIFU)
• 10 + years follow-up
• Outpatient procedure
• Single session
• Urologist performed
• FDA clearance since November 2015
• mpMRI targeting with fusion technology
Hifu: more than 15 years of evolution
More than 15 years of evolution

1st prototype 1993 - 1995

2nd prototype 1995 - 2000

ABLATHERM « Maxis » 2000 - 2005

Integrated Imaging 2006


30,000

20,000

10,000

40,000

50,000
Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Whole-gland Ablation of Localized Prostate Cancer with High-intensity Focused Ultrasound: Oncologic Outcomes and Morbidity in 1002 Patients

Sebastien Crouzet a,b,*, Jean Yves Chapelon b, Olivier Rouvière c, Florence Mege-Lechevallier d, Marc Colombel a, Hélène Tonoli-Catez a, Xavier Martin a, Albert Gelet a,b

Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer

Roman Ganzer, Hans-Martin Fritsche, Andreas Brandtner, Johannes Bründl, Daniel Koch *, Wolf F. Wieland and Andreas Blana *
Caritas St. Josef Medical Center, University of Regensburg, Regensburg, and *Department of Urology, Fuerth Hospital, Fuerth, Germany

BJUI, 2013
WHOLE GLAND ABLATION

1997-2009
T1-T2, G6-8
PSA < 30ng/ml
Risk groups (%)
  low: 35.6
  Int: 45.1
  High: 19.3

1997-2009
T1-T3, G6-8
PSA < 30ng/ml
(mean: 11.2)
Risk groups (%)
  low: 42.6
  Int: 39.2
  High: 16.9

Ganzer R, BJUJ, 2013
WHOLE GLAND ABLATION

1997-2009: 538 pts
T1-T3, G6-8
PSA < 30ng/ml
Risk groups (%)
  low: 42.6
  Int: 39.2
  High: 16.9

8 - 10 years BDFS (%):
Low: 71 - 76
Int: 63
High: 32 - 57

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8 - 10 years BDFS (%):
Low: 71 - 76
Int: 63
High: 32 - 57


Ganzer R, BJUI, 2013
Long-term Clinical Results – First-line Treatment

**Ganzer et al. 2013**
Regensburg, Germany

538 patients up to 14 years of f/u

**Thüroff et al. 2013**
Munich, Germany

702 patients up to 15 years of f/u

**Crouzet et al. 2013**
Lyon, France

1002 patients up to 17 years of f/u

<table>
<thead>
<tr>
<th></th>
<th>10 Year Cancer Specific Survival</th>
<th>10 Year Metastasis Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ablatherm® HIFU</td>
<td>Prostatectomy</td>
</tr>
<tr>
<td>Low</td>
<td>99-100%</td>
<td>99-100%*</td>
</tr>
<tr>
<td>Intermediate</td>
<td>96-98%</td>
<td>96-97%*</td>
</tr>
<tr>
<td>High</td>
<td>92%</td>
<td>92-95%*</td>
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Long-term Clinical Results – First-line Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Follow-up</th>
<th>Ablatherm HIFU 10 Year Cancer Specific Survival</th>
<th>Prostatectomy 10 Year Cancer Specific Survival</th>
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<td>Thuroff et al. 2013</td>
<td>Munich, Germany</td>
<td>15 years</td>
<td>96-98%</td>
<td>96-97%*</td>
<td>94-95%</td>
<td>94%*</td>
</tr>
<tr>
<td>Crouzet et al. 2013</td>
<td>Lyon, France</td>
<td>17 years</td>
<td>92%</td>
<td>92-95%*</td>
<td>86%</td>
<td>89%*</td>
</tr>
</tbody>
</table>

Ablatherm HIFU Cancer specific survival and freedom from metastasis rates are similar to radical prostatectomy at 10 years.

Focal treatment concept

- Partial treatment:
  - Mono-focal ("index lesion")
  - Multi-focal or bilateral
  - Hemi-ablation
  - 2/3
Image Guided Prostate Cancer Therapy

• Department of Urology, Andrology and Kidney transplantation
  Paul Sabatier University – Toulouse
  Rangueil Hospital and 9 different hospitals and medical centers

• 22 Urologists

• 20,000 patients / year
  5,000 surgeries

  300 RP (2 DaVinci)
  100 EBR
  60 Brachy
  60 Hifu
  Cryo
HIFU and localized prostate cancer

Today and tomorrow

Pascal Rischmann

Professor and Chairman
Department of Urology, Andrology and Renal transplant
Rangueil Hospital - Toulouse
Université Paul Sabatier
Hemi ablation study (étude HIFU/AFU/08.06)

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

P.Rischmann, A.Gelet, A.Villers, G.Pasticier, J.Petit

N.Surga, H.Bugel, P.Bondil, S.Mallick, H.Toledano, J.Jung, S. Crouzet

Patients and Methods

• Prospective multicenter (10) study
• Patients > 50 yrs, T1C or T2, PSA <15ng/ml
• Unilateral tumor, ≤ Gleason 7
• max 2 consecutive sextants
• MRI distance tumor-urethra and tumor-apex: ≥ 5 mm

Primary endpoint: oncological results (biopsy)
Secondary endpoints: functional results
Patients and Methods

• Prospective multicenter (10) study
• Patients > 50 yrs, T1C or T2, PSA <15ng/ml
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Primary endpoint: oncological results (biopsy)
Secondary endpoints: functional results
Treatment

- Hemi-ablation with Ablatherm® : 1 session

Apex safety distance : 4 mm
Treatment

- Hemi-ablation with Ablatherm®: 1 session
Patients

- Volume at inclusion: $44.2 \pm 22.2$ cc (median 40)

- Endoscopic procedures: 67
  - TURP prior to Hifu: 26
  - At time of Hifu (TURP or TUIP): 41

- Volume at Hifu: 31.6 cc (median 28.3)

- Mean treated volume: $16.1 \pm 5$ cc

- Median FU: 30.4 months [12-68] (mean: 27±14 months)
Biopsy findings (n=101) and Secondary Treatments

33 Bx +

14 Bx + in the treated lobe

- 8 significant
- 6 non-significant

- 4 Active Surveillance
- 5 Repeat HIFU
- 4 Prostatectomy
- 1 Radiation Therapy

19 Bx + in the untreated lobe

- 7 significant
- 12 non-significant

- 12 Active Surveillance
- 3 HIFU
- 2 Prostatectomy
- 2 Radiation Therapy

Kaplan-Meier Radical Treatment Free Survival Rate: 89% at 2 years
PSA after Hemi-ablation

Pre op = 6.2

Nadir = 1.8
(- 71%)

PSA (mean)  
6.2  1.8  2.3  2.5
Secondary objectives

• IPSS at 12 months
  - $6 \pm 6.3$

• Continence : 97.1 %
  – Incontinence grade 1 : 3 patients
IIEF score

- 66 pts with pre and post HIFU score

Score pre HIFU 17.4 [15.4-19.33]
Score post HIFU 16.6 [14.8-18.4)

p > 0.05

- 51 patients: IIEF-5 ≥ 16 at baseline
- At 12 months post Hifu:
  - 40 (78.4%) IIEF-5 ≥ 16 post Hifu
  - 4 (7.8%) moderate ED
  - 7 severe ED
Clavien AEs: 105 subjects with 12 month follow-up

<table>
<thead>
<tr>
<th>Clavien grading system score</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td></td>
</tr>
<tr>
<td>Transient acute urine retention</td>
<td>5</td>
</tr>
<tr>
<td>Urinary meatus stricture</td>
<td>1</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>5</td>
</tr>
<tr>
<td>IIIb</td>
<td></td>
</tr>
<tr>
<td>Chronic urine retention or poor urinary flow</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Deep phlebitis</td>
<td>1</td>
</tr>
<tr>
<td>Superficial phlebitis</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18</td>
</tr>
<tr>
<td>Orchitis</td>
<td>8</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>8</td>
</tr>
<tr>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Transient urge incontinence</td>
<td>4</td>
</tr>
<tr>
<td>Transient dysuria</td>
<td>17</td>
</tr>
<tr>
<td>Tissue sloughing / lower urinary tract symptoms</td>
<td>7</td>
</tr>
<tr>
<td>Hematospermia</td>
<td>2</td>
</tr>
<tr>
<td>Anejaculation</td>
<td>16</td>
</tr>
<tr>
<td>Transient anal and perineal pain</td>
<td>10</td>
</tr>
</tbody>
</table>
Quality of life

- EORTC QLQ-C28: baseline and 12 months

$p > 0.05$
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PSA Pre</th>
<th>Max Gl</th>
<th>Vol</th>
<th>F/u</th>
<th>Bx+</th>
<th>Cont</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Fugoun 2011</td>
<td>12</td>
<td>7.3</td>
<td>4+3</td>
<td>37</td>
<td>10 yr</td>
<td>8%</td>
<td>1 yr</td>
<td>100% n/a</td>
</tr>
<tr>
<td>Ahmed (focal) 2012</td>
<td>41</td>
<td>6.6</td>
<td>4+3</td>
<td>n/a</td>
<td>12 mo</td>
<td>23%</td>
<td>6 mo</td>
<td>100% 89%</td>
</tr>
<tr>
<td>Ahmed (index) 2015</td>
<td>56</td>
<td>7.4</td>
<td>4+3</td>
<td>27</td>
<td>12 mo</td>
<td>19%</td>
<td>sig</td>
<td>92% 77%</td>
</tr>
<tr>
<td>Van Velthoven 2015</td>
<td>50</td>
<td>6.6</td>
<td>4+3</td>
<td>27</td>
<td>40 mo</td>
<td>12%</td>
<td></td>
<td>94% 80%</td>
</tr>
<tr>
<td>Feijoo (Barret) 2015</td>
<td>67</td>
<td>6.1</td>
<td>3+4</td>
<td>36</td>
<td>12 mo</td>
<td>16%</td>
<td>1 yr</td>
<td>100% IIEF: 17.9 to 15.4</td>
</tr>
<tr>
<td>Present study</td>
<td>111</td>
<td>6.2</td>
<td>3+4</td>
<td>44</td>
<td>2 yr</td>
<td>15%</td>
<td>sig</td>
<td>97% 78% IIEF &gt; 16</td>
</tr>
</tbody>
</table>

**Notes:**
- IIEF: International Index of Erectile Function
- sig: statistically significant
Focal hifu: advantages

• Resonates with patients
• Fills a gap between AS and radical treatments
• Indicated even for men with urinary symptoms (turp first)
• Previous Turp is not a contraindication
• No hormonal treatment
• Technically feasible, reproducible
• Few side effects
• Acceptable oncological results
• Doesn’t burn the bridge
Focal hifu : Important points

- rigorous selection of patients
- re-biopsy if needed
- MRI dependant (NPV ≈ 0.80)
- Safety margins
- Consider second session Hifu (RP in « young » patients?)
- Post- treatment surveillance is essential
Hifu: « Focal one »

- Conformational treatment
- Very performing software
- Parameters easy to modify
- US – MRI fusion: ROI
- 3D reconstruction
- Treat deeper
- Treat faster
- Contrast US mode for immediate control
Selection of patients

D'Amico Risk Groups

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Unfavorable</td>
<td></td>
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</table>

Non-recommended indications

- Bilateral apical tumors
- Gleason 3+4
- Anterior tumors in large glands
## HIFU indication: Age and size

<table>
<thead>
<tr>
<th></th>
<th>Younger patient</th>
<th>Older patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small prostate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical lesion</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Large / multiple lesions</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Large prostate</strong> (may require TURP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small lesion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Large / multiple lesions</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>
Focal treatments and safety margins

MRI targets and RP specimen

Le Nobin J, J Urol 2015
Image Guided Prostate Cancer Therapy

- Image
- Target
- Treat
- Assess
- Follow
Image Guided Prostate Cancer Therapy

- External Beam Radiotherapy (Image Guided Intensity Modulated Radiation Therapy) (IGIMRT)
- Transperineal US Guided Brachytherapy
- Transperineal US Guided Cryotherapy
- Transrectal US Guided Focused Ultrasound (HIFU)
- Transrectal MRI Guided Focused Ultrasound
- Transurethral MRI Guided Focused Ultrasound
- Transperineal MRI Guided Laser Ablation
- Transperineal MRI Guided Photodynamic Therapy
SUMMARY

• Image guided prostate cancer therapy is developing with many techniques.
• Approved therapies include cryotherapy, laser ablation, electroporation and HIFU
• Alternative approaches need to be compared in regards to safety and effectiveness
• Ablative therapy is a real option in selected patients.