TRUS-guided HIFU focal therapy: MRI features during follow-up

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1. PRINCIPLES OF HIFU ABLATION
HIFU ablation: principle

• Focalisation of a high-intensity ultrasound beam

  → Concentration of beam energy at the focal point

  → Dramatic temperature rise (60-100°C in a few seconds)

  → Small volume of tissue destruction at focal point
     → Cigar shaped volume of 10-20 mm by 1-3 mm
     → Multiple shots needed to destroy the target
HIFU ablation: advantages

• Prostate easily accessible through an endorectal approach

• Small amount of tissue destroyed
  – Precise treatment
  – Ideal for focal therapy

• Treatment planning easy, owing to real-time US guidance

• Easily repeatable (no radiation involved)
HIFU ablation: pitfalls and limitations

• No tissue destruction beyond the focal point
  – Risk of under-treatment of the anterior part of the gland if focal length not adapted to prostate size

• Extension of tissue necrosis towards the transducer during the shot
  – Risk of necrosis of the rectal wall if improper treatment parameters

• Risk of heat diffusion into the sphincter
  – 4-6 mm Safety margin above the apex
Available Devices

• Ablatherm™ Device: EDAP, France

• Sonablate™ Device: Focus Surgery, USA
2. WHOLE-GLAND HIFU ABLATION: CLINICAL RESULTS
Current indications in prostate cancer

• Clinically localized cancer in non-surgical patients

• Local cancer recurrence after External-Beam Radiation Therapy
2. WHOLE-GLAND HIFU ABLATION: CLINICAL RESULTS

2.1. First-line treatment
<table>
<thead>
<tr>
<th>Author, Location</th>
<th>Device</th>
<th>Study Population</th>
<th>Nb of sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaussy, Munich</td>
<td>Ablatherm</td>
<td>184</td>
<td>9.8</td>
<td>Mean PSA nadir = 1.8 ng/ml</td>
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<tr>
<td></td>
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<td>232</td>
<td>PSA nadir &lt; 0.5 ng/ml = 61%</td>
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<td>(1.3 / Pt)</td>
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<tr>
<td></td>
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<td>Mean Follow-up (months)</td>
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<td>232</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(1.3 / Pt)</td>
<td></td>
</tr>
<tr>
<td>Blana, Regensburg</td>
<td>Ablatherm</td>
<td>146</td>
<td>7.64</td>
<td>Negative biopsy rate = 93.4%</td>
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<td>15</td>
<td>Median PSA nadir = 0.07 ng/ml</td>
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<td>171</td>
<td>PSA nadir &lt; 0.5 ng/ml = 83%</td>
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<td>(1.17 / Pt)</td>
<td>PSA nadir &lt; 0.5 ng/ml = 83%</td>
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<td>Negative biopsy and PSA&lt;4 ng/ml = 71.5%</td>
</tr>
<tr>
<td>European Multicentric Study</td>
<td>Ablatherm</td>
<td>402</td>
<td>10.9</td>
<td>Negative biopsy rate = 87.2%</td>
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<tr>
<td></td>
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<td></td>
<td>402</td>
<td>Final PSA &lt; 1 ng/ml = 83.8%</td>
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<td>(1.4 / Pt)</td>
<td></td>
</tr>
<tr>
<td>Uchida, Hachioji</td>
<td>Sonablate</td>
<td>63</td>
<td>8.5</td>
<td>Negative biopsy rate = 87%</td>
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<td>22</td>
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<td>76</td>
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<td>(1.2 / Pt)</td>
<td></td>
</tr>
<tr>
<td>Crouzet, French</td>
<td>Ablatherm</td>
<td>803</td>
<td>9.1</td>
<td>Negative biopsy rate = 85%</td>
</tr>
<tr>
<td>Multicentric Study</td>
<td></td>
<td></td>
<td>42</td>
<td>Median PSA nadir = 0.25 ng/ml</td>
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<tr>
<td></td>
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<td>1.4 / Pt</td>
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</tbody>
</table>
Prognostic factors

• Crouzet S et al, Eur Urol 2010; 58:559

  – 803 pts, 6 French centers

  – Significant prognostic factors
    • Gleason score
    • Preoperative PSA value

  – 7-year additional treatment-free survival rates
    - 79% for low-risk patients
    - 61% for intermediate-risk patients
    - 54% for high-risk patients
Prognostic factors: location within the gland

- Boutier R et al, BJUI 2011; 108:1776
  
  - 99 pts treated by HIFU (6-mm safety margin at the apex)
  
  - Sextant biopsy before and 3-6 months after HIFU
  
  - Significantly more recurrences at the apex
    
    - Probability for a sextant to remain positive at control biopsy
      
      - 5.9% (1.9-17%) in the base
      - 9.9% (3.8-23.2%) in the midgland
      - 27.3% (13.7-47%) in the apex
Complications

• Recto-urethral fistula: 0.7 – 3.2 %
  – Essentially in early experience
  – Implementation of safety features (rectal cooling, rectal wall automatic recognition systems, ...)
  – More frequent if:
    • Rectal wall thickness > 6 mm (contraindication)
    • Multiple treatments
    • History of EBRT

• Grade III urinary incontinence: 0 – 3.9%
2. WHOLE-GLAND HIFU ABLATION: CLINICAL RESULTS

2.1. Local recurrences after EBRT
HIFU for post-EBRT local recurrences

• Crouzet S et al, Radiother Oncol 2012; 105:198
  – 290 pts
  – Mean follow-up: 48 months
  – Negative control biopsies: 81%
  – 127 pts (43.8%) did not require Hormone Therapy at the end of follow-up
Prognostic factors

- PSA Level
- Gleason score ≥ 8
- History of Hormone Therapy

- 5-year progression-free survival rate
  - 45% for low-risk patients
  - 31% for intermediate-risk patients
  - 21% for high-risk patients
Prognostic factors: location within the gland

- Rouvière O et al, Clin Radiol 2013; in press

  - 46 pts treated by salvage HIFU for local post-EBRT recurrence

  - Evaluation of PSA value, clinical data and MR findings as predictors of salvage HIFU failure

  - Two independent factors
    - PSA level at HIFU treatment
    - Extension of recurrence anterior to urethra
Complications

- Complication rate
  - Higher than for first-line treatment
  - Significantly reduced since the use of dedicated firing parameters

<table>
<thead>
<tr>
<th></th>
<th>Overall % (n)</th>
<th>Standard parameters % (n)</th>
<th>Post-radiation parameters % (n)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>100 (167)</td>
<td>33.5 (56)</td>
<td>66.5 (111)</td>
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<tr>
<td>Long-term complications</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urinary incontinence</td>
<td>49.5 (83)</td>
<td>56 (31)</td>
<td>47 (52)</td>
<td>0.3</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18 (30)</td>
<td>16 (9)</td>
<td>19 (21)</td>
<td>0.65</td>
</tr>
<tr>
<td>Grade 2</td>
<td>22 (37)</td>
<td>29 (16)</td>
<td>19 (21)</td>
<td>0.16</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9.5 (16)</td>
<td>11 (5)</td>
<td>9 (10)</td>
<td>0.72</td>
</tr>
<tr>
<td>Artificial urinary sphincter implantation</td>
<td>11 (18)</td>
<td>20 (11)</td>
<td>6 (7)</td>
<td>0.009</td>
</tr>
<tr>
<td>Bladder outlet obstruction</td>
<td>20 (33)</td>
<td>30 (17)</td>
<td>14.5 (16)</td>
<td>0.01</td>
</tr>
<tr>
<td>Anal incontinence</td>
<td>1.2 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Urethro-rectal fistula</td>
<td>3 (5)</td>
<td>9 (5)</td>
<td>0 (0)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

3. FOCAL HIFU ABLATION: CLINICAL RESULTS
First-line Hemi-ablation

- Ahmed HU et al. J Urol 2011; 185:1246
  - 20 pts
  - Negative biopsy: 89%
  - Excellent results on potency and continence

- French multicentric study
  - Ongoing trial (83 pts included)
  - Negative biopsy: 85%
  - Excellent results on potency and continence

- Hemi-ablation does not jeopardize a subsequent prostatectomy
Salvage Hemi-ablation after EBRT

• Bi-centric study (Oslo, Lyon)
  – 48 patients with unilateral recurrence
  
  – Results
    • Post-HIFU progression in 16 patients (35.5%)
    • Local recurrence at biopsy
      – In the untreated lobe: 4 pts
      – Bilaterally: 8 pts
    • Progression-free survival rates
      – 83% at 1 year
      – 52% at 2 years
    • Low complication rate
      – 75% patients pad-free
      – No rectal fistula
True focal treatment

• Ahmed et al, Lancet Oncol 2012; 13:622
  – 42 patients with Gleason 6-7 cancers
  – Safety margin defined by MRI and/or template biopsy
  – Results
    • Excellent tolerance
    • 77% of negative control biopsy
4. THE ROLE OF MRI

4.1. Patient selection
Localization of prostate cancer foci

- Patient selection for whole-gland ablation
  - Apical tumor
  - Anterior tumors

- Focal treatment +++
4. THE ROLE OF MRI

4.2. Assessing the treated volume
Assessment of the treated volume

• After HIFU ablation
  – Coagulation necrosis surrounded by oedema and hemorrhage
  – Devascularized area + peripheral rim of enhancement

• Gadolinium-enhanced MRI
  – Size and position of the treated volume
  – Evaluation of the rectal wall

Kirkham APS et al, Radiology 2008; 246:833
Two days after HIFU ablation

5 months after HIFU ablation
Contrast-Enhanced US

- But... MRI performed a few days after treatment

- Contrast-enhanced Ultrasound
  - Sonovue (Bracco)
  - Shows the devascularized area just as MRI
  - Possible in the operating room
  - Possibility of immediate re-treatment
  - Does not evaluate the rectal wall

Rouvière O et al, Radiology 2011; 259: 583
Current imaging protocol in Lyon

- Contrast-enhanced US in the OR, at the end of HIFU ablation
- Immediate re-treatment if needed
- Gd-enhanced MRI 2-5 days later
  - Final result
  - Evaluation of the rectal wall
4. THE ROLE OF MRI

4.3. Long-term follow-up
Evolution of the PSA level

• Dramatic drop of the PSA level after HIFU ablation

• Nadir reached within 3-6 months \(^{(1)}\)

• Nadir < 0.3 ng/ml : predictor of good outcome \(^{(2)}\)

\(^{(2)}\) Crouzet S et al, Eur Urol 2010; 58:559
Biochemical failure

• No definition of biochemical failure

• Phoenix criteria (PSA nadir + 2 ng/ml) ?
  – But validated only for radiotherapy

• Stuttgart criteria (PSA nadir + 1.2 ng/ml) (1) ?
  – But controversial
  – No external validation

(1) Blana A et al. BJUI 2009; 104:1058
Do we have salvage options?

• YES!

• Repeat HIFU ablation
  – Always possible (no radiation dose issue)
  – Slight increase in morbidity \(^1\)

• Radiation therapy \(^2\)
  – Effective control of recurrences
  – Mild additional toxicity

(1) Blana A et al. World J Urol 2006; 24:585
Ultrasound

- Prostate heterogeneous and diffusely hypoechoic
  - Systematic random biopsy

- Colour Doppler:
  - Increases biopsy sensitivity after HIFU \(^{(1)}\)
  - Odds ratio = 4
  - Depicts only 38% of recurrences detected at Doppler-guided biopsy

T2-weighted MRI

- Dramatic shrinkage of the prostate
- Heterogeneous, difficult to analyze
- Mostly residual BPH tissue
DCE MRI

• Rouvière O et al. Eur Radiol 2010; 20:48
  
  – 59 pts with rising PSA after HIFU ablation
  
  – T2-weighted and DCE MRI
    • Recurrence = Early-enhancing area at DCE MRI
  
  – Prostate biopsy with two operators
    
    • Op. 1:
      – Blinded to MRI findings
      – Random biopsy (6 prostatic + 1 in each seminal vesicle) ± Color-Doppler guided biopsy
  
    • Op. 2:
      – Targeted biopsies based on MRI findings (cognitive guidance)
      – 3 biopsies per MR lesion
DCE MRI

• Percentage of positive biopsy cores
  – Random biopsy: 10.7 ± 15.2%
  – Targeted biopsy: 37.6 ± 39.2% (p <0.0001)

• Percentage of invasion of biopsy cores
  – Random biopsy: 3.5 ± 6.5%
  – Targeted biopsy: 13.9 ± 19.8% (p<0.001)
## DCE MRI

<table>
<thead>
<tr>
<th>Random and Color Doppler-guided biopsy</th>
<th>Targeted biopsy based on MR findings</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>23</td>
</tr>
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<td>-</td>
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<td>19</td>
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<td>+</td>
<td>-</td>
<td>4</td>
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<tr>
<td>-</td>
<td>+</td>
<td>13</td>
</tr>
</tbody>
</table>

\[ P < 0.05 \]
Random biopsy: 0/8

Targeted biopsy: 2/3 (Gleason 6, 4mm max)

Initial PSA: 5.5 ng/ml
Initial Gleason score: 7

PSA Nadir: 1.84 ng/ml

Last PSA: 2.84 ng/ml
Initial PSA: 6.97 ng/ml
Initial Gleason score: 6

PSA Nadir: 0

Last PSA: 3.03 ng/ml

Random biopsy: 0/8

Targeted biopsy: 3/3 (Gleason 7, 6 mm max)
Brachytherapy and salvage HIFU

PSA : 1.45 ng/ml
DCE MRI

• Lack of specificity of DCE imaging
  – 53% of early enhancing areas were malignant
  – Difficulties in distinguishing recurrent cancer from residual BPH nodules

• Could quantitative DCE imaging or Diffusion-weighting imaging help?
Quantitative DCE and DW MRI

- 50 pts with rising PSA after HIFU ablation

- 1.5T mp-MRI
  - T2w imaging
  - Diffusion-weighted imaging (b= 0 and 600 s/mm²)
  - DCE imaging (temporal resolution: 15 sec)

- Random and targeted biopsies
Quantitative DCE and DW MRI

• 73 suspicious areas
  – 45 positive at targeted biopsy
  – 28 negative

• Evaluation of the following quantitative parameters
  – Quantitative DCE
    • Area under the curve, Wash-in rate, Wash-out rate, T onset, TTP, A
    • Ktrans, ve
  – DW imaging
    • ADC
Quantitative DCE and DW MRI

• Highly correlated variables
  – Selection of 4 variables
    • Wash in rate
    • Wash out rate
    • TTP
    • ADC

• Generalized mixte linear model
  – No significant predictor of malignancy
Quantitative DCE and DW MRI

- Residual cancer remains difficult to distinguish from residual BPH tissue, even by quantitative analysis
- Targeted biopsy of all early-enhancing areas
Hemi ablation

- Dramatic shrinkage of the treated lobe
- Same MR appearance of recurrent cancers
Controlateral « new » cancer

6 months after hemi HIFU
Hemi ablation for Gleason 6 cancer (left apex and midgland)

6-month MRI: left early enhancing lesion

Targeted biopsy: Gleason 6 residual cancer

Prostatectomy: Gleason 7 cancer
« True » focal treatment

• MR follow-up will be challenging

• Longitudinal follow-up to monitor changes within and adjacent to the treated area