How to interpret PSA changes after focal therapy?
Focal therapy a hot topic!

- Overtreatment?
- Side effects?

Radical prostatectomy

- Tumor progression
- Safety?
- Anxiety?

Active Surveillance
Active Surveillance

Focal therapy - a hot topic!

- Overtreatment?
- Side effects?

Radical prostatectomy

Focal Therapy

Active Surveillance

- Tumor progression
- Safety?
- Anxiety?
Focal therapy a hot topic!

- Patient selection
- Biopsy
- Imaging
- Technology
Focal therapy a hot topic!

New paradigm in prostate cancer treatment
What studies show

- Feasibility
  - With different technologies
What studies show

- **Feasibility**
  - With different technologies

- **Favorable functional outcome**
  - Preservation of genitourinary function in 80-90%
What studies show

- Feasibility
  - With different technologies

- Favorable functional outcome
  - Preservation of genitourinary function in 80-90%

- Early oncologic results
  - Biopsy results after 6 to 12 months
Focal studies oncologic endpoints

- Biopsy results
- Imaging
- Impact of additional therapy
... But what about?
PSA after focal therapy why difficult?

- No accepted definition of biochemical failure following focal therapy of prostate cancer!
PSA after focal therapy why difficult?

- No accepted definition of biochemical failure following focal therapy of prostate cancer!

- Variety of different definitions is used
PSA after focal therapy why difficult?

- No accepted definition of biochemical failure following focal therapy of prostate cancer!
- Variety of different definitions is used
- **Biology of prostate cancer**
  - Long natural history
  - High number needed to treat to save one life
PSA after focal therapy some difficulties...
PSA after focal therapy some difficulties...

What is focal therapy? – Different types of definitions
PSA after focal therapy some difficulties...

What is focal therapy? – Different types of definitions

Hemiablation
PSA after focal therapy some difficulties...

What is focal therapy? – Different types of definitions

- Hemiablation
- 3/4-Ablation
PSA after focal therapy: some difficulties...

What is focal therapy? – Different types of definitions

- Hemiablation
- ¾-Ablation
- Index-Tu Ablation
PSA after focal therapy some difficulties...

What is focal therapy? – Different types of definitions

- Hemiablation
- 3/4 Ablation
- Index-Tu Ablation
- Focal Ablation
PSA in a partially ablated prostate...
PSA in a partially ablated prostate...

1. Ablated tissue
PSA in a partially ablated prostate...

1. Ablated tissue

2. Healthy tissue
PSA in a partially ablated prostate...

1. Ablated tissue
2. Healthy tissue
3. Untreated insignificant cancer
Different treatment modalities influence on PSA?

- Cryotherapy
- HIFU
- Interstitial Lasertherapy
Different treatment modalities influence on PSA?

- Cryotherapy
- HIFU
- Interstitial Lasertherapy

Ablative-specific treatment response of PSA?
PSA in a partially ablated prostate...
PSA in a partially ablated prostate... Unlikely to be zero
PSA in a partially ablated prostate...

- Unlikely to be zero
- Criteria for active surveillance might not be suitable
PSA in a partially ablated prostate...

- Unlikely to be zero
- Criteria for active surveillance might not be suitable (ASTRO, Phoenix)
- Criteria for RTX failure might not be suitable (ASTRO, Phoenix)
... Knowledge on PSA after focal therapy...

PSA is the less understood parameter in focal prostate cancer treatment
Biochemical failure criteria in standard procedures

RPE + RTX

- Variety of biochemical failure definitions:
  - 53 definitions for radical prostatectomy
  - 99 definitions for radiation therapy

(review of literature 1991 - 2004)

Cookson et al. J Urol 2007
Biochemical failure criteria in whole gland ablation
no consensus exists!

Prostate Cancer

Control of Prostate Cancer by Transrectal HIFU in 227 Patients

Laura Poissonnier a, Jean-Yves Chocron a, Olivier Rouvière a,b, Laura Curiel b,
Raymonde Bouvier a, Xavier Melaïn a, Jean Michel Dubernard a, Albert Gelet a,b,*

a Urology, Radiology and Pathology Department, Edouard Herriot Hospital, Lyon, France
b Therapeutic Ultrasound Research Laboratory, INSERM Unit 556, Lyon, France

PSA > 1 ng/ml + 3 consecutive rises
Biochemical failure criteria in whole gland ablation
no consensus exists!
Biochemical failure criteria in whole gland ablation

no consensus exists!

Prostate Cancer

Control of Prostate Cancer by Transrectal HIFU in 227 Patients

ORIGINAL ARTICLE


Accepted after revision: November 14, 2000

Transrectal High Intensity Focused Ultrasound for the Treatment of Localized Prostate Cancer: Factors Influencing the Outcome

A. Gelet, R. Bouvier, O. Rouvière, D. Lyonnet, J.M. Dubernard

*Urology Department, Edouard Herriot Hospital, and †INSERM Unit 281, Lyon, France

3 consecutive rises in PSA

PSA velocity >0.75 ng/ml/year
Biochemical failure criteria in whole gland ablation

no consensus exists!
Table 1: Phase I trials of focal therapy in men with localized prostate cancer

<table>
<thead>
<tr>
<th>Incidence of incontinence (%)</th>
<th>Potency maintained (%)</th>
<th>Cancer control (%)</th>
<th>Tumor localization</th>
<th>Modality</th>
<th>Number of patients</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>92 (BFR)</td>
<td>Mapping biopsy</td>
<td>Cryotherapy</td>
<td>48</td>
<td>Onik et al.²⁹</td>
</tr>
<tr>
<td>3.6</td>
<td>72</td>
<td>80.4 (BFR)</td>
<td>Biopsy</td>
<td>Cryotherapy</td>
<td>60</td>
<td>Ellis et al.³⁰</td>
</tr>
<tr>
<td>0</td>
<td>71</td>
<td>88 (BFR)</td>
<td>Biopsy</td>
<td>Cryotherapy</td>
<td>25</td>
<td>Lambert et al.³⁰</td>
</tr>
<tr>
<td>0</td>
<td>88</td>
<td>93 (BFR and biopsy)</td>
<td>Doppler ultrasound-directed biopsy</td>
<td>Cryotherapy</td>
<td>31</td>
<td>Bahn et al.¹²³</td>
</tr>
<tr>
<td>0</td>
<td>Not studied</td>
<td>75 (biopsy)</td>
<td>Biopsy and MRI</td>
<td>HIFU</td>
<td>29</td>
<td>Muto et al.⁵¹</td>
</tr>
<tr>
<td>0</td>
<td>No change</td>
<td>50 (MRI)</td>
<td>Biopsy and MRI</td>
<td>Laser</td>
<td>12</td>
<td>Lindner et al.⁶⁹</td>
</tr>
</tbody>
</table>

Duration of follow-up varied between studies, although was most often months (as opposed to years), illustrating the lack of sufficient long-term data regarding focal therapy. Abbreviations: BFR, biochemical-free recurrence; HIFU, high-intensity focused ultrasound.
Short follow-up of focal studies

Table 1 | Phase I trials of focal therapy in men with localized prostate cancer

<table>
<thead>
<tr>
<th>Incidence of incontinence (%)</th>
<th>Potency maintained (%)</th>
<th>Cancer control (%)</th>
<th>Tumor localization</th>
<th>Modality</th>
<th>Number of patients</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>92 (BFR)</td>
<td>Mapping biopsy</td>
<td>Cryotherapy</td>
<td>48</td>
<td>Onik et al.</td>
</tr>
<tr>
<td>3.6</td>
<td>72</td>
<td>80.4 (BFR)</td>
<td>Biopsy</td>
<td>Cryotherapy</td>
<td>60</td>
<td>Ellis et al.</td>
</tr>
<tr>
<td>0</td>
<td>71</td>
<td>88 (BFR)</td>
<td>Biopsy</td>
<td>Cryotherapy</td>
<td>25</td>
<td>Lambert et al.</td>
</tr>
<tr>
<td>0</td>
<td>88</td>
<td>93 (BFR and biopsy)</td>
<td>Doppler ultrasound-directed biopsy</td>
<td>Cryotherapy</td>
<td>31</td>
<td>Bahn et al.</td>
</tr>
<tr>
<td>0</td>
<td>Not studied</td>
<td>75 (biopsy)</td>
<td>Biopsy and MRI</td>
<td>HIFU</td>
<td>29</td>
<td>Muto et al.</td>
</tr>
<tr>
<td>0</td>
<td>No change</td>
<td>50 (MRI)</td>
<td>Biopsy and MRI</td>
<td>Laser</td>
<td>12</td>
<td>Lindner et al.</td>
</tr>
</tbody>
</table>

Duration of follow-up varied between studies, although it was most often months (as opposed to years), illustrating the lack of sufficient long-term data regarding focal therapy. Abbreviations: BFR, biochemical-free recurrence; HIFU, high-intensity focused ultrasound.

• Few studies with too short follow-up
• No 10-year follow-up data
• PC-specific death + time to metastasis: much longer follow-up needed
Focal therapy more reviews than originals

Lindner et al. *Nature* 2010
Focal therapy more reviews than originals

Lindner et al. Nature 2010
What parameter can be used?

- PSA cut off?
- ASTRO?
- Phoenix?
- PSA doubling time?
- PSA velocity?
- PSA nadir?
Focal studies which PSA criteria are used?

An Evaluation of Patient Selection Criteria on Predicting Progression-Free Survival After Primary Focal Unilateral Nerve-Sparing Cryoablation for Prostate Cancer

Recommendations for Follow Up

Matthew D. Truesdale, BA, Philippa J. Cheetham, MD, Gregory W. Hruby, MS, Sven Wenske, MD, Alison K. Conforto, BA, Amy B. Cooper, MS, and Aaron E. Katz, MD

- 77 patients, unilateral prostate cancer
- Hemi – Cyroablation
- Follow-up
  - Serial PSA
  - TRUS guided biopsy (in 22 patients with suspicion of recurrence)

Truesdale et al. Cancer 2010
Focal studies which PSA criteria are used?

An Evaluation of Patient Selection Criteria on Predicting Progression-Free Survival After Primary Focal Unilateral Nerve-Sparing Cryoablation for Prostate Cancer

Recommendations for Follow Up

Matthew D. Truesdale, BA, Philippa J. Cheetham, MD, Gregory W. Hruby, MS, Sven Wenske, MD, Alison K. Conforto, BA, Amy B. Cooper, MS, and Aaron E. Katz, MD

- 77 patients, unilateral prostate cancer
- Hemi – Cyroablation
- Follow-up
  - Serial PSA
  - TRUS guided biopsy (in 22 patients with suspicion of recurrence)
- Definition of biochemical failure: Phoenix criteria (PSA nadir + 2ng/ml)

Truesdale et al. Cancer 2010
Focal studies which PSA criteria are used?

An Evaluation of Patient Selection Criteria on Predicting Progression-Free Survival After Primary Focal Unilateral Nerve-Sparing Cryoablation for Prostate Cancer

Recommendations for Follow Up

Matthew D. Truesdale, BA, Philippa J. Cheetham, MD, Gregory W. Hruby, MS, Sven Wenske, MD, Alison K. Conforto, BA, Amy B. Cooper, MS, and Aaron E. Katz, MD

• Results:
  – Median follow-up: 24 (0-87 months)
  – 10/22 (45.5%) had positive biopsies

Truesdale et al. Cancer 2010
Focal studies use of Phoenix criteria?

- **Biochemical Progression-Free Survival (Phoenix Criteria)**
  - Proportion: <=2 vs. >2
  - Number at risk: <=2 59, >2 16

- **Pathologic Persistence of Disease**
  - Proportion: <=2 vs. >2
  - Number at risk: <=2 59, >2 17

Truesdale et al. Cancer 2010
Focal studies use of Phoenix criteria?

Truesdale et al. Cancer 2010

75% failure at 3 years
Focal studies use of Phoenix criteria?

Truesdale et al. Cancer 2010

Biochemical Progression-Free Survival (Phoenix Criteria)

#Positive Cores: <=2 vs. >2

Pathologic Persistence of Disease

#Positive Cores: <=2 vs. >2

75% failure at 3 years

35% failure at 3 years
Focal studies use of Phoenix criteria?

- High biochemical failure rates
- Poor correlation with pathological results

Truesdale et al. Cancer 2010
Focal studies use of Phoenix criteria?

- High biochemical failure rates
- Poor correlation with pathological results
- Conclusion: Phoenix criteria might not be accurate to define cancer progression

Truesdale et al. Cancer 2010
Focal studies without PSA failure criteria

Focal Therapy for Localized Prostate Cancer: A Phase I/II Trial

H. U. Ahmed,*,† A. Freeman, A. Kirkham, M. Sahu, R. Scott, C. Allen,‡ J. Van der Meulen and M. Emberton§

From the Division of Surgery and Interventional Science, University College London (HUA, RS, ME), Department of Urology (HUA, ME), Department of Histopathology (AK) and Department of Imaging (IAK, CA), University College London Hospitals NHS Foundation Trust, Clinical Effectiveness Unit, Royal College of Surgeons of England (JV, ME), and Health Services Research Unit, London School of Hygiene and Tropical Medicine (JV), London, United Kingdom

• 20 patients, unilateral cancer following HIFU hemiablation

• Follow-up:
  – PSA at 1, 3, 6, 9, 12 months
  – MRI at 1 + 6 months
  – Perineal template biopsy at 6 months

Ahmed et al. J Urol 2011
Focal Therapy for Localized Prostate Cancer: A Phase I/II Trial

H. U. Ahmed,* † A. Freeman, A. Kirkham, M. Sahu, R. Scott, C. Allen, ‡ J. Van der Meulen and M. Emberton§

From the Division of Surgery and Interventional Science, University College London (HUA, RS, ME), Department of Urology (HUA, ME), Department of Histopathology (AP) and Department of Imaging (AK, CA), University College London Hospitals NHS Foundation Trust; Clinical Effectiveness Unit, Royal College of Surgeons of England (JV, ME), and Health Services Research Unit, London School of Hygiene and Tropical Medicine (JV), London, United Kingdom

• Results:
  – Trifecta in 89% of patients at 12 months

Ahmed et al. J Urol 2011
Focal studies without PSA failure criteria

Focal Therapy for Localized Prostate Cancer: A Phase I/II Trial

H. U. Ahmed,* † A. Freeman, A. Kirkham, M. Sahu, R. Scott, C. Allen,‡
J. Van der Meulen and M. Emberton§

From the Division of Surgery and Interventional Science, University College London (HUA, RS, ME), Department of Urology (HUA, ME), Department of Histopathology (AP) and Department of Imaging (AK, CA), University College London Hospitals NHS Foundation Trust; Clinical Effectiveness Unit, Royal College of Surgeons of England (JV, ME), and Health Services Research Unit, London School of Hygiene and Tropical Medicine (JV), London, United Kingdom

• Results:
  – Trifecta in 89% of patients at 12 months

Biochemical. An 80% decrease in mean PSA was seen at 3 months. This reduction persisted to 12 months (7.3 vs 1.5 ng/ml, fig. 5, B).
 Proposed + ongoing multicentre phase II trials

<table>
<thead>
<tr>
<th>Center</th>
<th>Trial design</th>
<th>Ablative technology</th>
<th>Risk category</th>
<th>Disease localization</th>
<th>Outcomes functional</th>
<th>Biopsy</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK Multicenter (Lead center:</td>
<td>Phase II, prospective</td>
<td>HIFU (Sonablate</td>
<td>Low to intermediate</td>
<td>Multifunctional MRI and template prostate-mapping biopsies</td>
<td>Biopsy at 6 and 36 months</td>
<td></td>
<td>Multifunctional MRI</td>
</tr>
<tr>
<td>University College London)</td>
<td>3-year follow-up</td>
<td>500)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early (1–2 weeks) to quality control and optimize treatment delivery in new centers</td>
</tr>
<tr>
<td></td>
<td>Hemiation with absence of</td>
<td></td>
<td></td>
<td></td>
<td>Absence of clinically significant cancer in treated and untreated areas</td>
<td></td>
<td>6 and 36 months</td>
</tr>
<tr>
<td></td>
<td>clinically significant</td>
<td></td>
<td></td>
<td></td>
<td>Absence of any cancer in treated areas and untreated areas</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cancer in untreated areas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France, Multicenter (Association of French Urology)</td>
<td>Phase II, hemiation</td>
<td>HIFU (Ablatherm®, Edap TMS, France)</td>
<td>Low to intermediate risk</td>
<td>Multifunctional MRI plus TRUS-guided biopsy</td>
<td>Biopsy at 6 months</td>
<td></td>
<td>Multifunctional MRI</td>
</tr>
<tr>
<td>(n = 100)</td>
<td>(n = 100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early (1–2 weeks) to quality control and optimize treatment delivery in new centers</td>
</tr>
<tr>
<td>European Multicenter (Lead center: University College London)</td>
<td>Phase II, unilateral and bilateral</td>
<td>Photodynamic therapy (Tookad Soluble)</td>
<td>Low</td>
<td>Multifunctional MRI plus either template biopsies or TRUS-guided biopsies (dependent on local practice)</td>
<td>Validated questionnaires (IPSS, IIEF)</td>
<td>Biopsy at 6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Italy Multicenter (Lead center: San Raffaele, Milan)</td>
<td>Phase II, multicenter Hemiation (n = 100)</td>
<td>Cryosurgery</td>
<td>Low</td>
<td>TRUS-guided biopsies (with burden criteria applied)</td>
<td>Validated questionnaires</td>
<td>Biopsy at 6 months</td>
<td></td>
</tr>
</tbody>
</table>


### Proposed + ongoing multicentre phase II trials

<table>
<thead>
<tr>
<th>Center</th>
<th>Trial design</th>
<th>Ablative technology</th>
<th>Risk category</th>
<th>Disease localization</th>
<th>Outcomes functional</th>
<th>Biopsy</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK Multicenter (Lead center: University College London)</td>
<td>Phase II, prospective 3-year follow-up</td>
<td>HIFU (Sonablate 500)</td>
<td>Low to intermediate</td>
<td>Multifunctional MRI and template prostate-mapping biopsies</td>
<td>Validated questionnaires at 0, 1, 3, 6, 9, 12, 18, 24, 30, and 36 months</td>
<td>Biopsy at 6 and 36 months</td>
<td>Multifunctional MRI Early (1–2 weeks) to quality control and optimize treatment delivery in new centers</td>
</tr>
<tr>
<td></td>
<td>Hemiresection with absence of clinically significant cancer in untreated areas (n = 200)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 and 36 months</td>
</tr>
<tr>
<td>France, Multicenter (Association of French Urology)</td>
<td>Phase II, hemiresection (n = 100)</td>
<td>HIFU (Ablatherm®, Edap TMS, France)</td>
<td>Low to intermediate risk</td>
<td>Multifunctional MRI plus TRUS-guided biopsy</td>
<td>Validated questionnaires (IPSS, IIEF)</td>
<td>Biopsy at 6 months</td>
<td>Multifunctional MRI Early (1–2 weeks) to quality control and optimize treatment delivery in new centers</td>
</tr>
<tr>
<td>European Multicenter (Lead center: University College London)</td>
<td>Phase II, unilateral and bilateral</td>
<td>Photodynamic therapy (Tookal Soluble)</td>
<td>Low</td>
<td>Multifunctional MRI plus either template biopsies or TRUS-guided biopsies (dependent on local practice)</td>
<td>Validated questionnaires</td>
<td>Biopsy at 6 months</td>
<td>Multifunctional MRI Early (1–2 weeks) to quality control and optimize treatment delivery in new centers</td>
</tr>
<tr>
<td>Italy Multicenter (Lead center: San Raffaele, Milan)</td>
<td>Phase II, multicenter Hemiresection (n = 100)</td>
<td>Cryosurgery</td>
<td>Low</td>
<td>TRUS-guided biopsies (with burden criteria applied)</td>
<td>Validated questionnaires</td>
<td>Biopsy at 6 months</td>
<td>—</td>
</tr>
</tbody>
</table>
### Suitable outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Active surveillance</th>
<th>Focal therapy</th>
<th>Radiotherapy</th>
<th>Radical surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA nadir</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>PSA doubling time/velocity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Biopsy status</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>−</td>
</tr>
<tr>
<td>Further therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clinical progression</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Local</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nodal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prostate cancer death</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Ahmed et al. *WJU* 2010
Focal studies
Biochemical versus biopsy results
Conclusion 1

- No consensus on biochemical failure following focal prostate cancer treatment
No consensus on biochemical failure following focal prostate cancer treatment

Failure criteria for other treatments are not suitable
- Radical prostatectomy
- Radiation therapy
- Full gland ablation
- Active surveillance
Conclusion 2

Follow-up biopsy
• 12 month treated area

Imaging
• Multiparametric MRI

Time of secondary treatment
Conclusion 2

Follow-up biopsy
- 12 month treated area

Imaging
- Multiparametric MRI

Time of secondary treatment

PSA every three months

Sensitivity analyses of different PSA scenarios to find an adequate definition of PSA failure following focal therapy of prostate cancer
Thank you very much