Salvage Possibilities for Focal Therapy Failures

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Focal Therapy: Three pillars


<table>
<thead>
<tr>
<th>Target</th>
<th>Treatment</th>
<th>Control</th>
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</table>

- [Images of medical scans]
FT: Outcomes Assessment

- **Imaging:** Post-Op CEUS or Post-operatory MRI (Ablation assessment).

- **PSA levels and kinetics:** every three months.
  - Validated questionnaires for Continence and potency.

- **Imaging:** mpMRI.

- **Control Biopsy:** Guided on MRI Information.
mpMRI post FT

- Local Recurrence After FT occurs at the Site of Primary partial treatment.

- Performed to guide control biopsies and to before to rule out locally advanced disease.
  
  - Negative mpMRI Post-FT should not preclude control biopsies (Saturation transperineal)

Nunes Silva et al, J Urol 2017
Choosing a salvage treatment will depend on the disease being treated. Characteristics of residual PCa SHOULD be defined by control biopsy. Major difficulty: limitations of recognizing the failure.

Control Biopsy is mandatory.
Outcome within the treated zone

Eradication of all aggressive or clinically significant disease

- NO RESIDUAL CANCER
- Small volume GS 3+3

Success

- Significant volume (≥0.2 cc or 7 mm diameter)
- GS 3+4 (Prognostic Grade Gr 2)

Failure

Polascik et al, SIU-ICUD 2015
Success/Failure in the Untreated Zone

– Low-risk disease in the untreated zone should be monitored with **standard of care AS protocols**.

**Definition of Failure in the Untreated Zone**

Development of **any foci of clinically significant cancer** requiring further therapy (foci developed within 12–18 months—probably selection failure)

Polascik et al, SIU-ICUD 2015
Salvage possibilities for FT failures

• **Salvage radical prostatectomy (RP)**
  - After focal therapy (not specified): 2*† papers
  - After focal VTP: 1* paper
  - After whole-gland HIFU: 6 papers
  - After whole-gland Cryotherapy: 2 papers

• **Salvage Cryotherapy**
  - After cryotherapy: 3 papers (1 only after focal cryo*)

• **Salvage HIFU**
  - After whole-gland HIFU: 1 paper

• **Salvage Radiotherapy**
  - After whole-gland HIFU: 2 papers

* Papers specify primary treatment was focal
† Only 2 comparative studies
## Focal Therapy Outcomes

<table>
<thead>
<tr>
<th>Technique</th>
<th>Ablation</th>
<th>Image guidance</th>
<th>Number of studies (patients)</th>
<th>FU range</th>
<th>Oncological outcome</th>
<th>Incontinence</th>
<th>Urinary retention</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cryotherapy</td>
<td>Freeze–thaw cycles</td>
<td>TRUS, mpMRI</td>
<td>12 (n = 2118)</td>
<td>6–58 mo</td>
<td>4–25% biopsy positive</td>
<td>&lt;1%</td>
<td>5% (6 mo)</td>
<td>0–31%</td>
</tr>
<tr>
<td>2 HIFU</td>
<td>Heat</td>
<td>TRUS, mpMRI</td>
<td>5 (n = 171)</td>
<td>6–24 mo</td>
<td>0–21% biopsy positive</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>0–25%</td>
</tr>
<tr>
<td>3 IRE</td>
<td>Electroporation</td>
<td>mpMRI</td>
<td>5 (n = 157)</td>
<td>6–12 mo</td>
<td>3–33% biopsy positive</td>
<td>&lt;1%</td>
<td>&lt;3%</td>
<td>5–10%</td>
</tr>
<tr>
<td>4 Laser</td>
<td>Heat</td>
<td>mpMRI</td>
<td>6 (n = 85)</td>
<td>3 wk–12 mo</td>
<td>4–64% biopsy positive</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>5 Photodynamic therapy</td>
<td>Vascular targeting therapy</td>
<td>TRUS</td>
<td>3 (n = 313)</td>
<td>6–24 mo</td>
<td>26–51% biopsy positive</td>
<td>&lt;5%</td>
<td>7%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>6 Brachytherapy</td>
<td>Radiation</td>
<td>TRUS, MRI</td>
<td>7 (n = 541)</td>
<td>24–60 mo</td>
<td>0–17% biopsy positive</td>
<td>&lt;5%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction, as defined and reported by the studies; FU = follow-up; HIFU = high-intensity focused ultrasound; IRE = irreversible electroporation; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; TRUS = transrectal ultrasound.

Van der Poel et al, Eur Urol 2018
Treatment Failure

The control biopsy remains essential:

- Negative PB
- Failure: Positive PB in the treated lobe
- Positive PB in the untreated lobe
Focal Therapy Failure Management

Positive PB in the treated lobe

Active Surveillance
- Unchanged cancer
- Micro lesion
- Drop of PSA

Focal Treatment
- HIFU
- Cryotherapy
- Brachytherapy
- VTP-Laser

Salvage Treatment

Global Treatment
- RP
- Brachytherapy
- Radiotherapy
- Cryotherapy
- HIFU
- ADT
Focal salvage therapy

The first the logical option is to offer patients a focal re-treatment using the same procedure

The Re-treatment will be determined by:

- Imaging: Saturation vs. targeted biopsy.
- Control Biopsy Results: Unilateral prostate cancer with same characteristics
- PSA levels and kinetics

Technical limitations of each energy must be taken into consideration

<table>
<thead>
<tr>
<th></th>
<th>HIFU</th>
<th>CRYO</th>
<th>VTP-Laser</th>
<th>BRACHY</th>
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<tbody>
<tr>
<td>Limitations</td>
<td>Apical tumor</td>
<td>Large prostate</td>
<td>Anticoagulation</td>
<td>Dysuria</td>
</tr>
<tr>
<td></td>
<td>Anterior zone</td>
<td></td>
<td></td>
<td>Large prostate</td>
</tr>
<tr>
<td></td>
<td>Large prostate</td>
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<td>Prior TURP</td>
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Which technology to select?

- **Expert consensus:**
  - Posterior lesions are better amenable to FT using HIFU.
  - Cryotherapy provides best possible outcomes for anterior tumors.
  - Apical lesions: FBT.
- Side effects were low.
- Urinary continence rates of 90-100%.
- Erectile dysfunction between 5 and 52%.
- Short to medium cancer control based on post-treatment biopsies were variable between ablative modalities.

Ganzer et al, Prostate Cancer Prostatic Dis 2018
S-RALP Post FT

• Endopelvic fascia opening.

• Deep dorsal venous complex.

• **Primary approach on NON TREATED SIDE.**
  – Inter-fascial or Intrafascial plane is feasible.

• **Wide excision of the lateral prostatic fascia and neurovascular bundle on the treated side. Complete excision of the seminal vesicles.**
  – To optimize oncologic outcomes.

• **The apex of the prostate.**
  – Periapical fibrosis may be found on the treated side.
Salvage RP for Focal Therapy failures

- **Most studied salvage treatment**

- **Technical challenge:**
  - **Seminal vesicles and posterior plane:** dense fibrosis
  - **Difficulty apex dissection** in whole-gland energy treatment
  - **Bilat nerve sparing:** s-RRP 54.5% vs 84.1% (p=0.03) (Nunes-Silva e al.)
  - Nerve sparing not feasible after VTP due lateral fibrosis (Lebdai et al.)
  - Association between bilateral VTP, difficulty and PSM (Lebdai et al.)
  - PSM comparable in a comparative study (Nunes-Silva et al.)
  - Operative time, blood loss and hospital stay comparable

- "Tackle the untreated side first as a reference to search for anatomic planes, especially in the apical dissection" (Linares-Espinós et al.)
Assuming that the index lesion was adequately treated

Inflammatory reaction created after the index lesion ablation.

Actual progression potential on those indolent lesions left behind?

- These lesions might remain non-aggressive vs. take the position of the index lesion and eventually become aggressive.
FT: Unanswered questions

• **Residual cancer after ablation** – Are those resistant cancer cells?

• **Natural history of non-index lesion** – will it behave like a de novo low risk cancer?.

• **Immune / hormonal manipulations** along with focal therapy?
Conclusion

• Focal treatments could allow to eradicate the prostate cancer. There are limitations and we should be aware.

Pca is multifocal: only the predominant tumor is destroyed and small amounts of cancer remain in the treated lobe. In those cases:

  o Active surveillance can be proposed
  o Retreatment with energy is possible, as needed
  o Global therapies are still possible

In cases of Focal Therapy Failure, additional treatments are possible without greater risk for the patients