Focal Therapy is a Fool’s Paradise: The whole prostate must be treated!

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Preaching against focal therapy in a “focal therapy” session...
Arguing against focal therapy ...

- Lack of quality data regarding its long term oncologic benefit
- Not supported by contemporary evidence on prostate cancer biology, heterogeneity and multifocality
- Oncologic and functional outcomes of available salvage therapies are unfavorable / unknown
- Active surveillance as an adequate alternative
- Not supported by contemporary guidelines
Long-term oncologic outcomes

NONE!

Have studies been UNIFORMLY preoccupied with emphasizing the superiority of FT over whole gland therapy in terms of functional outcomes?
Objectives by clinical states

Initial evaluation: no cancer diagnosis

Localized disease

Rising PSA

Clinical metastases: non-castrate

Clinical metastases: Castrate

PREVENT METASTASES

MINIMIZE MORBIDITY/ MAXIMIZE CURE

164,690

Scher H. Urology, 2000, American Cancer Society website 2018

DEATH OF DISEASE

29,430
The Role of Focal Therapy in the Management of Localised Prostate Cancer: A Systematic Review

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No studies (pts)</th>
<th>FU range (months)</th>
<th>% pos biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy</td>
<td>12 (n=2118)</td>
<td>6-58 m</td>
<td>4-25%</td>
</tr>
<tr>
<td>HIFU</td>
<td>5 (n=171)</td>
<td>6-24 m</td>
<td>0-25%</td>
</tr>
<tr>
<td>IRE</td>
<td>5 (n=157)</td>
<td>6-12 m</td>
<td>3-33%</td>
</tr>
<tr>
<td>Laser</td>
<td>6 (n=85)</td>
<td>3w – 12m</td>
<td>4-64%</td>
</tr>
<tr>
<td>PDT (TOOKAD)</td>
<td>3 (n=313)</td>
<td>6-48*</td>
<td>25-51%</td>
</tr>
<tr>
<td>Focal Brachy</td>
<td>7 (n=541)</td>
<td>24-60</td>
<td>0-17%</td>
</tr>
</tbody>
</table>
A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer


- 559 patients, 189 (32%) of whom were high-risk (PSA > 20 in 13, GS ≥ 4+3 in 97, cT3a/b in 75)
- At a median FU of 56 months: Failure free survival - 88%, metastasis free survival - 98%

- Is the follow-up adequate to assess the risk of metastatic progression?
Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

19.5y of follow-up (median 12.7, IQR 7.3, 15.5)
559 patients, 189 (32%) of whom were high-risk (PSA > 20 in 13, GS ≥ 4+3 in 97, cT3a/b in 75)

At a median FU of 56 months: Failure free survival - 88%, metastasis free survival - 98%

Post HIFU + biopsy rate: overall 56/222 (25%), in-field 18%

Repeat HIFU focal therapy in 121 (21%) patients
Focal therapy for prostate cancer does not equal organ preserving surgery in other malignancies (Breast, Kidney):

- Partial prostatectomy (true surgical lumpectomy) has been suggested, but only for anterior tumors (Villers et al, EU 2017).

- Imaging techniques remain limited, particularly in the post therapy setting (IRE - Eur Urol focus 11/2017, HIFU - J Urol 04/2018)
Focal therapy for prostate cancer does not equal organ preserving surgery in other malignancies (Breast, Kidney):

- Partial prostatectomy (true surgical lumpectomy) has been suggested, but only for anterior tumors (Villers et al, EU 2017).
- Imaging techniques remain limited, particularly in the post therapy setting
- The true risk of \textit{de novo} development of cancer outside the “index lesion” remains unknown
The “index lesion” concept

Truth or myth?
23 consecutive patients who had RP for D1 PCa.

The dominant focus of the primary tumor was compared to matched nodal metastases using FISH analysis

Concordance rate between the dominant lesion in the prostate and cancer cells in the LN - only 42%!
Metastatic progression in prostate cancer – clonal theory

• Primary prostate cancers are multifocal and are composed of multiple genetically distinct cancer cell clones

• Methods: genetic analysis (chromosomal CGH) on 94 cancer samples from 30 men who died of prostate cancer

• Conclusion: most if not all metastatic cancers arise from a single precursor aberrant cell

• **Whether the index lesion includes the lethal clone remains unknown!**

Ref: Liu, Nature Medicine 2014
• whole-genome sequencing and molecular pathological analyses in a patient who died of prostate cancer

• Samples collected during disease progression (metastases) and at the time of death – over 17y of FU

• The lethal clone arose from a small, relatively low-grade cancer focus in the primary tumor, and not from the bulky, higher-grade primary cancer or from a lymph node metastasis resected at RP

Ref: Haffner, JCI 2013
Gleason Score 7 Prostate Cancers Emerge through Branched Evolution of Clonal Gleason Pattern 3 and 4

Gp3 and Gp4 tumors emerge early from a common precursor and subsequently undergo substantial divergence

Sowalsky et al, Clin Can Res 07/2017

Spatial genomic heterogeneity within localized, multifocal prostate cancer

Sowalsky et al, Clin Can Res 07/2017
these cases still required a minimum amount of Gleason 6 cancer to qualify. Our UK focal HIFU programme now does not allow treatment in instances of low-volume Gleason 6 disease because the probability of progression for such lesions is rare, unless there are extenuating circumstances such as psychological distress to the patient due to being on active surveillance or family history [30]. This stance
Salvage therapy
Pelvic sidewall following HIFU hemiablation

Pelvic sidewall following Right focal HIFU

V. Patel personal communication (AUA 2016): EBRT >> Brachytherapy >> HDR >> HIFU >> Cryo
Similar perioperative morbidity (OR time, EBL, hospital admission, catheterization time)

Similar postoperative continence rates (~50% pad-free at 1y in both groups)

Higher rates of ED with sRP

Higher BCR rates with sRP (BCR free probability at 2y : 65% vs 90%, adjusted for PSM rate, Gleason upgrading, upstaging)
Guidelines
recommendations
“…if HIFU is offered as an alternative treatment modality for localized prostate cancer, it should be done within the context of a clinical trial.”

“…focal therapy or HIFU treatment options lack robust evidence of efficacy.”

“…even though HIFU is approved by the FDA for the destruction of prostate tissue, it is not approved explicitly for the treatment of prostate cancer.”

“….tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence”

“…focal therapy may not be curative and that further treatment for prostate cancer may be necessary.”
For low risk cancer - AS is the preferred approach. Data supporting the benefit of FT are unlikely with less than 10y follow-up.

For intermediate risk patients - accurate detection of higher risk clones remains problematic d/t paucity of data.

For those in whom treatment is advocated - focal therapy should be offered in the context of a clinical trial!
Thank you