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Focal therapy in primary localised prostate cancer: The EAU Position in 2018

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Abstract: Radical treatment of localised prostate cancer is recognised to be an unnecessary intervention or overtreatment in many men. Consequently, there has been a rapid uptake in the use of focal ablative therapies. However, there are several biological and practical concerns about such approaches as they have yet to be proven as robust treatment options. In particular, the multi-focal nature of prostate cancer argues against unifocal treatment, while limitations in imaging can preclude the accurate identification of the number, location and extent of prostate cancer foci. To date, a number of ablative options have reported results on mainly low risk disease. Most series are relatively immature, with a lack of consistent follow up, and the morbidity of retreatment is often not considered. The authors consider focal therapy to be an investigational modality and
encourage prospective recording of outcomes and the recruitment of suitable patients.

I. Introduction

Whole gland treatment is currently considered the optimum treatment for localised prostate cancer (PCa). However, since treatment of the entire prostate gland results in damage to surrounding tissue such as urinary sphincter, neurovascular bundle, bowel and bladder, a focused treatment for PCa lesions only, should they be accurately identified, would be of interest. Focal therapy (FT) of the prostate can be defined as treatment of specific areas of the prostate to minimise treatment-related morbidity and is facilitated by improvements in PCa imaging. The options for FT are numerous and focal ablation may reduce complications associated with whole gland treatment provided the same oncological efficacy is maintained (1, 2).

Recent data from the ProtecT trial showed no difference in 10-yr cancer specific survival between active monitoring, radical prostatectomy (RP) or external beam radiotherapy (EBRT) in men with mainly low- and intermediate-risk PCa, but considerable differences in functional outcomes (3). Since FT has been mainly performed in smaller low-risk lesions where active surveillance (AS) is a valid option, the efficacy of FT should be compared to AS and, as such, long-term follow-up studies are required. In intermediate-risk lesions, a comparable oncological outcome with a lower side-effect profile would be the main advantages of FT in comparison with whole gland treatment, in a situation where an active treatment is needed.

To date, most FTs have been achieved with ablative technologies: cryotherapy, high-intensity focused ultrasound (HIFU), photodynamic therapy, electroporation, and focal radiotherapy by brachytherapy or stereotactic EBRT. All reported modalities of FT are at IDEAL (Idea, Development, Exploration, Assessment and Long-term follow-up Framework) stage 2b, i.e. they are at an exploratory phase, with assessment and longer follow-up not yet available (4) with the exception of PDT where RCT data are available (IDEAL phase 3) (5). The literature search used for this position paper was similar to that done for the EAU prostate cancer guidelines (6).
The concept of FT can only provide long-term benefit to patients if it satisfies the following requirements:

a) survival efficacy at least equivalent compared to standard of care (SOC);

b) fewer complications and less functional side effects compared to SOC

c) reliable follow-up of remaining prostatic tissue and

d) potential secondary or salvage treatment not impaired by the primary FT.

Although FT has also been used for salvage treatments of PCa following local recurrences after whole gland treatment, this paper will focus on primary treatment only.

II. Patient selection

Detailed local staging is essential for selecting patients suitable for focal gland treatment. Several consensus meetings have strived to define criteria for patient selection (Table 1) (7-17). In the most recent publications these have been men with low-risk (GS 3+3) tumours and a life-expectancy of at least 10 yr. Nowadays AS is considered to be a valid option in those patients, as well as whole gland treatments. Any form of FT in low-risk PCa should be associated with significant clinical benefit compared to these SOC. Patients with a small Gleason 7 (Gleason sum score 3+4, ISUP 2) lesion might be better candidates although, so far, this group is rarely considered in the published trials. Multiparametric magnetic resonance imaging (mpMRI) has been used to select patients in clinical trials (18-21) and is the standard imaging tool for FT, allowing targeted biopsies. However, an international consensus project recognised that adding systematic biopsies remain essential to accurately stage disease (16). These imaging and sampling modalities must be associated with a high negative predictive value of significant PCa in regions considered as “normal”. Sextant random biopsies are insufficient to accurately map tumour locations within the prostate. Instead, standardised, preferably perineal template-guided saturation, biopsies are suggested to aid patient selection (19, 22-24).

Table 1: Summary of consensus reports on focal therapy
<table>
<thead>
<tr>
<th>Publication</th>
<th>Consensus topic</th>
<th>Consensus setup</th>
<th>Patient selection</th>
<th>Follow-up</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostwick DG, et al. 2007 (7)</td>
<td>Pathobiology definition, patient selection, biopsy</td>
<td>Not provided</td>
<td>LE &gt; 5 y, T1-3, PSA &lt; 15 ng/mL, no LUTS, bladder stones, infections excluded, 3D mapping biopsies 5 mm interval</td>
<td>Biopsy 6 mo, 12 mo, future: mpMRI or CEUS, 3 mo PSA first year and 6 mo thereafter, PROMS</td>
<td>FT reasonable consideration in selected patients</td>
</tr>
<tr>
<td>De la Rosette J, et al. 2010 (8)</td>
<td>Patient selection, imaging</td>
<td>Workshop, discussion group, informal</td>
<td>Template biopsies, LE &gt; 10 Y, cave in patients with LUTS, low-intermediate risk, &lt; T2c, anterior/apical lesions may be difficult, long term effects not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smeenge M, et al. 2012 (9)</td>
<td>Role of TRUS</td>
<td>Workshop, discussion group, informal</td>
<td>TRUS value limited, CEUS promising, systematic biopsy schemes needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahmed HU, et al. 2012 (10)</td>
<td>FT and AS</td>
<td>Workshop, discussion group, informal</td>
<td>Transperineal mapping biopsy</td>
<td></td>
<td>Suggested study sequence: proof of tumour ablation, compare FT to existing whole gland and/or AS</td>
</tr>
<tr>
<td>Langley S et al. 2012 (11)</td>
<td>Focal LDR</td>
<td>Consensus meeting</td>
<td>LE &gt; 10 y, PSA ≤ 15 ng/mL, mpMRI, template biopsies, unilateral &lt; 0.5 cc, contralateral &lt; 3 mm insignificant disease(GS 3 + 3, &lt; 3 mm), index lesion ≤ GS 3 + 4, &lt;T2c, prostate size &lt; 60 cc</td>
<td>PSA 3 mo intervals y 1 and 6 mo thereafter, Phoenix criteria, mpMRI, PROMS</td>
<td>Distinction of ultra-FT (part of lobe), FT (hemi gland), focused therapy (combining whole gland and FT)</td>
</tr>
<tr>
<td>Muller BG, et al. 2014 (12)</td>
<td>Role of mpMRI</td>
<td>Delphi method, panel meeting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Bos W, et al. 2014 (13)</td>
<td>Trial design</td>
<td>Delphi method, panel meeting</td>
<td>PSA &lt; 15 ng/mL, T1c-2a, GS 3 + 3 or 3 + 4, LE &gt; 10 y</td>
<td>Biopsy 6 mo, 12 mo</td>
<td></td>
</tr>
<tr>
<td>Muller BG, et al. 2015 (14)</td>
<td>Follow up</td>
<td>Delphi method, panel meeting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donaldson IA, et al. 2015 (15)</td>
<td>Patients, interventions and outcomes</td>
<td>Delphi method, panel meeting</td>
<td>Intermediate risk, MRI-targeted or template biopsies, 5 mm treatment margin, GS 6, &lt; 3 mm can be left untreated, &lt;20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**III. Techniques of focal therapy**

Several ablative and radiotherapy approaches to FT have been reported. Comparative studies are scarce and most studies included low- to intermediate-risk PCa treated with curative intent. Regardless of technique, total ablation of the tumour within the treated area is crucial. Several treatment templates have been chosen, including hemi-gland, quadrant and lesion targeting. Attempts have been made to identify the index lesion, i.e. the largest lesion with the highest Gleason grade in the prostate, to target for FT. In 20% of cases, however, high-grade tumour cells can be found in non-targeted smaller lesions (25) questioning the validity of this approach. When selecting foci for treatment (15), planning should include a 5-mm margin to account for microscopic spread and targeting error although other authors have suggested a larger safety margin to be important (26). Foci of indolent cancer, which can also be present in the prostate, might be left untreated when treating the dominant index lesion. Table 2 shows the techniques used for FT of primary PCa.

**Table 2: Focal therapy options for primary prostate cancer management**

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

1. **Focal cryosurgery ablation of the prostate (fCSAP)**

Cryotherapy uses freezing of tissue under ultrasound (US) guidance in one or multiple cycles to ablate tissue. This results in a combination of protein denaturation, direct rupture of cellular membranes by ice crystal formation, and vascular stasis with development of microthrombi, and consecutive ischaemic apoptosis. Biochemical recurrence (BCR) at 60 mo for fCSAP was comparable to whole gland treatment with better erectile function preservation for fCSAP but similar incidence of voiding problems and fistulas (27). The short follow-up and comparison of different definitions of BCR render conclusions on oncological efficacy problematic. The incontinence rates at 1 yr for fCSAP were very low (< 1%), whilst erectile dysfunction rates (ranging from 0–40%) were close to those for men after RP. Procedural complication rates were generally low, with the most common being acute urinary retention (range 1.2–8.0%). When compared to whole gland cryotherapy, fCSAP resulted in a higher rate of erectile function preservation while continence and oncological outcomes were similar for both options (28). Using mpMRI-guidance, fCSAP resulted in no deterioration in erectile function from baseline, and lower urinary tract symptoms remained unchanged from baseline (29).
2. **Focal high intensity focused ultrasound (fHIFU)**

The principle of HIFU ablation is to focus a high-intensity US beam on a given target point. The concentration of the beam energy at that point produces a dramatic temperature rise (up to 80 °C in a few seconds). Tissue destruction is caused by coagulation necrosis and cavitation effects. Systematic reviews (SRs) of the literature, comparing outcomes of fHIFU with RP or EBRT, found no comparative studies reporting on oncological continence or potency at 1 yr or more (30). In a low-to-intermediate risk population treated by hemi-ablation the local radical retreatment rate was 11% at 2 yr with a 13% grade-3 adverse event rate (31). In 5 patients who underwent MR-guided focal ablation before RP, no residual cancer was found in the treated area, but Gleason 7 bilateral cancer, overlooked by mpMRI, was present outside the treated area in 2 of 5 patients (32). Three out of fourteen men in a small series with mpMRI guided fHIFU were diagnosed with Gleason 7 or higher cancer at 24 mo after treatment (33). Barrett et al. (34) reported a reduction in IIEF score after fHIFU and a moderate increase in IPSS, suggesting that fHIFU does carry some morbidity.

3. **Irreversible electroporation (IRE) and radiofrequency ablation (RFA)**

IRE applies electric current to ablate tissue with a small transition zone between treated and non-treated tissue (35). However, the IRE ablation zone cannot be sufficiently visualised by TRUS guidance and although contrast-enhanced US and mpMRI show promising results, difficulties in targeting tissue remain unresolved (36, 37) (38). This is confirmed by recent data which showed a narrow safety margin as a strong predictor of local treatment failure (39) with an infield recurrence rate of 16%. In 19 men treated with nanoknife IRE, residual disease was found in 39% (40). Toxicity after IRE is low for ED (<10%) and urinary retention (3%) (table 2).

4. **Focal laser ablation**

MRI-guided laser treatment allows for thermal ablation of specific areas of the prostate (41-44). In 5 reported series, follow-up was less than 1 yr and residual disease was present in up to 22% of cases (41). In-bore MRI-guidance may improve outcome (45). Toxicity for focal laser ablation is reported in under 5%
5. **Photodynamic focal therapy (PFT)**

Photosensitisers can be used to ablate tissue by applying light. The formation of oxygen radicals is believed to underlie the thromboembolic effects of photodynamic therapy. PFT is the only FT for PCa that was evaluated in a randomised phase III clinical trial (RCT) comparing hemi-gland ablation (n=207) and AS (n=206) in men with low-risk disease. This level 1b evidence showed a reduced rate of positive prostate biopsies at 2 yr in the PFT arm as primary endpoint (5, 46). In September 2017, the European Medicines Agency granted marketing authorisation of PFT by padeliporfin for low-risk unilateral PCa. Although valid at the time of initiation, the study was criticised for including men with low-risk disease whom, according to current standard practice, would all be offered AS; therefore, the clinical relevance of this finding is, at the very least, questionable. Longer follow-up studies are needed to evaluate overall survival (OS) data. The most common toxicity for PFT was urinary retention in 7% of cases early after treatment.

6. **Focal brachytherapy**

In a SR, Peach et al. (47) described data from 6 clinical studies and 9 dosimetry studies on focal high- and low-dose rate brachytherapy. Follow-up in all studies was less than 60 mo and the recurrence rate was found to be up to 29% in one series. Toxicity was less, or similar, to whole gland brachytherapy, but this was found to be dependent on the location of the treated lesion (48). Targeting the peripheral zone only by iodine-125 sources was found to be associated with high recurrence rates in intermediate-risk patients (49). In comparison to whole gland brachytherapy, focal brachytherapy resulted in a markedly lower PSA reduction in a small group of men (50). Toxicity was reported as less, or similar, to whole gland treatment, but detailed data are lacking.

IV. **Statements**

1. **Can focal therapy treat the tumour cell clones most likely to metastasise?**
The concept of FT is valid when the potentially metastasising tumour clones can be identified and therefore targeted. The frequent multi-focality of PCa argues for accurate imaging and histology which is generally obtained by mpMRI and mapping template biopsies. Potentially metastasising clones may appear early in the course of the disease (51, 52). Although mpMRI is promising for identifying larger lesions, it lacks sufficient sensitivity for the detection of smaller lesions and additional template biopsies are recommended for more accurate staging and better patient selection (53). In-field recurrences after most focal ablative treatments do occur and the toxicity of secondary treatments for recurrent disease is less well known; therefore, further data are essential.

Focal therapy can ablate cancer cells but currently, imaging methods cannot reliably identify all high-risk cancer clones within the prostate

2. What is the evidence regarding the clinical effectiveness of focal therapy for localised prostate cancer?

Two recent SRs summarised the data regarding clinical effectiveness of FT. Ramsay et al. (54) undertook a SR and network meta-analysis of ablative therapy in men with localised PCa, which included a sub-group analysis of FT vs. RP and EBRT. Nine case series reporting on FT were identified (5 studies reporting on focal CSAP, 3 studies on focal HIFU, and 1 study reporting on both). For FT vs. RP or EBRT, no statistically significant differences were found for BCR at 3 yr. For focal HIFU vs. RP or EBRT, again, there were no data to compare oncological outcomes at 1 yr or more, making it impossible to assess oncological effectiveness of FT. The high risk of bias and the overall poor data quality of published papers preclude any reliable conclusions (54).

Similarly, Valerio et al. (30), in a SR including data from 3,230 patients across 37 studies, covering 7 different energy sources for FT, found that the toxicity of FT is low but, due to lack of a comparator group in most studies, evaluation against SOC remains to be done.

It should be recognised that most studies on FT include men with low-risk disease for whom AS is the preferred option. The short-term results from the only RCT comparing FT and AS are promising. The co-primary endpoints were
treatment failure at 2 yr (histological progression based on an increased number of positive cores, an increase in the length of cancer, an increased Gleason score, an increased PSA > 10 ng/mL or an increased T stage) and absence of definite cancer. A significant reduced treatment failure was observed with FT even if evidence of clinical benefit is still missing and clearly deserves longer follow-up (5). Remarkable variations in follow-up intervals and positive biopsy rates is apparent among studies (Table 1), possibly reflecting the experimental setup of most studies.

The literature suggests that the oncological effectiveness of focal therapy remains unproven due to the lack of reliable comparative data against SOC including AS. We recommend awaiting prospective comparative trial data before implementing FT in routine clinical practice.

3. **How does focal therapy compare with whole gland treatment in terms of complications?**

Toxicity of whole gland treatment of localised PCa is caused by damage to surrounding anatomical structures and depends on the treatment modality (55). Although less frequent, reports on non-whole gland ablative treatment show similar types of toxicity compared to whole gland treatment (1, 34) but with earlier recovery (56). Phase III data suggests that toxicity of photodynamic hemi-ablation exceeds side effects of AS in the initial 2 yr after treatment (46).

Focal therapy studies targeting smaller regions of the prostate have reported reduced toxicity compared to whole-gland treatment options but robust comparative studies with toxicity end-points are still lacking.

4. **Is reliable follow-up of remaining prostatic tissue after focal therapy for cancer progression possible?**

Close follow-up is essential after FT, since residual disease in the prostate may lead to disease recurrence and or progression. Neither PSA nor imaging has been standardised to define recurrence / progression after FT (30). A consensus panel (15) recommended that histologic outcomes are assessed by targeted biopsy at 1
yr after treatment (16). Residual disease in the treated area of <3mm in size and of Gleason 3 + 3 score were not considered to be in need of further treatment and focal retreatment rates of less than 20% were considered clinically acceptable. The need for subsequent whole-gland treatment should be categorised as failure. Muller et al. (14) presented results from a consensus meeting on follow up after FT. Consensus was achieved for at least 5 yr of follow up using mpMRI, biopsies and functional outcomes assessment. A major limitation of focal therapy studies is the lack of a uniform definition of disease recurrence. For comparison with other local therapies comparative studies are needed.

**Given the considerable uncertainties regarding the optimal follow-up of men treated with focal therapy, patients should only be treated within the context of a clinical trial using predefined criteria (6).**

**5. Is there an increased toxicity for salvage treatment following failed FT /recurrence after FT compared to the initial whole gland treatment?**

Local recurrence after FT has been reported in 3.6-40% of cases (1, 20, 34). Several studies reported data on the toxicity of secondary treatment after FT (57-59). Local salvage therapy after primary whole gland treatment is usually associated with increased morbidity compared to primary whole gland treatment (60-63). Complications seem similar for salvage RP after whole gland and FT but appear to be related to the type of primary FT (57, 64). Data on retreatment with FT in men with recurrence are scarce.

**Better understanding of the toxicity of secondary and retreatments after focal therapy is needed and assessment of it should be part of prospective investigations.**

**Conclusions**

Focal therapy may reduce the toxicity of whole gland management while retaining cancer control. However, before widespread clinical introduction clear,
predefined, clinically relevant objectives are needed, such as a negative biopsy, OS, disease specific survival and toxicity, as well as optimal follow-up schedules. Based on the available data, it should be recognised that AS is the preferred option for many men with low-risk PCa. It is unlikely that FT will provide any oncological benefits in this population within 10 yr of diagnosis, considering the low cancer-specific mortality. In intermediate-risk disease, the accurate detection of higher-risk clones remains problematic and the paucity of relevant data regarding clinical outcome in such situations is highly problematic. Patients should be counselled and cautioned that no long-term comparative data on functional and oncological outcomes are available for FT. The presence of grade I-III toxicity occurs in up to 28% of cases (31) and the need for retreatment exists, along with its associated toxicities. Finally, no clear follow-up strategy has been clarified irrespective of the risk group considered. If long-term benefit is proven (functional or oncological), FT would represent significant progress in PCa care. However, thus far, FT must be considered investigational only.

**Patient summary**

Focal therapy of prostate cancer is the targeted destruction of cancer within a specific part of the prostate gland, sparing the rest of the prostate and nearby tissue. This procedure could potentially reduce side effects when compared to established standard treatments, such as surgery or radiotherapy, which treat the entire prostate. Studies show that for most men with low-risk cancer, active surveillance is the preferred treatment option. However, the available data regarding all forms of focal therapy is still poor and inconclusive. Consequently, due to both the lack of clear results associated with focal therapy and the difficulties in detecting all cancerous areas of the prostate, focal therapy should considered as investigational only.


References


