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**Article:**
van der Poel, HG, van den Bergh, RCN, Briers, E et al. (10 more authors) (2018) Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position in 2018. European Urology, 74 (1). pp. 84-91. ISSN 0302-2838

https://doi.org/10.1016/j.eururo.2018.01.001

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# Focal therapy in primary prostate cancer*:* The EAU Position in 2017

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Word count:
Abstract: 186
Manuscript: 2793

## Abstract

Radical treatment is recognized to be unnecessary or overtreatment for many men with localized prostate cancer. Regional, targeted and focal destruction of the cancer offers the potential for lower morbidity and improved quality of life whilst maintaining similar cancer outcomes. Consequently, there is currently a rapid uptake in the use of focal and regional ablative therapies for this disease. However, there are a number of biological and practical concerns about this approach and it has yet to be proven as a robust treatment option. In particular, the multi-focal nature of prostate cancer argues against unifocal treatment and limitations in imaging can preclude the accurate identification of the number, location and extent of prostate cancer foci. To date, at least seven ablative options have reported results. Most series are relatively immature (needing longer follow-up), there is a lack of consistent follow up, and the morbidity of retreatment is often not considered. Hence the EAU considers focal therapy to be an experimental modality that should only be performed within the scope of a clinical trial. The panel encourages the development of these trials and recruitment of suitable patients.

## I. Introduction

Whole gland treatment is the current gold-standard for localized prostate cancer. (PCa). Since treatment of the entire prostate gland results in toxicity due to damage to surrounding tissue such as urinary sphincter, neurovascular bundle, bowel and bladder a focused treatment of an accurately located lesion would be

of interest. Focal therapy (FT) of the prostate can be defined as treatment of parts of the prostate in order to minimize treatment-related morbidity. Improved imaging of prostate cancer facilitates the concept of FT. The options for FT are numerous and in suitable men focal ablation may reduce complications associated with whole gland treatment (1, 2) while maintaining the same oncological efficacy. Recent data from the ProtecT trial showed no difference in 10-year cancer specific survival between active monitoring, prostatectomy or external beam radiotherapy for men with mainly low and intermediate risk prostate cancer but considerable differences in functional outcome (3, 4). Therefore, a comparable oncological outcome with lower side-effect profile would be an important asset of FT in comparison with whole gland treatment, in the situation where an active treatment is needed. When considered in low risk prostate cancer, as done in many cohorts with small solitary lesions, efficacy of FT should be compared to active surveillance (AS) and long term follow up studies are required.

To date, most focal therapies have been achieved with ablative technologies: cryotherapy, high-intensity focused ultrasound (HIFU), photodynamic therapy, electroporation, and focal radiotherapy by brachytherapy or stereotactic external beam radiotherapy. All reported modalities of focal therapy are at IDEAL stage 2b, i.e. that they are at an exploratory phase with assessment and longer follow-up not yet available (5).

The concept of FT can only provide long term benefit to patients if it satisfies the following requirements:

a) proven survival efficacy equivalent to whole gland treatment
b) fewer complications and less impact on functional outcomes than radical treatment
c) reliable follow-up of remaining prostatic tissue and
d) the benefits of primary treatment outweigh the possible harms of secondary or salvage treatment.

Although focal therapy can be also used for salvage treatments of prostate cancer local recurrences after whole gland treatment (6), this paper will focus on primary treatment only.

## II. Patient selection

To select patients for focal in comparison to whole gland treatment, detailed local staging is essential. Multiparameter magnetic resonance imaging (mpMRI) improves detection of multiple tumor locations in the prostate and could therefore aid in selecting patients in the context of clinical trials (7, 8) (9, 10). An international consensus project proposed mpMRI as the standard imaging tool for FT but still recognized systematic biopsies are required to investigate mpMRI-negative areas in the prostate (11). These imaging and sampling modalities must be associated with a high negative predictive value of significant PCa in regions considered as being "normal". Sextant random biopsies are insufficient to accurately map tumor locations within the prostate. Therefore, standardized, preferably perineal template-guided saturation biopsies are suggested for patients selection (8, 12, 13)(14).

Several consensus meetings have defined criteria for patient selection (**Table 1**) (1) (11, 15, 16). FT is considered for both low and intermediate risk (GS<4+3) tumors in men with a life-expectancy of at least 10 years and workup with mpMRI and template biopsies. Interestingly, in most recent reports, limited Gleason 6 disease is accepted in the untreated prostate areas clearly indicating that follow up strategies after FT should be similar to that for active surveillance.

## III. Techniques of focal therapy

Several ablative and radiotherapy approaches to focal therapy have been reported. Comparative studies are scarce and most studies included low to intermediate-risk prostate cancer treated with curative intent. Options for FT are either hemigland treatment or ablation of isolated tumor foci. Regardless of technique total tumor ablation within the treated area is crucial. Several treatment templates have been chosen including hemigland, quadrant and lesion targeting. When selecting foci for treatment (16) treatment planning should

include a 5 mm margin to account for microscopic spread and treatment uncertainties. Foci of indolent cancer, which can also be present in the prostate, could be left untreated when treating the dominant index lesion. Other authors favor a larger safety margin of 9 mm (17). **Table 2** shows the techniques used for FT of primary prostate cancer.

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

Cryotherapy uses freezing of tissue under ultrasound guidance in one or multiple cycles to ablate tissue through dehydration resulting in protein denaturation; direct rupture of cellular membranes by ice crystal formation, and vascular stasis and development of microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis. BCR at 60 months for fCSAP was comparable to whole gland treatment with better erectile function preservation for fCSAP but similar incidence of voiding problems and fistulas (18). The short follow-up and comparison of different definitions of biochemical recurrence render conclusions on oncological efficacy problematic. The incontinence rates at 1 year for fCSAP were very low (< 1%), whilst erectile dysfunction rates (ranging from 0-40%) were close to those for men after prostatectomy. 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 outcome was similar for both options (19). Using mpMRI-guidance, fCSAP resulted in no deterioration in erectile function from baseline, and LUTS remained unchanged from baseline (20).

### *2. Focal high intensity focused ultrasound (fHIFU)*

The principle of HIFU ablation is to focus a high-intensity ultrasound 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 of the literature comparing outcomes of fHIFU with radical prostatectomy or external beam radiotherapy, found no comparative studies reporting on oncological,

continence or potency at 1 year or more (21). In a low-to-intermediate risk population treated by hemi-ablation the local radical retreatment rate was 11% at 2 years and there was a 13% grade-3 adverse event rate (22). In 5 patients who underwent MR-guided focal ablation before radical prostatectomy, 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 (23). Three of fourteen men in a small series with mpMRI guided fHIFU were diagnosed with Gleason 7 or higher cancer at 24 months after treatment (24). Barrett et al. (25) 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 (26). However, the IRE ablation zone cannot be sufficiently visualized by TRUS guidance and although contrast-enhanced ultrasound and mpMRI show promising results, difficulties in targeting tissue remain unresolved (27) (28, 29). This is confirmed by recent data that showed a narrow safety margin as a strong predictor of local treatment failure (30) with an infield recurrence rate of 16%. In 19 men treated with nanoknife IRE residual disease was found in 39% (31). 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 (32-35). In 5 reported series, follow-up was less than 1 year and residual disease was present in up to 22% of cases (32). In-bore MRI-guidance may improve outcome (36). Toxicity for focal laser ablation is reported in under 5% of patients.

### *5. Photodynamic focal therapy (PFT)*

Photosensitizers 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 prostate cancer that was evaluated

in a randomized phase III clinical trial comparing hemigland ablation (n=207) and active surveillance (n=206) in men with low risk disease. This level 1b evidence showed a reduced rate of positive prostate biopsies at 2 years in the PFT arm as primary end point (37, 38). September 2017, EMEA granted marketing authorization of PFT by padeliporfin for low risk unilateral prostate cancer. Although valid at the time of initiation the study was criticized for including men with low-risk disease which according to current standard practice would all be offered active surveillance, therefore the clinical relevance of this finding is at least questionable. Longer follow up studies are needed and ongoing to evaluate overall survival data. The most common toxicity for PFT was urinary retention in 7% of cases early after treatment.

### *6. Focal brachytherapy*

In a systematic review, Peach et al. (39) 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 months and the recurrence rate was found to be up to 29% in one series , but this was found to be dependent on the location of the treated lesion (40). Targeting the peripheral zone only by iodine-125 sources, was found to be associated with high recurrence rates in intermediate-risk patients (41). In comparison to whole gland, focal brachytherapy resulted in a markedly lower PSA reduction in a small group of men (42). Toxicity was reported as less or similar to whole gland treatment, but detailed data are lacking.

## IV. Statements

### *1. Can focal therapy treat the tumor cell clones most likely to metastasize?*

The concept of focal therapy is valid when the potentially metastasizing tumor clones can be defined and therefore targeted. The frequent multi-focality of prostate cancer argues for accurate imaging and histology i.e. obtained by mpMRI and mapping template biopsies. The presence of potentially metastasizing clones appears to be early in the course of the disease (43, 44). The index lesion, i.e. the largest lesion with the highest Gleason grade in the

prostate is currently the usual target of FT. In 20% of cases, however, high grade tumor cells can be found in non-targeted smaller lesions (45) questioning the validity of this concept. Although mpMRI was promising for identifying larger lesions additional template biopsies are recommended for more accurate staging and better patient selection as mpMRI lacks sufficient sensitivity for the detection of smaller lesions (46). In-field recurrences after most focal ablative treatments do occur and the toxicity of secondary treatments for recurrent disease is less well known; 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 localized prostate cancer?***

Two recent systematic reviews summarized the data regarding clinical effectiveness of focal therapy. Ramsay et al. (47) undertook a systematic review and network meta-analysis of ablative therapy in men with localised prostate cancer, 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 years. For focal HIFU vs. RP or EBRT, there were no data to compare data on oncological outcomes at 1 year or more, making it impossible to assess oncological effectiveness of focal therapy.

Similarly, Valerio et al. (21) found in a systematic review including data from 3,230 patients across 37 studies, covering 7 different energy sources for FT that the toxicity of FT is low but due to lack of a comparator group in most studies evaluation against standard of care is needed.

It should be recognized that most studies on FT include men with low-risk disease for whom active surveillance is the preferred option. The short term results from the only randomized trial comparing FT and AS are promising at a reduced clinical progression rate of FT but longer follow up is needed (38).

Among studies remarkable variations in follow up intervals and positive biopsy rates are apparent (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 standard interventions such as radical prostatectomy and EBRT as well as against active surveillance. 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 localized prostate cancer is caused by damage to surrounding anatomical structures and depends on the type of treatment (3). Although less frequent, reports on non-whole gland ablative treatment showed similar types of toxicity compared to whole gland treatment (1, 25) but with earlier recovery (48). Phase III data suggests that toxicity of PDT hemiablation exceeds side effects of active surveillance in the initial 2 years after treatment (37).

**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 focal therapy since residual disease in the prostate may lead to disease recurrence and or progression. Neither PSA nor imaging has been standardized to define recurrence / progression after FT (21). A recent consensus panel (16) recommended histologic outcomes are assessed by targeted biopsy at 1 year after treatment (49). Residual disease in the treated area of <3mm in size and of Gleason 3 + 3 score were considered not 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, however, be categorized as failure of focal therapy (16). Muller et al. (50) presented results from a consensus meeting on the methods of follow up after FT. At least 5 years of follow up using mpMRI, biopsies and functional outcome assessment were elements consensus was obtained on.

**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 (51)**.

5. ***Is there an increased toxicity for salvage treatment compared to the initial whole gland treatment ?***

Local recurrence after focal therapy has been reported in 3.6-40% of cases (1, 9, 25). Several studies reported data on the toxicity of secondary treatment after focal therapy (52-54). Local salvage therapy after primary whole gland treatment is usually associated with increased morbidity compared to primary whole gland treatment (55-58). Complications seem similar for salvage prostatectomy after whole gland and FT but seem to be related to the type of primary FT (52, 59) 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 analyses.**

**Conclusions**

Focal therapy is still an experimental intervention that should only be performed within the scope of a clinical trial. Clear predefined clinically relevant objectives are needed, such as a negative biopsy, overall survival, disease specific survival and toxicity, as well as robust comparative studies with optimal schedules and duration of follow-up. Based on the available data, it should be recognized that active surveillance is the preferred option for many men with low-risk prostate

cancer. It is unlikely that focal therapy will provide any oncological benefits in this population within 10 years of diagnosis, considering the low cancer-specific mortality. In intermediate-risk disease the accurate detection of higher risk clones remains problematic. Patients should be counseled and cautioned that no long-term comparative data on functional and oncological outcomes are available for focal therapy. The presence of grade I-III toxicity occurs in up to 13%, the need for retreatment exists with its associated toxicities. Finally no clear follow up strategy has been clarified whatever the risk group considered.

If long-term benefit is proven (functional or oncological), focal therapy would represent a real progress in prostate cancer care. But so far it must be considered as experimental only.

**Patient summary**

Focal therapy of prostate cancer is the targeted destruction of a focus of cancer within the prostate gland whilst sparing the rest of the prostate and nearby organs. This procedure could potentially reduce side effects as compared to established standard treatments, such as surgery or radiotherapy, which treat the entire gland. Studies show that for most men with low risk cancer, active surveillance is the preferred option. The available data of all forms of focal therapy is still poor and inconclusive. For intermediate risk cancer the difficulties in identifying all areas of cancer and the lack of clear results lead us to consider focal therapy only within clinical trials.

**Glossary**

| | |
|---|---|
| EAU | European association of urology |
| FT | focal therapy |
| IDEAL | Idea, Development, Exploration, Assessment, Long-term Follow-up, Improving the Quality of Research in Surgery |
| fCSAP | focal cryosurgery of the prostate |
| fHIFU | focal high intensity focused ultrasound |
| IPSS | international prostate symptom score |
| IRE | irreversible electroporation |
| mpMRI | multiparameter magnetic resonance imaging |

| | |
|---|---|
| PDT | photodynamic therapy |
| PSA | prostate specific antigen |
| RFA | radiofrequency ablation |
| TRUS | transrectal ultrasound |

**Table 1.** Summary table of consensus reports on FT.

| | Publication | Year | Consensus topic | Consensus setup | Patient selection | Follow up | Conclusion |
|---|---|---|---|---|---|---|---|
| 1 | bostwick Urology 70 (2007) 42-44 | 2007 | pathobiology, definition, patient selection, biopsy | not provided | LE>5y, T1-3, PSA<15ng/ml, no LUTS, bladder stones/infections excluded, 3D-mapping biopsies 5mm interval | | FT reasonable consideration in selected patients |
| 3 | de la Rosette J Endourol | 2010 | patient selection, imaging | workshop discussion group, informal | template biopsies, LE>10y, cave in patients with LUTS, low-intermediate risk, <T2c, anterior/apical lesions may be difficult, long term effects not know | biopsy 6m, 12m, future: mpMRI or CEUS, 3m PSA first year and 6m thereafter, PROMs | |
| 2 | smeenge BJU 110 (2012) 942-948 | 2012 | role of TRUS | workshop discussion group, informal | TRUS value limited, CEUS promising, systematic biopsy schemes needed | | |
| 4 | ahmed BJU 109 (2012) 1636-1647 | 2012 | FT and AS | workshop discussion group, informal | transperineal mapping biopsy | | suggested study sequence: proof of tumor ablation, compare FT to existing whole gland and/or active surveillance. |
| 5 | langley BJU 109 (2012), 7-16 | 2012 | focal LDR | consensus meeting | LE>10y, PSA<=15ng/ml, mpMRI, template biopsies, unilateraal <0.5cc, contralateral <3mm insignificant disease (GS3+3, <3mm), index lesion <=GS3+4, <T2c, prostate size <60cc | PSA 3m intervals first year, then 6 monthly, Phoenix criteria, mpMRI, PROMs | distinction of ultra-FT (part of lobe), focal therapy (hemi gland), focused therapy (combining whole gland and FT) |
| 6 | muller BJU 114 (2014) 698-707 | 2014 | role of mpMRI | Delphi method, panel meeting | | biopsy 6m, 12m | mpMRI preferred imaging, FU 6m, yearly mpMRI no consensus on whether mpMRI could replace biopsies |
| 7 | vd bos EUROPEAN UROLOGY 65 (2014) 1078–1083 | 2014 | trial design | Delphi method, panel meeting | PSA<15ng/ml, T1c-2a, GS3+3 or 3+4, LE>10y | biopsy 6m, 12m | |
| 8 | muller World J Urol. 2015 Oct;33(10):1503-9 | 2015 | follow up | Delphi method, panel meeting | | minimal 5y, (fusion) template TRUS biopsies after 1y. mpMRI (T2WI, DWI, DCE, T1W1) at 6m and 12m, yearly thereafter till 5y. | |
| 9 | donaldson European urology. 2015;67(4):771-7 | 2015 | patients, interventions, and outcomes | Delphi method, panel meeting | intermediate risk, MRI-targeted or template biopsie, 5mm treatment margin, GS6, <3mm can be left untreated, <20% retreatment | | |
| 10 | scheltema World journal of urology. 2017;35(5):695-701 | 2017 | mpMRI | Delphi method, panel meeting | mpMRI to plan treatment | biopsy | use 1.5T mpMRI only with endorectal coil, fusion MRI-TRUS when supect lesion besides systematic biopsies. |
| 11 | tay Prostate Cancer Prostatic Dis. 2017 Sep;20(3):294-299. | 2017 | patient selection | Delphi method, panel meeting | mpMRI standard imaging tool, low/int risk PCA, GS4+3, GS3+4, focl<1.5cc on mpMRI, <20% of the prostate, 3cc or25% of the prostate for hemigland treatment. Gleaosn 6 in one core in the non-treated region is acceptable. | | |

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

| | Technique | Ablation | Image guidance | Number of studies (patients) | FU range | Oncological outcome | Incontinence | Urinary retention | ED |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Cryotherapy | freeze-thaw cycles | TRUS, mpMRI | 12 (n=2118) | 6-58m | 4-25% biopsy positive | <1% | 5% (6m) | 0-31% |
| 2 | HIFU | heat | TRUS, mpMRI | 5 (n=171) | 6-24m | 0-21% biopsy positive | <1% | <5% | 0-25% |
| 3 | IRE | electroporation | mpMRI | 5 (n=157) | 6-12m | 3-33% biopsy positive | <1% | <3% | 5-10% |
| 4 | Laser | heat | mpMRI | 6 (n=85) | 3w-12m | 4-64% biopsy positive | <1% | <1% | <5% |
| 5 | Photodynamic therapy | vascular targeting | TRUS | 3 (n=313) | 6-24m | 26-51% biopsy positive | <5% | 7% | <2% |
| 6 | Brachytherapy | radiation | TRUS, MRI dosimetry | 7 (n=541) | 24-60m | 0-17% biopsy positive | <5% | nr | nr |

ED = erectile dysfunction, as defined and reported by the studies

FU = follow up

HIFU = high intensity focused ultrasound

IRE = irreversible electroporation

mpMRI = multiparameter magnetic resonance imaging

TRUS = transrectal ultrasound

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