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1 **Focal therapy in primary localised prostate cancer: The EAU Position in**
2 **2018**

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31
32 **Abstract**

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

44 encourage prospective recording of outcomes and the recruitment of suitable
45 patients.

46

47 **I. Introduction**

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

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

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

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

- 79 a) survival efficacy at least equivalent compared to standard of care (SOC);
- 80 b) fewer complications and less functional side effects compared to SOC
- 81 c) reliable follow-up of remaining prostatic tissue and
- 82 d) potential secondary or salvage treatment not impaired by the primary FT.

83

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

87

88 II. Patient selection

89 Detailed local staging is essential for selecting patients suitable for focal gland
90 treatment. Several consensus meetings have strived to define criteria for patient
91 selection (**Table 1**) (7-17). In the most recent publications these have been men
92 with low-risk (GS 3+3) tumours and a life-expectancy of at least 10 yr. Nowadays
93 AS is considered to be a valid option in those patients, as well as whole gland
94 treatments. Any form of FT in low-risk PCa should be associated with significant
95 clinical benefit compared to these SOC. Patients with a small Gleason 7 (**Gleason**
96 **sum score 3+4**, ISUP 2) lesion might be better candidates although, so far, this
97 group is rarely considered in the published trials. Multiparametric magnetic
98 resonance imaging (mpMRI) has been used to select patients in clinical trials
99 (18-21) and is the standard imaging tool for FT, allowing targeted biopsies.
100 However, an international consensus project recognised that adding systematic
101 biopsies remain essential to accurately stage disease (16). These imaging and
102 sampling modalities must be associated with a high negative predictive value of
103 significant PCa in regions considered as “normal”. Sextant random biopsies are
104 insufficient to accurately map tumour locations within the prostate. Instead,
105 standardised, preferably perineal template-guided saturation, biopsies are
106 suggested to aid patient selection (19, 22-24).

107

108 **Table 1: Summary of consensus reports on focal therapy**

109

Publication	Consensus topic	Consensus setup	Patient selection	Follow-up	Conclusion
Bostwick DG, et al. 2007 (7)	Pathobiology definition, patient selection, biopsy	Not provided	LE > 5 y, T1-3, PSA < 15 ng/mL, no LUTS, bladder stones, infections excluded, 3D mapping biopsies 5 mm interval		FT reasonable consideration in selected patients
De la Rosette J, et al. 2010 (8)	Patient selection, imaging	Workshop, discussion group, informal	Template biopsies, LE > 10 Y, cave in patients with LUTS, low-intermediate risk, < T2c, anterior/apical lesions may be difficult, long term effects not known	Biopsy 6 mo, 12 mo, future: mpMRI or CEUS, 3 mo PSA first year and 6 mo thereafter, PROMS	
Smeenge M, et al. 2012 (9)	Role of TRUS	Workshop, discussion group, informal	TRUS value limited, CEUS promising, systematic biopsy schemes needed		
Ahmed HU, et al. 2012 (10)	FT and AS	Workshop, discussion group, informal	Transperineal mapping biopsy		Suggested study sequence: proof of tumour ablation, compare FT to existing whole gland and/or AS
Langley S et al. 2012 (11)	Focal LDR	Consensus meeting	LE > 10 y, PSA ≤ 15 ng/mL, mpMRI, template biopsies, unilateral < 0.5 cc, contralateral < 3 mm insignificant disease(GS 3 + 3, < 3 mm), index lesion ≤ GS 3 + 4, <T2c, prostate size < 60 cc	PSA 3 mo intervals y 1 and 6 mo thereafter, Phoenix criteria, mpMRI, PROMS	Distinction of ultra-FT (part of lobe), FT (hemi gland), focused therapy (combining whole gland and FT)
Muller BG, et al. 2014 (12)	Role of mpMRI	Delphi method, panel meeting		Biopsy 6 mo, 12 mo	mpMRI preferred imaging, FU 6 mo, yearly mpMRI, no consensus on whether mpMRI could replace biopsies
Van den Bos W, et al. 2014 (13)	Trial design	Delphi method, panel meeting	PSA < 15 ng/mL, T1c-2a, GS 3 + 3 or 3 + 4, LE > 10 y	Biopsy 6 mo, 12 mo	
Muller BG, et al. 2015 (14)	Follow up	Delphi method, panel meeting		Minimal 5 y, (fusion) template TRUS biopsies after 1 y, mpMRI (T2WI, DWI, DCE, T1W1) at 6 mo and 12 mo, yearly thereafter until 5 y	
Donaldson IA, et al. 2015 (15)	Patients, interventions and outcomes	Delphi method, panel meeting	Intermediate risk, MRI-targeted or template biopsies, 5 mm treatment margin, GS 6, < 3 mm can be left untreated, <20%		

			retreatment		
Scheltema MJ, et al. 2017 (16)	mpMRI	Delphi method, panel meeting	mpMRI to plan treatment	biopsy	Use 1.5T mpMRI only with endorectal coil, fusion MRI-TRUS when suspect lesion besides systemic biopsies
Tay KJ, et al. 2017 (17)	Patient selection	Delphi method, panel meeting	mpMRI standard imaging tool, low/int risk PCa, GS 4 + 3, GS 3 + 4, foci < 1.5 cc on mpMRI, < 20% of the prostate, 3 cc or 25% of the prostate for hemigland treatment. Gleason 6 in one core in the non-treated region is acceptable.		

110

111 *AS = active surveillance; CEUS = contrast-enhanced ultrasound; FT = focal therapy;*
 112 *FU = follow up; LE = life-expectancy; LUTS = lower urinary tract symptoms; mpMRI*
 113 *= multiparametric magnetic resonance imaging ; PROMs = patient-reported*
 114 *outcome measures; TRUS = transrectal ultrasound.*

115

116 III. Techniques of focal therapy

117 Several ablative and radiotherapy approaches to FT have been reported.

118 Comparative studies are scarce and most studies included low- to intermediate-
 119 risk PCa treated with curative intent. Regardless of technique, total ablation of
 120 the tumour within the treated area is crucial. Several treatment templates have
 121 been chosen, including hemi-gland, quadrant and lesion targeting. Attempts have
 122 been made to identify the index lesion, i.e. the largest lesion with the highest
 123 Gleason grade in the prostate, to target for FT. In 20% of cases, however, high-
 124 grade tumour cells can be found in non-targeted smaller lesions (25) questioning
 125 the validity of this approach. When selecting foci for treatment (15), planning
 126 should include a 5-mm margin to account for microscopic spread and targeting
 127 error although other authors have suggested a larger safety margin to be
 128 important (26). Foci of indolent cancer, which can also be present in the
 129 prostate, might be left untreated when treating the dominant index lesion. **Table**
 130 **2** shows the techniques used for FT of primary PCa.

131

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

133

Technique	Ablation	Image guidance	Number of studies	FU range	Oncological outcome	Incontinence	Urinary retention	ED
-----------	----------	----------------	-------------------	----------	---------------------	--------------	-------------------	----

				(patients)					
1	Cryotherapy	Freeze-thaw cycles	TRUS, mpMRI	12 (n = 2118)	6 – 58 mo	4 – 25% biopsy positive	< 1 %	5% (6 mo)	0 – 31%
2	HIFU	heat	TRUS, mpMRI	5 (n = 171)	6 – 24 mo	0 – 21% biopsy positive	< 1 %	< 5 %	0 – 25%
3	IRE	electroporation	mpMRI	5 (n = 157)	6 – 12 mo	3 – 33% biopsy positive	< 1 %	< 3 %	5 – 10%
4	Laser	heat	mpMRI	6 (n = 85)	3 w – 12 mo	4 – 64% biopsy positive	< 1 %	< 1 %	< 5%
5	Photodynamic therapy	Vascular targeting	TRUS	3 (n = 313)	6 – 24 mo	26 – 51% biopsy positive	< 5 %	7%	< 2 %
6	Brachytherapy	radiation	TRUS, MRI dosimetry	7 (n = 541)	24 – 60 mo	0 – 17% biopsy positive	< 5 %	nr	nr

134

135 *ED = erectile dysfunction, as defined and reported by the studies; FU = follow up;*

136 *HIFU = high intensity focused ultrasound; IRE = irreversible electroporation;*

137 *mpMRI = multiparametric magnetic resonance imaging; TRUS = transrectal*

138 *ultrasound.*

139

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

141 Cryotherapy uses freezing of tissue under ultrasound (US) guidance in one or
142 multiple cycles to ablate tissue. This results in a combination of protein
143 denaturation, direct rupture of cellular membranes by ice crystal formation, and
144 vascular stasis with development of microthrombi, and consecutive ischaemic
145 apoptosis. Biochemical recurrence (BCR) at 60 mo for fCSAP was comparable to
146 whole gland treatment with better erectile function preservation for fCSAP but
147 similar incidence of voiding problems and fistulas (27). The short follow-up and
148 comparison of different definitions of BCR render conclusions on oncological
149 efficacy problematic. The incontinence rates at 1 yr for fCSAP were very low (<
150 1%), whilst erectile dysfunction rates (ranging from 0-40%) were close to those
151 for men after RP. Procedural complication rates were generally low, with the
152 most common being acute urinary retention (range 1.2-8.0%). When compared
153 to whole gland cryotherapy, fCSAP resulted in a higher rate of erectile function
154 preservation while continence and oncological outcomes were similar for both
155 options (28). Using mpMRI-guidance, fCSAP resulted in no deterioration in
156 erectile function from baseline, and lower urinary tract symptoms remained
157 unchanged from baseline (29).

158

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

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

175

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

177 IRE applies electric current to ablate tissue with a small transition zone between
178 treated and non-treated tissue (35). However, the IRE ablation zone cannot be
179 sufficiently visualised by TRUS guidance and although contrast-enhanced US and
180 mpMRI show promising results, difficulties in targeting tissue remain unresolved
181 (36, 37) (38). This is confirmed by recent data which showed a narrow safety
182 margin as a strong predictor of local treatment failure (39) with an infield
183 recurrence rate of 16%. In 19 men treated with nanoknife IRE, residual disease
184 was found in 39% (40). Toxicity after IRE is low for ED (<10%) and urinary
185 retention (3%) (table 2).

186

187 **4. Focal laser ablation**

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

192 of patients.

193

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

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

209

210 **6. Focal brachytherapy**

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

221

222 **IV. Statements**

223 **1. Can focal therapy treat the tumour cell clones most likely to**
224 **metastasise?**

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

235

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

238

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

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

251 Similarly, Valerio et al. (30), in a SR including data from 3,230 patients across
252 37 studies, covering 7 different energy sources for FT, found that the toxicity of
253 FT is low but, due to lack of a comparator group in most studies, evaluation
254 against SOC remains to be done.

255 It should be recognised that most studies on FT include men with low-risk
256 disease for whom AS is the preferred option. The short-term results from the
257 only RCT comparing FT and AS are promising. The co-primary endpoints were

258 treatment failure at 2 yr (histological progression based on an increased number
259 of positive cores, an increase in the length of cancer, an increased Gleason score,
260 an increased PSA > 10 ng/mL or an increased T stage) and absence of definite
261 cancer. A significant reduced treatment failure was observed with FT even if
262 evidence of clinical benefit is still missing and clearly deserves longer follow-up
263 (5). Remarkable variations in follow-up intervals and positive biopsy rates is
264 apparent among studies (‘Table 1), possibly reflecting the experimental setup of
265 most studies.

266

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

271

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

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

280

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

284

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

287 Close follow-up is essential after FT, since residual disease in the prostate may
288 lead to disease recurrence and or progression. Neither PSA nor imaging has been
289 standardised to define recurrence / progression after FT (30). A consensus panel
290 (15) recommended that histologic outcomes are assessed by targeted biopsy at 1

291 yr after treatment (16). Residual disease in the treated area of <3mm in size and
292 of Gleason 3 + 3 score were not considered to be in need of further treatment
293 and focal retreatment rates of less than 20% were considered clinically
294 acceptable. The need for subsequent whole-gland treatment should be
295 categorised as failure. Muller et al. (14) presented results from a consensus
296 meeting on follow up after FT. Consensus was achieved for at least 5 yr of follow
297 up using mpMRI, biopsies and functional outcomes assessment. **A major**
298 **limitation of focal therapy studies is the lack of a uniform definition of disease**
299 **recurrence. For comparison with other local therapies comparative studies are**
300 **needed.**

301

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

305

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

308 Local recurrence after FT has been reported in 3.6-40% of cases (1, 20, 34).
309 Several studies reported data on the toxicity of secondary treatment after FT
310 (57-59). Local salvage therapy after primary whole gland treatment is usually
311 associated with increased morbidity compared to primary whole gland
312 treatment (60-63). Complications seem similar for salvage RP after whole gland
313 and FT but appear to be related to the type of primary FT (57, 64). Data on
314 retreatment with FT in men with recurrence are scarce.

315

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

319

320 **Conclusions**

321 Focal therapy may reduce the toxicity of whole gland management while
322 retaining cancer control. However, before widespread clinical introduction clear,

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

338

339 **Patient summary**

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

350

351

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353

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