CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

ORCA – Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:https://orca.cardiff.ac.uk/id/eprint/113341/

This is the author's version of a work that was submitted to / accepted for publication.

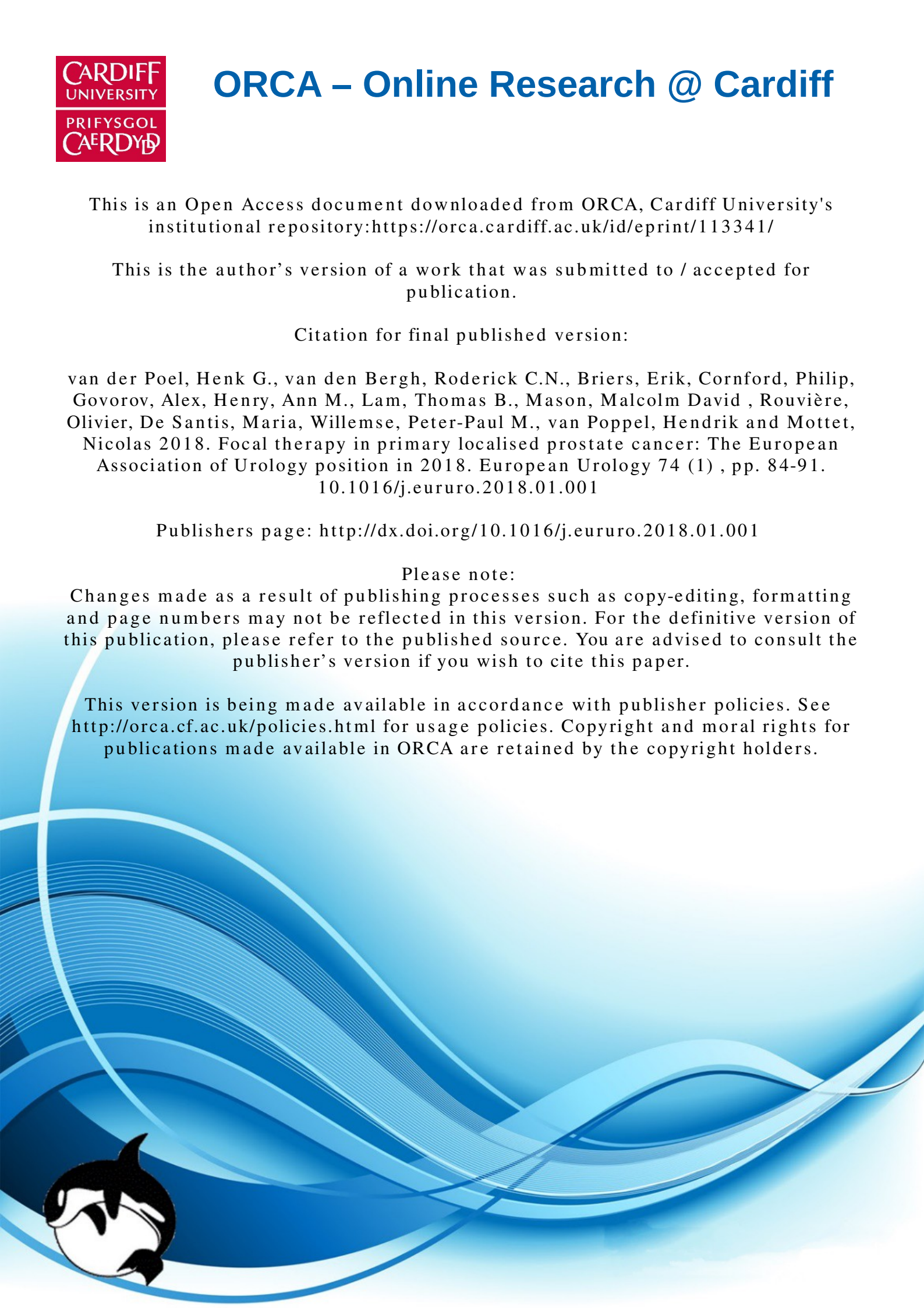
Citation for final published version:

van der Poel, Henk G., van den Bergh, Roderick C.N., Briers, Erik, Cornford, Philip, Govorov, Alex, Henry, Ann M., Lam, Thomas B., Mason, Malcolm David , Rouvière, Olivier, De Santis, Maria, Willemse, Peter-Paul M., van Poppel, Hendrik and Mottet, Nicolas 2018. Focal therapy in primary localised prostate cancer: The European Association of Urology position in 2018. European Urology 74 (1) , pp. 84-91. 10.1016/j.eururo.2018.01.001

Publishers page: http://dx.doi.org/10.1016/j.eururo.2018.01.001

Please note:
Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



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

Henk G. van der Poel[a], Roderick C.N. van den Bergh[a], Philip Cornford[b], Alex Govorov[c], Ann M. Henry[d], Thomas B. Lam[e,f], Malcolm D. Mason[g], Olivier Rouvière[h], Maria De Santis[i,j], Peter-Paul M. Willemse[k], Hendrik Van Poppel[l], Nicolas Mottet[m]

[a]Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands;
[b]Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK;
[c]Department of Urology, Moscow State University of Medicine and Dentistry, Moscow, Russia;
[d]Leeds Cancer Centre, St. James's University Hospital, Leeds, UK;
[e]Academic Urology Unit, University of Aberdeen, Aberdeen, UK;
[f]Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK;
[g]Division of Cancer & Genetics, School of Medicine Cardiff University, Velindre Cancer Centre, Cardiff, United Kingdom;
[h]Hospices Civils de Lyon, Radiology Department, Edouard Herriot Hospital, Lyon, France;
[i]Clinical Trials Unit, University of Warwick, United Kingdom;
[j]Department of Urology, Medical University of Vienna, Austria;
[k]Department of Urology, Erasmus Medical Center, Rotterdam, The Netherlands;
[l]Department of Urology, University Hospital K.U. Leuven, Leuven, Belgium;
[m]Department of Urology, University Hospital, St. Etienne, France;

Word count:
Abstract: 186
Manuscript: 2793

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

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 1and 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.		

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

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

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

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%

of patients.

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

1. Valerio M, Ahmed HU, Emberton M, Lawrentschuk N, Lazzeri M, Montironi R, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. European urology. 2014;66(4):732-51.
2. Baydoun A, Traughber B, Morris N, Abi Zeid Daou M, McGraw M, Podder TK, et al. Outcomes and toxicities in patients treated with definitive focal therapy for primary prostate cancer: systematic review. Future Oncol. 2017;13(7):649-63.
3. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415-24.
4. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.
5. Abdel-Rahmène Azzouzi, Sébastien Vincendeau, Eric Barret, Antony Cicco, François Kleinclauss, Henk G. van der Poel, et al. Padeliporfin Vascular-targeted Photodynamic Therapy Versus Active Surveillance: A Randomised Clinical Trial in Men with Low-risk Prostate Cancer. Lancet Oncol. 2017;18(2):181-91.
6. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European urology. 2017;71:618-29.
7. Bostwick DG, Waters DJ, Farley ER, Meiers I, Rukstalis D, Cavanaugh WA, et al. Group consensus reports from the Consensus Conference on Focal Treatment of Prostatic Carcinoma, Celebration, Florida, February 24, 2006. Urology. 2007;70(6 Suppl):42-4.
8. de la Rosette J, Ahmed H, Barentsz J, Johansen TB, Brausi M, Emberton M, et al. Focal therapy in prostate cancer-report from a consensus panel. J Endourol. 2010;24(5):775-80.
9. Smeenge M, Barentsz J, Cosgrove D, de la Rosette J, de Reijke T, Eggener S, et al. Role of transrectal ultrasonography (TRUS) in focal therapy of prostate cancer: report from a Consensus Panel. BJU Int. 2012;110(7):942-8.
10. Ahmed HU, Akin O, Coleman JA, Crane S, Emberton M, Goldenberg L, et al. Transatlantic Consensus Group on active surveillance and focal therapy for prostate cancer. BJU international. 2012;109(11):1636-47.
11. Langley S, Ahmed HU, Al-Qaisieh B, Bostwick D, Dickinson L, Veiga FG, et al. Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer. BJU international. 2012;109 Suppl 1:7-16.
12. Muller BG, van den Bos W, Brausi M, Cornud F, Gontero P, Kirkham A, et al. Role of multiparametric magnetic resonance imaging (MRI) in focal therapy for prostate cancer: a Delphi consensus project. BJU international. 2014;114(5):698-707.
13. van den Bos W, Muller BG, Ahmed H, Bangma CH, Barret E, Crouzet S, et al. Focal Therapy in Prostate Cancer: International Multidisciplinary Consensus on Trial Design. European urology. 2014;65:1078-83.
14. Muller BG, van den Bos W, Brausi M, Futterer JJ, Ghai S, Pinto PA, et al. Follow-up modalities in focal therapy for prostate cancer: results from a Delphi consensus project. World journal of urology. 2015;33(10):1503-9.

15. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. European urology. 2015;67(4):771-7.
16. Scheltema MJ, Tay KJ, Postema AW, de Bruin DM, Feller J, Futterer JJ, et al. Utilization of multiparametric prostate magnetic resonance imaging in clinical practice and focal therapy: report from a Delphi consensus project. World J Urol. 2017;35(5):695-701.
17. Tay KJ, Scheltema MJ, Ahmed HU, Barret E, Coleman JA, Dominguez-Escrig J, et al. Patient selection for prostate focal therapy in the era of active surveillance: an International Delphi Consensus Project. Prostate Cancer Prostatic Dis. 2017;20(3):294-9.
18. Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. European urology. 2013;64(5):713-9.
19. Singh PB, Anele C, Dalton E, Barbouti O, Stevens D, Gurung P, et al. Prostate cancer tumour features on template prostate-mapping biopsies: implications for focal therapy. European urology. 2014;66(1):12-9.
20. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG, et al. Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: a Prospective Development Study. European urology. 2015;68(6):927-36.
21. Tran M, Thompson J, Bohm M, Pulbrook M, Moses D, Shnier R, et al. Combination of multiparametric MRI and transperineal template-guided mapping biopsy of the prostate to identify candidates for hemi-ablative focal therapy. BJU international. 2016;117(1):48-54.
22. Onik G, Miessau M, Bostwick DG. Three-dimensional prostate mapping biopsy has a potentially significant impact on prostate cancer management. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(26):4321-6.
23. Crawford ED, Rove KO, Barqawi AB, Maroni PD, Werahera PN, Baer CA, et al. Clinical-pathologic correlation between transperineal mapping biopsies of the prostate and three-dimensional reconstruction of prostatectomy specimens. Prostate. 2013;73(7):778-87.
24. Crawford ED, Wilson SS, Torkko KC, Hirano D, Stewart JS, Brammell C, et al. Clinical staging of prostate cancer: a computer-simulated study of transperineal prostate biopsy. BJU international. 2005;96(7):999-1004.
25. Wise AM, Stamey TA, McNeal JE, Clayton JL. Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. Urology. 2002;60(2):264-9.
26. Le Nobin J, Orczyk C, Deng FM, Melamed J, Rusinek H, Taneja SS, et al. Prostate tumour volumes: evaluation of the agreement between magnetic resonance imaging and histology using novel co-registration software. BJU Int. 2014;114(6b):E105-E12.
27. Mendez MH, Passoni NM, Pow-Sang J, Jones JS, Polascik TJ. Comparison of Outcomes Between Preoperatively Potent Men Treated with Focal Versus Whole Gland Cryotherapy in a Matched Population. J Endourol. 2015;29(10):1193-8.
28. Tay KJ, Polascik TJ, Elshafei A, Tsivian E, Jones JS. Propensity Score-Matched Comparison of Partial to Whole-Gland Cryotherapy for Intermediate-

449 Risk Prostate Cancer: An Analysis of the Cryo On-Line Data Registry Data. J
450 Endourol. 2017;31(6):564-71.
451 29. Valerio M, Shah TT, Shah P, McCartan N, Emberton M, Arya M, et al.
452 Magnetic resonance imaging-transrectal ultrasound fusion focal cryotherapy of
453 the prostate: A prospective development study. Urol Oncol. 2017;35(4):150 e1-
454 e7.
455 30. Valerio M, Cerantola Y, Eggener SE, Lepor H, Polascik TJ, Villers A, et al.
456 New and Established Technology in Focal Ablation of the Prostate: A Systematic
457 Review. European urology. 2016;71:17.
458 31. Rischmann P, Gelet A, Riche B, Villers A, Pasticier G, Bondil P, et al. Focal
459 High Intensity Focused Ultrasound of Unilateral Localized Prostate cancer: A
460 Prospective Multicentric Hemiablation Study of 111 Patients. European urology.
461 2017;71(2):267-73.
462 32. Napoli A, Anzidei M, De Nunzio C, Cartocci G, Panebianco V, De Dominicis
463 C, et al. Real-time magnetic resonance-guided high-intensity focused ultrasound
464 focal therapy for localised prostate cancer: preliminary experience. European
465 urology. 2013;63(2):395-8.
466 33. Tay KJ, Cheng CWS, Lau WKO, Khoo J, Thng CH, Kwek JW. Focal Therapy
467 for Prostate Cancer with In-Bore MR-guided Focused Ultrasound: Two-Year
468 Follow-up of a Phase I Trial-Complications and Functional Outcomes. Radiology.
469 2017:161650.
470 34. Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, et al.
471 Morbidity of focal therapy in the treatment of localized prostate cancer.
472 European urology. 2013;63(4):618-22.
473 35. Davalos RV, Bhonsle S, Neal RE, 2nd. Implications and considerations of
474 thermal effects when applying irreversible electroporation tissue ablation
475 therapy. Prostate. 2015;75(10):1114-8.
476 36. Beyer LP, Pregler B, Niessen C, Michalik K, Haimerl M, Stroszczynski C, et
477 al. Percutaneous irreversible electroporation (IRE) of prostate cancer: Contrast-
478 enhanced ultrasound (CEUS) findings during follow up. Clin Hemorheol
479 Microcirc. 2016;64(3):501-6.
480 37. van den Bos W, de Bruin DM, van Randen A, Engelbrecht MR, Postema
481 AW, Muller BG, et al. MRI and contrast-enhanced ultrasound imaging for
482 evaluation of focal irreversible electroporation treatment: results from a phase I-
483 II study in patients undergoing IRE followed by radical prostatectomy. Eur
484 Radiol. 2016;26(7):2252-60.
485 38. Wendler JJ, Ganzer R, Hadaschik B, Blana A, Henkel T, Kohrmann KU, et al.
486 Why we should not routinely apply irreversible electroporation as an alternative
487 curative treatment modality for localized prostate cancer at this stage. World
488 journal of urology. 2017;35:11.
489 39. van den Bos W, Scheltema MJ, Siriwardana AR, Kalsbeek AMF, Thompson
490 JE, Ting F, et al. Focal irreversible electroporation as primary treatment for
491 localized prostate cancer. BJU international. 2017;Aug 10. doi:
492 10.1111/bju.13983.
493 40. Valerio M, Dickinson L, Ali A, Ramachadran N, Donaldson I, McCartan N, et
494 al. Nanoknife Electroporation Ablation Trial: A Prospective Development Study
495 Investigating Focal Irreversible Electroporation for Localized Prostate Cancer.
496 The Journal of urology. 2017;197(3 Pt 1):647-54.

41. Oto A, Sethi I, Karczmar G, McNichols R, Ivancevic MK, Stadler WM, et al. MR imaging-guided focal laser ablation for prostate cancer: phase I trial. Radiology. 2013;267(3):932-40.
42. Lepor H, Llukani E, Sperling D, Futterer JJ. Complications, Recovery, and Early Functional Outcomes and Oncologic Control Following In-bore Focal Laser Ablation of Prostate Cancer. European urology. 2015;68(6):924-6.
43. Natarajan S, Raman S, Priester AM, Garritano J, Margolis DJ, Lieu P, et al. Focal Laser Ablation of Prostate Cancer: Phase I Clinical Trial. The Journal of urology. 2016;196(1):68-75.
44. Bomers JG, Cornel EB, Futterer JJ, Jenniskens SF, Schaafsma HE, Barentsz JO, et al. MRI-guided focal laser ablation for prostate cancer followed by radical prostatectomy: correlation of treatment effects with imaging. World journal of urology. 2016.
45. Natarajan S, Jones TA, Priester AM, Geoghegan R, Lieu P, Delfin M, et al. Focal Laser Ablation of Prostate Cancer: Feasibility of MRI/US Fusion for Guidance. The Journal of urology. 2017;198:839.
46. Azzouzi AR, Barret E, Moore CM, Villers A, Allen C, Scherz A, et al. TOOKAD((R)) Soluble vascular-targeted photodynamic (VTP) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer. BJU international. 2013;112(6):766-74.
47. Peach MS, Trifiletti DM, Libby B. Systematic Review of Focal Prostate Brachytherapy and the Future Implementation of Image-Guided Prostate HDR Brachytherapy Using MR-Ultrasound Fusion. Prostate cancer. 2016;2016:4754031.
48. Srougi V, Barret E, Nunes-Silva I, Baghdadi M, Garcia-Barreras S, Pierrat N, et al. Focal brachytherapy for localized prostate cancer: Urinary toxicity depends on tumor location. Brachytherapy. 2017;16:988.
49. Nguyen PL, Chen MH, Zhang Y, Tempany CM, Cormack RA, Beard CJ, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. The Journal of urology. 2012;188(4):1151-6.
50. Mahdavi SS, Spadinger IT, Salcudean SE, Kozlowski P, Chang SD, Ng T, et al. Focal application of low-dose-rate brachytherapy for prostate cancer: a pilot study. J Contemp Brachytherapy. 2017;9(3):197-208.
51. Haffner MC, Mosbruger T, Esopi DM, Fedor H, Heaphy CM, Walker DA, et al. Tracking the clonal origin of lethal prostate cancer. J Clin Invest. 2013;123(11):4918-22.
52. Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med. 2009;15(5):559-65.
53. Le JD, Tan N, Shkolyar E, Lu DY, Kwan L, Marks LS, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. European urology. 2015;67(3):569-76.
54. Ramsay CR, Adewuyi TE, Gray J, Hislop J, Shirley MD, Jayakody S, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess. 2015;19(49):1-490.

55. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016;375:1425.
56. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol. 2012;13(6):622-32.
57. Linares Espinos E, Sanchez-Salas R, Sivaraman A, Perez-Reggeti JI, Barret E, Rozet F, et al. Minimally Invasive Salvage Prostatectomy After Primary Radiation or Ablation Treatment. Urology. 2016;94:111-6.
58. Lebdai S, Villers A, Barret E, Nedelcu C, Bigot P, Azzouzi AR. Feasibility, safety, and efficacy of salvage radical prostatectomy after Tookad(R) Soluble focal treatment for localized prostate cancer. World journal of urology. 2015;33(7):965-71.
59. Stone NN, Unger P, Crawford ED, Stock RG. Diagnosis and management of local recurrence after low-dose-rate brachytherapy. Brachytherapy. 2015;14(2):124-30.
60. van Stam MA, Aaronson NK, Pos FJ, Bosch JL, Kieffer JM, Tillier CN, et al. The Effect of Salvage Radiotherapy and its Timing on the Health-related Quality of Life of Prostate Cancer Patients. European urology. 2016;70:751-7.
61. Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Holscher T, Gut P, et al. Acute Toxicity and Quality of Life After Dose-Intensified Salvage Radiation Therapy for Biochemically Recurrent Prostate Cancer After Prostatectomy: First Results of the Randomized Trial SAKK 09/10. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(35):4158-66.
62. Siddiqui KM, Billia M, Arifin A, Li F, Violette P, Chin JL. Pathologic, Oncologic and Functional Outcomes of a Prospective Registry of Salvage High Intensity Focused Ultrasound Ablation for Radio-Recurrent Prostate. The Journal of urology. 2017;197:97-102.
63. Chade DC, Eastham J, Graefen M, Hu JC, Karnes RJ, Klotz L, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. European urology. 2012;61(5):961-71.
64. Nunes-Silva I, Barret E, Srougi V, Baghdadi M, Capogrosso P, Garcia-Barreras S, et al. Effect of Prior Focal Therapy on Perioperative, Oncologic and Functional Outcomes of Salvage Robotic Assisted Radical Prostatectomy. The Journal of urology. 2017;198:1069-76.