

Platinum Priority – Prostate Cancer

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Focal High-intensity Focused Ultrasound Targeted Hemablation for Unilateral Prostate Cancer: A Prospective Evaluation of Oncologic and Functional Outcomes

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Abstract

Background: In selected patients with unilateral, organ-confined prostate cancer (PCa), hemiablation of the affected lobe might be feasible to achieve acceptable cancer control with fewer complications.

Objectives: To assess the oncologic and functional outcomes of focal high-intensity focused ultrasound (HIFU) hemiablation in unilateral organ-confined PCa.

Design, setting and patients: Single-center prospective evaluation of HIFU hemiablation for unilateral organ-confined PCa was performed from July 2009 through December 2013.

Intervention: Cancer localization was done with transrectal ultrasound-guided biopsy and multiparametric magnetic resonance imaging followed by HIFU hemiablation.

Outcome measurement and statistical analysis: Oncologic outcomes were analyzed with control biopsies and prostate-specific antigen (PSA) measurement. Functional outcomes were assessed with validated questionnaires for genitourinary symptoms.

Results and limitations: Of 71 HIFU hemiablation patients, 67 completed the study protocol. The mean age was 70.2 yr (standard deviation: 6.8 yr), and median PSA was 6.1 ng/ml (interquartile range [IQR]: 1.6–15.5 ng/ml). Median maximum cancer-core length was 3 mm (IQR: 2–10 mm), and total cancer length was 6.5 mm (IQR: 2–24 mm). Gleason score was 6 (3 + 3) in 58 patients (86.6%) and 7 (3 + 4) in 9 patients (13.4%). Median follow-up was 12 mo (IQR: 6–50 mo), and at 12 mo, 56 of 67 patients had a negative control biopsy in the treated lobe. At 3 mo, all patients were continent, and potency was maintained in 11 of 21 preoperatively potent patients (confidence interval, 0.18–0.69). Complications included 8% Clavien–Dindo grade 2 and 2.8% grade 3 events.

Conclusions: Focal HIFU hemiablation appears to achieve acceptable oncologic outcomes with low morbidity and minimal functional changes. Longer follow-up will establish future considerations.

Patient summary: This study showed that high-intensity focused ultrasound hemiablation in selected patients with unilateral organ-confined prostate cancer can be used for satisfactory cancer control with minimal effect on genitourinary functions.

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1. Introduction

The incidence of prostate cancer (PCa) is steadily increasing worldwide, and PCa is the most frequently diagnosed cancer in men [1]. Current screening strategies have led to earlier diagnosis of PCa at lower clinical stages, lower grades, and smaller volumes [2]. A wide variety of ablative methods have been introduced and applied in recent years as focal treatment (FT) alternatives with which cancer foci can be eradicated within the prostate gland, thus greatly reducing the associated side effects of radical treatment. Although FT is not yet the standard for organ-confined PCa, it is the therapeutic approach with the most important potential [3]. Among the multiple options for ablation, high-intensity focused ultrasound (HIFU) and cryoablation—the present authors have ample experience with both—have been clinically available during the past 15 yr and have undergone continuous development over time. In this context, HIFU is a promising technique that has proven medium- to long-term cancer control with a low rate of complications, comparable with those of established therapies [4]. In the present study, we assessed the oncologic and functional outcomes at 1-yr follow-up of patients with unilateral low-risk organ-confined PCa treated at our center with focal HIFU hemiablation.

2. Patients and methods

2.1. Study design and patients

From July 2009 to December 2013, focal HIFU hemiablation was offered to patients who had a diagnosis of unilateral localized PCa in our institution. Inclusion criteria were unilateral disease, clinical stage T1c–T2a, maximum positive biopsies <33%, Gleason score ≤ 7 (3 + 4), prostate-specific antigen (PSA) <15 ng/ml, no extraprostatic extension disease on multiparametric magnetic resonance imaging (mp-MRI), and life expectancy >10 yr. Patients with previous PCa-related treatment were excluded.

2.2. Study intervention

2.2.1. Cancer localization

Cancer grade and laterality were confirmed with transrectal ultrasound (TRUS)-guided biopsy and mp-MRI. For TRUS biopsy, a conventional two-dimensional gray-scale TRUS probe was used, and all patients had a minimum of 20 cores for cancer localization. For mp-MRI, all patients underwent 1.5-T MRI without endorectal coil for assessment of the prostate. The multiparametric components used were diffusion and perfusion images; however, all hemiablation was based on the TRUS biopsy results, including cases with a discrepancy in laterality between biopsy and MRI and “MRI-invisible” PCa.

2.2.2. Treatment

Hemablation was carried out using the Ablatherm HIFU system (EDAP TMS, Lyon, France). This system includes a treatment table, a probe-positioning system, an ultrasound power generator, a cooling system for preservation of the rectal wall, a computerized control module with specific software, and an endorectal probe with a biplane imaging probe working at 7.5 MHz and a 3-MHz treatment transducer focused at a maximum of 45 mm. In addition, automatic applicator adjustment and multiple security circuits excluded accidental focusing on the rectal wall, avoiding rectal injury.

For this procedure, the transducer was inserted into the rectum and was covered by a condom through which cooled water was circulated to cool the rectal wall; multiple gland images were taken. Because of the proximity of the prostate, the focal lengths of the transducer could be kept short, permitting the use of ultrasound frequencies in the range of 3–4 MHz. They produced small but very precisely defined lesions, with the aim of treating the gland partially (hemablation) by juxtaposition of elementary lesions. Larger areas were ablated by moving the transducer electronically and adding one lesion to another. The main sonication parameters were acoustic intensity, duration of exposure, on:off ratio, the distance between two elementary lesions, and the displacement path when multiple lesions were made. A safety margin of 4–6 mm from the sphincter was given to prevent sphincter damage. The entire procedure was carried out within 120 min, and an indwelling urethral catheter was placed after the procedure.

2.2.3. Follow-up

The Clavien–Dindo classification system was used to grade postoperative complications. Oncologic and functional outcomes were analyzed during follow-up. Control biopsies were performed within the first year of follow-up, constituting the primary end point. Prostate biopsies at 12 mo (12 core, bisextant, TRUS guided) were performed according to the mandatory protocol and directed at both treated and untreated portions of the prostate. Treatment failure was defined as a positive biopsy in the treated lobe or a need for salvage therapy.

Follow-up visits consisted of taking a history and a physical examination and completing International Continence Society (ICS), International Prostate Symptom Score (IPSS), and International Index of Erectile Function (IIEF-5) questionnaires, which were filled in at preoperative and follow-up visits. Continence was defined as the patient having no involuntary urine leak and being completely pad free. Potency was defined as an IIEF score ≥ 22 without any medications to improve erection. In addition, PSA evaluation was performed at 3, 6, and 12 mo and every 6 mo thereafter. Data were collected prospectively and analyzed retrospectively.

2.3. Statistical analysis

The Wilcoxon signed-rank test was used to compare variation in distribution of IPSS, ICS, and IIEF-5 scores between the preoperative and 3-mo follow-up scores. Box plot graphics were computed to describe PSA values over the follow-up period. Cross-tabs applying chi-square or Fisher exact tests were used to assess the relationships among categorical variables. A *p* value <0.05 was considered statistically significant. Statistical analysis was performed using PASW Statistics 18.0 for Windows (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Demographic and cohort data

During the period of inclusion, 71 patients with localized PCa were assigned to the focal HIFU hemiablation single-institution protocol. Four patients (5.6%) refused the control biopsy and thus were excluded from the final analysis. Sixty-seven patients (94.3%) had complete follow-up data and formed the study population. The mean age at time of treatment was 70.2 yr (standard deviation [SD]: 6.8 yr). Mean body mass index was 25.5 kg/m² (SD: 6.5 kg/m²). The median number of biopsy cores was 22 (interquartile range [IQR]: 20–69). Median maximum cancer-core length (MCCL) was 3 mm (IQR: 2–10 mm), and the total cancer length (TCL) was

Table 1 – Demographics and preoperative data

Variable	Value
No. of patients	67
Age, yr, mean (SD)	70.2 (6.8)
Follow-up, mo, median (IQR)	12 (6–50)
Body mass index, kg/m ² , mean (SD)	25.5 (6.5)
Number of biopsies, median (IQR)	22 (20–69)
MRI prostate volume, ml, mean (SD)	39.3 (13.7)
Preoperative PSA, ng/ml, median (IQR)	6.1 (1.6–15.5)
Gleason score, entry biopsy, n (%)	
3 + 3	58 (86.6)
3 + 4	9 (13.4)

IQR = interquartile range; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; SD = standard deviation.

6.5 mm (IQR: 2–24 mm). At baseline, Gleason score was 3 + 3 and 3 + 4 in 58 (86.6%) and 9 (13.4%) patients, respectively. Preoperative median PSA was 6.1 ng/ml (IQR: 1.6–15.5 ng/ml), and mean prostate volume was 39.3 ml (SD: 13.7 ml). Forty-two (62.7%) and 25 (37.3%) patients received HIFU hemiablation on the right and on the left prostatic lobes, respectively. Preoperative mp-MRI was performed in all patients, and 62.7% (42 of 67) had an index lesion detectable at MRI. All index lesions were detected at the side of the planned hemiablation, and the median maximal diameter of the index lesion was 6 mm (IQR: 4–9 mm). Baseline characteristics are shown in Table 1.

3.2. Postoperative data: early oncologic control at 12 months

The median follow-up was 12 mo (IQR: 6–50 mo), with 52 patients followed >16 mo. The negative control biopsy was noted in 50 of the 67 evaluated patients; specifically,

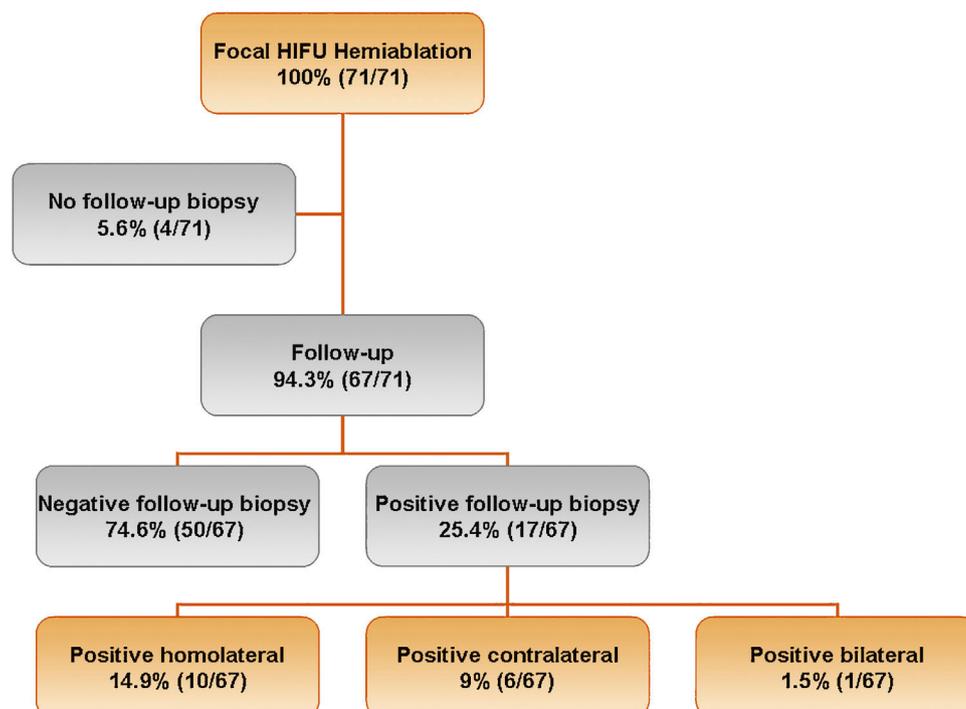
negative biopsy in the treated lobe was seen in 56 patients. Eleven patients presented with positive biopsies in the treated lobe; of those, 1 patient had a bilateral positive biopsy (nine positive biopsies on the right lobe and two on the left lobe), and 6 patients presented positive biopsies in the nontreated lobe along with negative biopsies in the treated lobe. Median MCCL of the positive control biopsy was 1 mm (IQR: 1–2 mm), and TCL was 2 mm (IQR: 1–3 mm). The patient flowchart is shown in Figure 1.

Failure was observed in 11 cases; of these, positive control biopsies were identified in the right side in 9 cases and in left side in 2 cases. Biopsies were positive at the base in four cases, at the midpart in six, and at the apex in one. Failure was significantly higher following right-lobe hemi-ablation than left hemi-ablation (21.4% vs 8%, $p < 0.05$); however, no significant differences were noted regarding the location of recurrence within the prostatic lobe.

The median PSA concentration dropped by 43% at 3 mo ($p < 0.001$), and this decline persisted throughout the follow-up period. No undetectable PSA was reported. The PSA results at follow-up are shown in Figure 2. The median PSA nadir was 2.6 ng/ml (IQR: 0.2–11.1 ng/ml). Of the 67 evaluable patients, biochemical recurrence was verified in 6 patients (9.7%) based on Phoenix criteria.

3.3. Postoperative data: functional outcomes

At baseline, preoperative mean scores were 6.24 (range: 0–26), 0.42 (range: 0–8), and 17.97 (range: 0–25) for the IPSS, ICS, and IIEF-5 questionnaires, respectively. All patients were continent before and after treatment. Evaluation at the 3-mo postoperative period showed no significant changes for both IPSS ($p = 0.217$) and ICS scores ($p = 0.840$). In the same time

**Fig. 1 – Patient flowchart.**

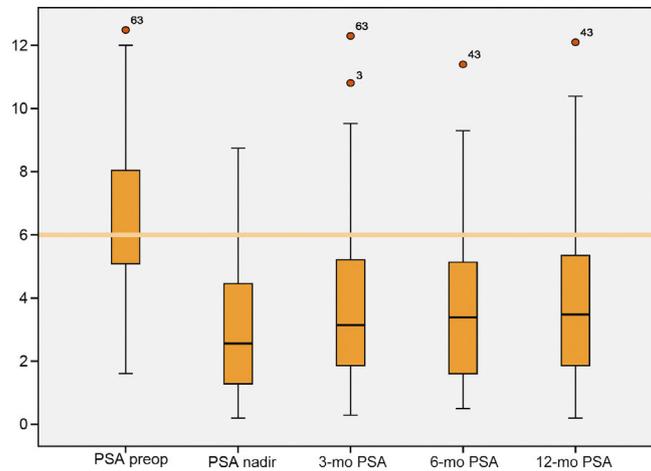


Fig. 2 – Prostate-specific antigen values over time in the follow-up period. Preop = preoperatively; PSA = prostate-specific antigen.

period, potency (defined by IIEF-5 score ≥ 22) was maintained in 11 of 21 preoperatively potent patients (confidence interval, 0.18–0.69). Data for IPSS and IIEF-5 scores over the follow-up period are shown in Figure 3.

3.4. Complications

All complications were encountered within the first postoperative month. Ten patients (14%) had postoperative complications: Eight complications were grade 2 (11.2%; four urinary infections and four urinary retentions) and two were grade 3b (2.8%; two urinary retentions treated with transurethral resection of the prostate [TURP]).

4. Discussion

Since the 1990s, HIFU has been used for the treatment of PCa [4]. Worldwide experience (whole gland, either as primary or salvage therapies) showed significant improvement in both

oncologic and functional outcomes with fewer complications [5–9]. To date, however, the available evidence for HIFU focal ablation is recent but limited.

Currently, the consensus definition states that FT is “any approach able to preserve part of the prostatic tissue, whether by targeted ablation, hemiablation and zonal ‘hockey stick’ ablation” [10,11]. Clinically acceptable cancer control following FT is generally agreed for retreatment rates of $\leq 20\%$ [12]. The goal of FT is to achieve “trifecta” outcomes: cancer control, fewer complications, and preservation of genitourinary function comparable to radical treatment options. In this context, our preliminary results are encouraging, as shown by the high efficacy rate with low morbidity rates and minimal functional changes.

In the present study, the rate of negative biopsy in the treated area was 83.6%, and the overall negative biopsy rate was 74.6%. PSA declined significantly at 3 mo and persisted throughout follow-up. These outcomes are consistent with the initial reports of reported HIFU hemiablation by Ahmed et al [13]. At 12-mo follow-up, mean PSA decreased to 1.5 ± 1.3 ng/ml, and 89% had no cancer in the treated area [13]. More recently, the same group published a prospective series of 41 patients, with HIFU FT delivered using the Sonablate 500 (SonaCare Medical, Charlotte, NC, USA) to all suspected tumor lesions and a maximum of 60% of the prostate ablated. Negative biopsy was noted in 30 of 39 patients (77%) at 6 mo, with a significant decrease in PSA from 6.6 to 1.9 ng/ml at 12 mo [14].

As for the functional outcomes, we found that both continence and urinary symptoms were not affected, but there was a significant negative impact on erection. This result is consistent with those of Ahmed et al [14], who reported significant deterioration between baseline and 12 mo for erectile ($p = 0.042$) and orgasmic ($p = 0.03$) function domains, followed by gradual return to baseline by 12 mo [14]. Data on contemporary oncologic and functional outcomes of HIFU focal ablation for PCa are shown in Table 2.

Complications noted in the present series were predominantly low grade and comparable to the consolidated outcomes of various energies in FT, as shown by Barret et al [16]. Prostate volume appears to be an important

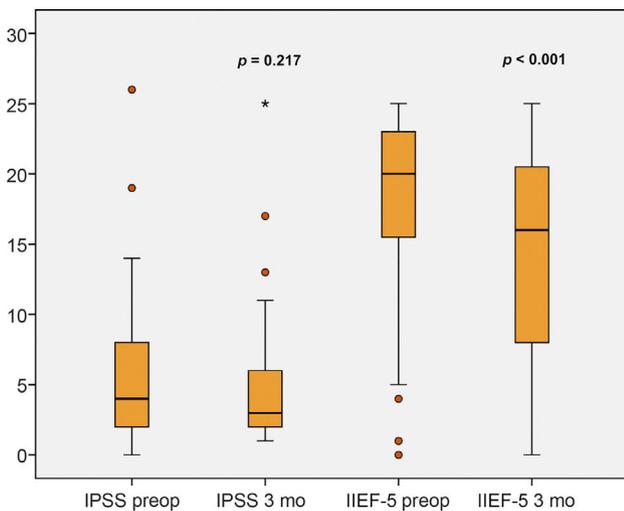


Fig. 3 – International Prostate Symptom Score and International Index of Erectile Function scores over the follow-up period. IIEF-5 = 5-item International Index of Erectile Function; IPSS = International Prostate Symptom Score; preop = preoperatively.

Table 2 – Contemporary outcomes on high-intensity focused ultrasound focal ablation for prostate cancer

Study	Patients, n	Mean preprocedural PSA	Mean prostate volume	Gleason score	Cancer localization	Mean follow-up	Biopsy recurrence	Continence, %	Potency
Ahmed et al (2011) [13]	20	7.3	NA	≤4 + 3	MRI and transperineal template-guided mapping biopsy	12 mo	11% at 6 mo	90	95%
El Fegoun et al (2011) [15]	12	7.3	37	≤4 + 3	TRUS biopsy	10 yr	8% at 1 yr	100	NA
Ahmed et al (2012) [14]	41	6.6		≤4 + 3	MRI and transperineal template-guided mapping biopsy	12 mo	23% at 6 mo	100	89%
Barret et al (2013) [16]	21	6	43	3 + 3	Transperineal template-guided mapping biopsy	12 mo	NA	100	Mean IIEF decreased from 20 to 19
Present study (2015)	67	6.1	36	≤3 + 4	MRI and TRUS biopsy	12 mo	16.4% at 1 yr	100	Mean IIEF decreased from 17.9 to 15.4

IIEF = International Index of Erectile Function; MRI = magnetic resonance imaging; NA = not available; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

factor in post-HIFU urinary retention. Although we did not perform statistical analysis, pretreatment TURP in large prostates can reduce urinary retention and improve treatment efficacy.

Another interesting finding of this study has not been reported in the literature previously. Significantly more positive control biopsies resulted following hemiablation of the right lobe than the left. We believe this trend of failure following right hemiablation might be related to the technical difficulties of the HIFU probe reaching the right side of the prostate, since patients lie on their left flank on the Ablatherm operating table; however, no statistical differences were found between the initial cancer location

in the treated area and the location of failure within the prostatic lobe. This finding needs verification in future studies with larger patient populations.

4.1. Clinical implications

The present study highlights the feasibility of tissue-preserving FT with acceptable tritector rates for PCA. Nonetheless, we understand that several key issues require standardization for routine use of FT in clinical practice. Accurate index lesion localization in terms of laterality and grade is vital for the success of FT. In our study, mp-MRI and TRUS biopsy were used, and Tables 2 and 3 show the

Table 3 – Comparison of outcomes among different energy modalities on high-intensity focused ultrasound hemiablation for prostate cancer

Study	Patients, n	Mean preprocedural PSA	Energy	Route of delivery	Gleason score	Cancer localization	Mean follow-up	Biopsy recurrence	Continence, %	Potency
Bahn et al (2006) [17]	31	4.9	Cryotherapy	Transperineal	≤7	Color Doppler ultrasonography with target and systemic biopsies	5.8 yr	4%	100	88.9%
Lambert et al (2007) [18]	25	6	Cryotherapy	Transperineal	≤7	TRUS biopsy	28 mo	1 patient treated of 7 biopsied patients	100	68%
Ellis et al (2007) [19]	60	7.2	Cryotherapy	Transperineal	3 + 3	TRUS biopsy	15.2 mo	23.3%	96	70.5%
Truesdale et al (2010) [20]	77	6.5	Cryotherapy	Transperineal	≤4 + 4	TRUS biopsy	24 mo	3 patient treated of 22 biopsied patients	100	NA
Bahn et al (2012) [21]	70	5.9	Cryotherapy	Transperineal	≤7	Color Doppler ultrasonography with target and systemic biopsies	3.7 yr	1 patient treated of 36 biopsied patients	100	86%
Cosset et al (2013) [22]	21	6.9	Brachytherapy	Transperineal	≤3 + 4	Saturation biopsy	12 mo	None of 6 patients biopsied had ipsilateral recurrence	100	Mean IIEF decreased from 20.1 to 19.8
Moore et al (2006) [23]	6	1.9–15	Photodynamic therapy	Transperineal	3 + 3	NA	NA	100%	NA	100%

IIEF = International Index of Erectile Function; NA = not available; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

localization techniques used in the previously published hemiablation series. Currently, mp-MRI appears to be a promising tool for accurate cancer detection, but real-time monitoring of FT appears to be technically demanding. Recent advances in multiparametric ultrasonography (shear wave elastography, contrast-enhanced ultrasound) will have interesting applications in FT for cancer localization and possibly real-time monitoring of therapy.

Presently, FT is often criticized as a psychological treatment for patients requiring active surveillance, with questionable oncologic control. Our series represents patients with longer MCCL and TCL and Gleason 7 (3 + 4) cancers. The early, encouraging oncologic control can potentially prompt the extension of FT to patients undergoing RP for small-volume, intermediate-risk PCa.

With regard to follow-up after primary HIFU with curative intent, we found that control biopsies and biochemical recurrence (BCR) were not systematically associated. The index lesion accounts for 80% of the PSA value, and the untreated insignificant satellite lesions, remaining prostate volume, and body mass index influence the postoperative PSA [24]. We believe BCR needs to be clearly defined, and both the Phoenix and the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria are of questionable value in FT. Recently, the Stuttgart definition (PSA increase of 1.2 ng/ml above the PSA nadir value) has been suggested for HIFU treatment [25]; however, this definition remains to be validated in prospective trials and seems difficult to use in so far as it has been established for the treatment of the whole prostate and does not take into account the residual PSA secretion from the untreated lobe.

The altered anatomy following FT limits the utility of imaging in follow-up. We strongly emphasize the need for systematic biopsies of both lobes at a 12-mo period for reliable cancer detection.

4.2. Limitations

First, the study size was relatively small, and the study was nonrandomized and had shorter follow-up. A larger study population with comparison of whole-gland treatment or radical treatment might have highlighted the specific advantages and drawbacks of HIFU hemiablation. Second, we used TRUS biopsy and MRI for index lesion localization, followed by control TRUS biopsies at 12 mo. Although this strategy was developed from previous experiences, we are still unaware of the percentage of significant disease missed; only longer follow-up will allow these cancers to surface. Third, the inclusion criteria resulted in involvement of low-volume, low-risk patients in FT; however, we included relatively larger cancers after encouraging early results. With the availability of MRI targeted biopsies, stringent inclusion criteria based on target and cancer core length with MRI grading will enable accurate reporting of the treated cancers.

4.3. Future directions

The emergence of FT as an intermediate treatment option between radical prostatectomy and active surveillance has

resulted in several energy modalities being developed (Table 3). Future research should focus on ultrafocal ablation of index lesions with maximal tissue preservation and reduction of the invasiveness of the therapy. The concept of the index lesion needs stronger validation, and genetic analysis should be explored as a potential guide for patient selection. Despite the high negative predictive value of mp-MRI, a few MRI-invisible, aggressive cancers can limit FT application. Improved reporting strategies like panel discussion and multiparametric ultrasonography fusion techniques for equivocal findings can potentially reduce errors. The role of imaging and PSA in follow-up should be critically analyzed and defined.

5. Conclusions

Focal HIFU hemiablation constitutes an attractive therapeutic alternative for selected patients with localized PCa. Our preliminary results are encouraging, as shown by the high efficacy rate along with low morbidity rates and minimal functional changes. Longer follow-up is expected to establish further considerations of this novel approach.

Author contributions: Eric Barret had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cordeiro Feijoo, Barret.

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