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Oncological Outcome and Value of Postoperative Magnetic Resonance Imaging after Focal High-Intensity Focused Ultrasound Therapy for Prostate Cancer

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Keywords
Prostate cancer · Focal therapy · High-intensity focused ultrasound · Magnetic resonance imaging

Abstract
Introduction: Focal therapy (FT) by high-intensity focused ultrasound (HIFU) is an emerging option for localized prostate cancer (PC). Due to the lack of long-term data, a close monitoring after FT is essential, but there are still uncertainties about the optimal follow-up regimen. Here we report on a series of FT-HIFU patients with the focus on oncological short-term outcome and the value of postoperative magnetic resonance imaging (MRI). ***Methods:*** We included 21 patients treated by FT-HIFU using the Focal One® device (EDAP TMS, France) between November 2015 and May 2018. PC localization was assessed by preoperative multiparametric MRI (mpMRI) and transrectal ultrasound-guided targeted and systematic biopsy. Oncological follow-up included prostate-specific antigen (PSA) development, mpMRI, control biopsies (targeted and systematic) of the treated and untreated areas and salvage treatment rate. Control mpMRI and control biopsy were performed after 6–12 months. ***Results:*** 15 patients (71.4%) were managed by focal ablation of a solitary lesion, while 6 patients (28.6%) underwent zonal tumor ablation. All patients underwent control mpMRI and biopsy. After a mean follow-up period of 11.7 months, cancer relapse was detected in 8 patients (38.1%), with 4 patients (19%) having infield recurrence. Postoperative mpMRI revealed 3 out of 4 infield PC relapses but missed 5 out of 7 outfield relapses. Clinically significant cancer recurrence was present in 1 patient (4.8%), which was missed by mpMRI. Posttreatment mpMRI had a sensitivity, specificity, positive and negative predictive value of 62.5, 92.3, 83.3 and 80.0%, respectively, for overall relapse detection based on patient level. Only 1 of the 8 recurrences was suspected based on PSA progression. 4 of the 8 patients with PC relapse (19%) underwent salvage therapy (2 patients by radical prostatectomy, 2 patients by salvage FT-HIFU). ***Conclusion:*** Postoperative mpMRI might play a valuable role during follow-up after focal HIFU therapy, particularly in terms of infield relapse detection. Irrespective of mpMRI results, the repeat biopsy regimen should incorporate systematic biopsy including cores of the treated and untreated prostate areas.

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Introduction

Focal therapy (FT) has been described as a feasible alternative for localized prostate cancer (PC) in the past years, especially for favorable risk stages [1]. The concept of FT has emerged given the fact that many patients with localized risk PC may experience over therapy and may oncologically not benefit from radical treatment. In the PIVOT and ProtecT trial, PC mortality was not reduced by local radical treatment [2, 3]. In contrast to radical whole gland treatment, FT is defined as any tissue-preserving approach aiming to reduce treatment-related toxicity while retaining oncological safety [4, 5]. Due to the lack of prospective trials with oncological long-term follow-up, there is no current guideline recommendation for FT to date. Hence, FT should be performed within a clinical trial setting [6].

Candidates considered for FT include not only patients with low-risk cancer not willing to undergo active surveillance but also patients who want to sidestep long-term side effects of radical treatment options (radical prostatectomy or radiotherapy). Regarding inclusion criteria, an international multidisciplinary consensus group determined patients with a prostate-specific antigen (PSA) <15 ng/mL, clinical stage T1c-T2a, and Gleason score max. 3 + 4 = 7a as eligible for clinical trials [7].

A key factor for FT is the exact localization of the tumor within the prostate. Therefore, preoperative multiparametric magnetic resonance imaging (mpMRI) of the prostate and prostate biopsy (including targeted biopsy) are essential. Several types of treatment strategies have been established. In case of unifocal or multifocal tumor localization, a lesion-targeted ablation can be performed. Unilateral tumor localization has been reported in approximately 20%, and in these cases, hemiablation seems to be a feasible option even when multifocal cancer within the same lobe is present [8, 9]. A further strategy for multifocal tumor growth may be the treatment of the so-called index lesion, which is supposed to be responsible for metastasis and disease progression [10].

Several focal treatment modalities have been described such as focal brachytherapy, electroporation, laser ablation, photodynamic therapy, cryotherapy, and high-intensity focused ultrasound (HIFU) [11]. Among these, HIFU is one of the few modalities with a decent amount of published data and even oncological long-term follow-up data for whole gland ablation [12]. Technically, HIFU is based on an ablative effect by high-intensity ultrasound waves inducing necrosis by cavitation and heat effects [13].

As oncological long-term safety of focal HIFU therapy (FT-HIFU) has yet to be proven, patients need to be counseled regarding stringent follow-up, the possibility of tumor relapse, and salvage therapy options. So far, there is no consistent follow-up concept established, and patients are monitored according to trial protocols. In this context, patients regularly raise the question of the necessity of prostate rebiopsy during follow-up, especially when postoperative MRI findings and PSA levels are without evidence of relapse.

Therefore, we evaluated the oncological outcomes after FT-HIFU, particularly focusing on the role of postoperative MRI for detection of tumor relapse.

Patients and Methods

Patient Selection and Preoperative Tumor Detection

Patients were selected and included during consultation hours in our department. FT was mainly offered to low- and early-intermediate-risk patients (PSA ≤15 ng/mL, Gleason score ≤7a) as recommended by consensus guidelines [7]. Few patients with higher-risk profiles were also treated according to their explicit wish. The study was performed following the approval of the local research Ethics Committee and written patient consent was taken. Patients with any previous PC therapy were excluded.

All imaging examinations were performed with a 3 Tesla MRI scanner. The mpMRI protocol consisted of axial, coronal, and transversal T2 turbo spin echo sequences, diffusion weighted imaging, and axial dynamic contrast-enhanced imaging. MRI data sets were evaluated by 2 experienced uroradiologists in consensus reading according to the Prostate Imaging – Reporting and Data System, version 2 (PI-RADS v2) 2015 [14].

Tumor localization was carried out by preoperative mpMRI of the prostate followed by targeted prostate biopsy if any PI-RADS 3–5 lesion was present (Urostation Touch®, KOELIS, France). Additionally, each patient received a systematic 12-core biopsy.

Before treatment, the following baseline parameters were recorded: age, total PSA, prostate volume estimated by transrectal ultrasound (TRUS), digital rectal examination, biopsy results, cancer localization within the prostate, and correlation with preoperative mpMRI findings.

Treatment and Follow-Up

Patients were treated by focal or zonal HIFU therapy using the semi-robotic Focal One® device (EDAP TMS, France) between November 2015 and May 2018. All treatments were performed in right lateral position under general anesthesia to exclude any patient movement. In a first step, mpMRI data sets with the lesion outlined were uploaded to the Focal One® device. TRUS images were automatically acquired by a prostate scan. The prostate was then contoured (TRUS + mpMRI data sets) to allow a software-based creation of a 3D model. The following elastic image fusion between the 2 imaging modalities allowed localization of the focal lesion (region of interest) in the TRUS images. In order to maximize treatment accuracy, the prostate mpMRI volume underwent an elastic 3D deformation to fit the prostate TRUS volume as close

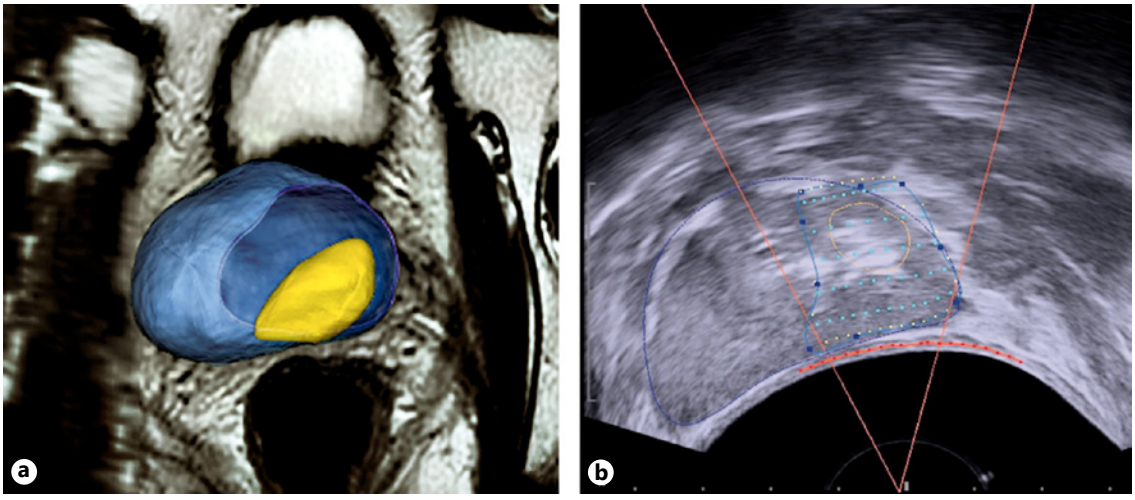

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Fig. 1. Biopsy-proven PC (yellow) within the left peripheral zone: planning of FT using mpMRI-TRUS-fusion (**a**), focal HIFU-treatment (**b**).

as possible (Fig. 1). In a second step, the ablation zone was planned including a safety margin of 10 mm around each focal lesion. The ablation process was continuously monitored by the surgeon and modified/interrupted if necessary. At the end of the procedure, an ultrasound-contrast enhancing agent was administered i.v. in order to enable a first gross judgment of the treated area by TRUS. Retreatment was applied to areas within the ablation zone that were still perfused.

Treatment-related adverse events were recorded according to the Clavien-Dindo classification.

A standardized follow-up protocol was used for all patients. The first follow-up visit was scheduled 1 month after therapy for clinical reevaluation. The initial oncological follow-up visit, including PSA monitoring, was scheduled after 3 months. Afterwards, PSA was monitored every 3 months. Repeat mpMRI was performed after 6–12 months followed by a targeted biopsy in case of any PI-RADS 3–5 lesion. In all cases, a systematic 12-core biopsy and additional cores from the treated area were taken. Only patients with control MRI and rebiopsy were included.

Statistical Analysis

For statistical analyses, SPSS, version 24.0 (Chicago, IL, USA), was used. Continuous variables are presented as the mean (SD) or median (interquartile range [IQR]), and categorical variables are presented as absolute numbers and percentages. Normal distribution was tested by Shapiro-Wilk test.

Results

A total of 21 patients with complete follow-up data were included into the statistical evaluation. Median age was 68.0 years, and median preoperative PSA was 8.3 ng/mL. Suspect digital rectal examination (all cT2a) was present in 3 patients (14.3%), and median preoperative prostate volume (estimated by TRUS) was 38.0 mL. Preoperative mpMRI revealed a PI-RADS 3–5 lesion in 20 patients, only 1 patient had no suspicious lesion. In total, 15 patients presented with a Gleason score 3 + 3 = 6 PC, 2 with a Gleason score 3 + 4 = 7a, and 4 with a Gleason score 4 + 3 = 7b PC. Taken together preoperative PSA, clinical T-stage, and Gleason score, 12 patients (57.1%) were low risk, 8 (38.1%) were intermediate risk, and 1 (4.8%) was high risk (PSA 24 ng/mL, Gleason score 3 + 4 = 7a) according to the d'Amico classification.

For baseline characteristics, see Table 1.

15 patients (71.4%) were managed by FT-HIFU of a solitary lesion. 6 patients (28.6%) were treated by zonal tumor ablation due to unilateral multifocal tumor growth. One patient without a PI-RADS 3–5 lesion on MRI received zonal ablation according to the tumor localization by systematic biopsy. Median treatment time (IQR) was 55 min (49–78). Median treated prostate volume (IQR) was 9.2 mL (7.5–10.6) and median treated volume ratio (IQR) 0.25 (0.20–0.32), respectively. Treatment data are shown in Table 2. A transurethral catheter was placed for 48–72 h depending on the treated prostate volume. No perioperative complications were observed.

At 3 months, 3 grade I and 1 grade IIIb complications were recorded. 3 patients experienced acute urinary retention after removal of the transurethral catheter (Clavien-Dindo grade I). One patient had to undergo TUR-P during follow-up due to bladder outlet obstruction (Clavien-Dindo grade IIIb). No infectious or rectal complica-

Table 1. Baseline characteristics

Number of patients	21
Age, years, median (IQR)	68.0 (62.0–73.0)
PSA/ng/mL, median (IQR)	8.3 (6.2–10.2)
DRE	
Suspect (≥ cT2a)	3/21 (all pT2a)
Negative (< cT2a)	18/21
TRUS prostate volume/mL, median (IQR)	38.0 (25.0–58.0)
IPSS, median (IQR)	7 (4–14)
Preoperative MRI	
PI-RADS 3–5 lesion present	20/21
Without PI-RADS 3–5 findings	1/21
Number of biopsy cores, median (IQR)	14 (10–16)
Number of positive biopsy cores, median (IQR)	2 (1–6)
Gleason score	
6	15/21
7a	2/21
7b	4/21
8–10	–
D'Amico risk classification	
Low risk	12/21
Intermediate risk	8/21
High risk	1/21

IQR, interquartile range; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; PI-RADS, Prostate Imaging-Reporting and Data System.

Table 2. Treatment data

Treatment strategy, *n* (%)	
Focal	15 (71.4)
Zonal	6 (28.6)
Treatment time, min, median (IQR)	55 (49–78)
No. of HIFU lesions per treatment, median (IQR)	213 (187–236)
Treated volume, mL, median (IQR)	9.2 (7.5–10.6)
Treated volume ratio: treated volume/prostate volume, median (IQR)	0.25 (0.20–0.32)

IQR, interquartile range; HIFU, high-intensity focused ultrasound.

tions (e.g., urethrorectal fistula) were reported. The majority of patients reported reduced ejaculation volume after treatment.

For follow-up data see Table 3. The mean follow-up period was 11.7 months. After 3 months, a mean PSA decrease to approximately 40% in relation to the preoperative PSA was detected and PSA levels remained stable at 6 and 12 months after therapy. Median PSA nadir was 2.3 ng/mL at a median time (IQR) of 6.0 months (3.0–12.0). Biochemical recurrence based on the Phoenix criteria (PSA nadir + 2 ng/mL) was present in 2 patients (9.5%), but both patients had a negative control mpMRI and negative rebiopsy results.

Overall histologically proven PC relapse was detected in 8 patients (38.1%) by rebiopsy. One was within the treated area (infield) only, 4 were outfield, and 3 patients showed both in- and outfield relapse. Accordingly, total infield relapse rate was 19.0%. Seven of the 8 relapses showed a Gleason score 3 + 3 = 6. One (initially low risk) patient experienced a high-risk tumor recurrence (Gleason score 4 + 4 = 8). All cancer core lengths were <3 mm.

Control mpMRI was performed in all patients (Fig. 2) and showed a PI-RADS 3–5 lesion in 6 cases (28.6%). Infield relapse was assumed in 1 patient, 4 relapses were assumed outfield, and 1 patient was assumed to have both in- and outfield relapses.

On patient level, postoperative MRI values for sensitivity, specificity, positive and negative predictive values were 62.5, 92.3, 83.3, and 80.0%, respectively. MRI missed recurrent cancer in 3 patients (overall false-negative rate 37.5%) with one being clinically significant.

Only one of the 8 recurrences was suspected based on PSA progression during follow-up, but this case was not a biochemical progress according to the Phoenix criteria.

Salvage therapy rate was 19% and was performed by radical prostatectomy (2 patients) or salvage FT-HIFU (2 patients). No patient underwent salvage radiotherapy. An active surveillance regimen was chosen by 4 patients with nonsignificant PC recurrence.

Discussion

FT is an emerging alternative for treatment of localized PC, which is also frequently chosen by patients potentially suitable for active surveillance. Among several treatment modalities, HIFU and cryosurgery are described in more detail by the current EAU guidelines as only these strategies provide a sufficient amount of data for initial judgment [6]. In contrast to whole gland HIFU, still limited data are available for focal HIFU therapy due to its recent development. The aim of the present study is to share our experiences focusing particularly on the role of mpMRI during the early follow-up stages.

Feasibility and Safety

According to our follow-up results, FT-HIFU is a feasible and functionally safe procedure. Three patients experienced acute urinary retention, but further surgical in-

Table 3. Follow-up data

Follow-up period, months mean (IQR)	11.7 (8–15)
PSA after 3/6/12 months, ng/mL, median	2.80/2.78/2.85
PSA after 3/6/12 months, %, mean	40.4/41.2/38.8
PSA nadir, ng/mL, median (IQR)	2.32 (0.84–3.80)
Time to PSA nadir/months, median (IQR)	6.0 (3.0–12.0)
Biochemical relapse/phoenix criteria	2/21 (both with negative repeat biopsy)
Postoperative MRI	
PI-RADS 3–5 lesion present	6/21 = 28.6%
In-field	1
Out-field	4
Both	1
Without PI-RADS 3–5 findings	15/21 = 71.4%
Repeat biopsy results	
Positive = relapse	8/21 = 38.1% (csPC 1/21 = 4.8%)
In-field	1
Out-field	4
Both	3
Negative = no relapse	13/21 = 61.9%
Value of MRI regarding repeat biopsy results (based on patient level)	
Sensitivity	5/8 = 62.5%
Specificity	12/13 = 92.3%
Positive predictive value	5/6 = 83.3%
Negative predictive value	12/15 = 80.0%
False negative	3/8 = 37.5%
False positive	1/13 = 7.7%
Infield relapse detection rate	3/4* = 75.0%
Outfield relapse detection rate	2/7* = 28.6%
Strategy in case of relapse (n = 8)	
Salvage treatment	4
Radiotherapy	–
Radical prostatectomy	2
Salvage FT-HIFU	2
Active surveillance	4

[#] csPC clinically significant prostate cancer.

* Three patients presented with both in- and outfield relapse.

IQR, interquartile range; IQR, interquartile range; PSA, prostate-specific antigen; PI-RADS, Prostate Imaging – Reporting and Data System; MRI, magnetic resonance imaging; FT-HIFU, focal therapy high-intensity focused ultrasound.

tervention by transurethral resection was only necessary in 1 patient (4.8%). No other local complications such as rectal bleeding, prostates, prolonged hematuria, or fistulae were observed. Similar findings were reported by other groups [15–18] where the need for transurethral intervention/resection was the only grade IIIb complication and occurred in 2–7% of the patients.

Oncological Results

Overall tumor relapse and infield relapse were present in 38% and 19% of the patients. With a Gleason score 3 + 3 = 6 and a cancer core length <3 mm, the majority of relapses were clinically nonsignificant as defined in a consensus meeting [19]. Only 1 patient (4.8%) experienced a significant recurrence. In the last years, several groups published their experiences providing varying and mostly limited sample sizes. Wide ranges of overall relapse rates (8–77%) and infield relapse rates (0–40%) have been reported [15–18, 20–27], and such data are not easy to compare as results depend on the treatment strategy (focal ablation, zonal ablation, multifocal ablation, hemiablation), inclusion criteria, different devices, and on varying rebiopsy strategies. Some groups, for example, performed only targeted biopsy of the treated area without systematic biopsy [15, 21, 23] or only TRUS-guided systematic biopsy (number of samples varying) without repeat MRI and targeted biopsy [16, 22, 24]. In contrast to other studies, rebiopsy results (including systematic +

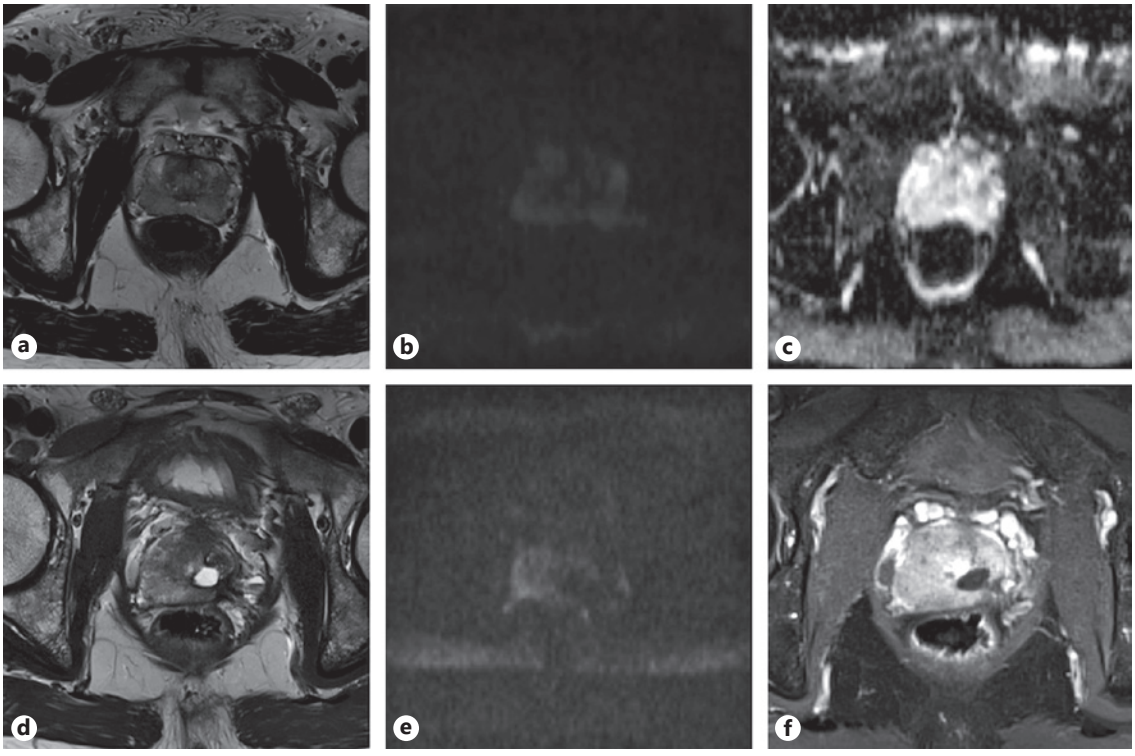

Fig. 2. Preinterventional MRI of a 72-year-old patient showing left-sided PI-RADS 4 lesion with indistinct hypointensity in T2-weighted images (**a**) with hyperintensity in diffusion-weighted imaging (**b**) and correlating hypointensity in acquired-diffusion-coefficient map (**c**). Postinterventional MRI showed shrinking of the treated area with a small cystic defect with hyperintensity in T2-weighted imaging (**d**). There were no hyperintensities in postinterventional diffusion-weighted imaging (**e**). Postinterventional contrast-enhanced imaging showed well-demarcated ablation defect with surrounding hyperemia (**f**).

targeted cores) were available for all included patients of our cohort.

More recently, the first medium-term oncological results on larger collectives were published and showed promising results regarding failure-free/retreatment-free survival, metastasis-free survival, cancer-specific, and overall survival [26, 27]. In contrast to many other series, these studies notably included not only patients at low or early intermediate risk but also a higher rate of patients with intermediate- and high-risk profiles. Nevertheless, the reported relapse rates are comparable to our results. Table 4 summarizes important strategies and findings of previous series. Our results with the Focal One® device are basically within the range of the cited studies and by all means not discouraging as the vast majority of relapses were clinically insignificant.

Regarding postoperative PSA development, we observed similar results compared to previous studies [16, 17]. The PSA level postoperatively declined below 50% after 3 months and basically remained stable afterwards. Around 10% of our patients showed a biochemical recurrence according to the Phoenix criteria (PSA nadir + 2 ng/mL), but none of them showed a cancer recurrence in rebiopsy. In contrast, 1 patient with PSA progression not fitting the Phoenix criteria had a PC relapse. Obviously, the available criteria for whole gland treatment are hardly suitable to define treatment failure and to trigger rebiopsy after FT as postinterventional PSA levels depend on the amount of remaining prostatic tissue. Accordingly, this implicates a more important role of mpMRI during follow-up.

Role of MRI and Clinical Implications

The tumor ablation by HIFU causes necrosis and fibrotic changes within the prostate, which can be visualized by MRI. Previous studies described that immediately after HIFU ablation, the ablation zone can be depicted on contrast-enhanced images as a devascularized zone surrounded by a rim of enhancement due to inflammation. After some months, the necrotic tissue gets replaced by fibrosis, and the described changes gradually disappear with loss of rim enhancement and shrink-

Table 4. Comparison of oncological outcomes after FT-HIFU from selected series

Author	Device	Strategy	Patients included, *n*	Patients with rebiopsy, *n*	Repeat biopsy regimen	Any relapse, %	Infield relapse, %	csPC relapse any location, %	Follow-up, months, mean/median
Our series	Focal One®	Focal	21	21	SB + TB	38	19	5	12
Von Hardenberg et al. [25], 2018	Focal One®	Focal	24	20	SB + TB	50	40	5–25*	18
Ahmed et al. [15], 2015	Sonablate®	Focal	56	52	TB	42	35	19	12
Ahmed et al. [23], 2012	Sonablate®	Focal	41	39	TB	23	23	8	12
Stabile et al. [26], 2019	Sonablate®	Hemiablation/focal/	1,032	424	SB or TB	77	NR	25	36
Guillaumier et al. [27], 2018	Sonablate®	Hemiablation/focal/	625	222	SB or TB	25	18	NR	56
Ganzer et al. [18]	Focal One®/ Ablatherm®	Hemiablation	54	49	SB + TB	61	27	10	17
Rischmann et al. [17], 2017	Ablatherm®	Hemiablation	111	101	SB + TB	33	14	12	30
Feijoo et al. [16], 2016	Ablatherm®	Hemiablation	71	67	SB	25	16	NR	12
Van Velthoven et al. [24], 2014	Ablatherm®	Hemiablation	31	5#	SB	11#	NR	NR	38

* Depending on definition of clinically significant.
# Only patients with PSA progression received repeat biopsy.
FT-HIFU, focal therapy high-intensity focused ultrasound; csPC, clinically significant prostate cancer; SB, systematic biopsy; TB, targeted biopsy; NR, not reported.

age of the ablation zone. At this stage, imaging techniques such as dynamic contrast enhanced may be able to distinguish residual tumor or relapse from regular post-HIFU effects [28–30]. Thus, post-HIFU mpMRI combined with targeted biopsies must be seen as a promising supplemental follow-up modality compared to solely PSA-triggered follow-up and "blind" control biopsies. By correlating the imaging findings with the control biopsy results, we aimed to get further insights into this issue.

Our data revealed a high false-negative rate of 37.5% for overall relapse and, moreover, the only clinically significant relapse was missed by post-HIFU mpMRI. As most of the observed relapses were Gleason 3 + 3 = 6 cancers, this is in line with the well-known fact that mpMRI only detects a limited amount of clinically insignificant cancers [31]. On the other hand, it is known that only about 10% of clinically significant cancers are missed by mpMRI of the prostate [32], but our limited sample size with only one significant relapse can understandably not reproduce these data of large collectives. While sensitivity for overall relapse detection in our study was low (62.5%), the performance at infield relapse detection (sensitivity 75%) was somewhat higher suggesting a potentially more valuable role for MRI in this context. Previously, only few studies reported details on control MRI results and the correlation to the rebiopsy results. Ganzer et al. [18] observed false-negative MRI results in 29.4% of the cases after hemiablation of the prostate, which is consistent with our findings, and sensitivity for clinically significant relapse was 25%. Moreover, they found an only 40% PPV of MRI for overall cancer relapse compared to the 83.3% in our study [18]. This might be based on varying definitions for positive mpMRI results as in their study only PI-RADS 4 or 5 lesions were defined as suspicious. More recently, von Hardenberg et al. [25] reported a poor MRI performance after focal/zonal therapy. Here, a positive control MRI (PI-RADS 5 lesion) was present in only one of 23 cases with a sensitivity for clinically significant recurrence of 25% [25]. A comprehensive analysis concerning the value of postoperative MRI and PSA for relapse detection was performed by Dickinson et al. [33] They reported a significantly superior performance of mpMRI (performed at 6 months after therapy) in detecting clinically significant cancer relapse compared to PSA nadir and 6-months PSA. In particular, mpMRI showed a high negative predictive value of over 95%, while positive predictive value was low [33]. While providing important conclusions for potential follow-up strategies, no subgroup analyses separating in- and outfield relapses were provided.

We believe that further reports on postoperative mpMRI performances are desirable in order to optimize follow-up regimens and patient counseling. These should include significant and insignificant relapse detection as well as the region of disease recurrence. As suggested by our data, mpMRI might have a potentially valuable role for infield relapse detection. In contrast, the weaker MRI performance for outfield relapse detection underlines the need for additional systematic control biopsy during follow-up irrespective of MRI results.

It has to be kept in mind that still many patients choose FT in low-risk cases when active surveillance could be ap-

plied. For these patients, even insignificant relapse may be relevant from a psychological point of view and may therefore influence further strategies.

Taken together our findings and those of previous studies, we propose that a reasonable follow-up regimen should comprise regular PSA testing (e.g., every 3months) and repeat mpMRI schedule at 6–12 months after treatment followed by control biopsy. We think that rebiopsy should still include both the treated area and systematic biopsy of the untreated prostate areas irrespective of a negative control MRI. Despite the fact that the majority of relapses in our collective were not significant, we think that the long-term follow-up regimen and patient counseling might turn out easier.

Limitations

Like some previous reports to this topic, our study also provides data of a limited number of patients with a limited follow-up period and only one clinically significant relapse. Nevertheless, it is essential to share all available results to gain further insights into the safety and efficacy of FT-HIFU as well as the value of mpMRI during follow-up.

Moreover, we do not provide detailed functional data as this was beyond the scope of this study. Despite being a noninvasive treatment alternative, FT-HIFU might possibly have long-term side effects, which are similar to those reported for whole gland ablation. These may include bladder outlet obstruction, rectourethral fistula, stress urinary incontinence, and erectile dysfunction [12]. Although long-term data are still lacking, it is tempting to speculate that side effects might be less frequent or intense after FT because of the lower volume of ablated tissue. Published functional mid-term data strengthen this assumption [27].

Conclusion

MRI might have the ability to play a valuable role during follow-up after focal HIFU therapy, particularly in terms of infield relapse detection and optimal timing of rebiopsy. Irrespective of postoperative MRI results, the repeat biopsy regimen should incorporate systematic biopsy including cores of the treated and untreated prostate areas.

Statement of Ethics

The study was performed following the approval of the local research Ethics Committee and informed consent (reference number: 7/10270; Ethics Committee, BLÄK, 81677 Munich, Germany).

Disclosure Statement

J.B.: serves as a paid instructor for EDAP-TMS. The other authors declare to have no conflicts of interest.

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Author Contributions

B.R., C.N., M.B., and J.B.: study concept and design. B.R., C.N., J.R., L.R., and J.B.: acquisition of data. B.R., C.N., and J.B.: analysis and interpretation of data. B.R., C.N., and J.B.: drafting of the manuscript. L.R., J.R., M.J.S., and M.B.: critical revision of the manuscript for important intellectual content. B.R. and M.J.S.: statistical analysis. J.B. and M.B.: supervision.

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. Eur Urol. 2014 Oct;66(4):732–51.
2 Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017 Jul;377(2):132–42.
3 Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al.; ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016 Oct;375(15):1415–24.
4 Lindner U, Trachtenberg J, Lawrentschuk N. Focal therapy in prostate cancer: modalities, findings and future considerations. Nat Rev Urol. 2010 Oct;7(10):562–71.
5 Eggener S, Salomon G, Scardino PT, De la Rosette J, Polascik TJ, Brewster S. Focal therapy for prostate cancer: possibilities and limitations. Eur Urol. 2010 Jul;58(1):57–64.
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. Eur Urol. 2017 Apr;71(4):618–29.
7 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. Eur Urol. 2014 Jun;65(6):1078–83.
8 Mouraviev V, Mayes JM, Sun L, Madden JF, Moul JW, Polascik TJ. Prostate cancer laterality as a rationale of focal ablative therapy for the treatment of clinically localized prostate cancer. Cancer. 2007 Aug;110(4):906–10.
9 Nevoux P, Ouzzane A, Ahmed HU, Emberton M, Montironi R, Presti JC Jr, et al. Quantitative tissue analyses of prostate cancer foci in an unselected cystoprostatectomy series. BJU Int. 2012 Aug;110(4):517–23.
10 Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med. 2009 Oct;361(17):1704–6.

11 Kasivisvanathan V, Emberton M, Ahmed HU. Focal therapy for prostate cancer: rationale and treatment opportunities. Clin Oncol (R Coll Radiol). 2013 Aug;25(8):461–73.
12 Ganzer R, Fritsche HM, Brandtner A, Bründl J, Koch D, Wieland WF, et al. Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer. BJU Int. 2013 Aug;112(3):322–9.
13 Chaussy CG, Thüroff S. High-Intensity Focused Ultrasound for the Treatment of Prostate Cancer: A Review. J Endourol. 2017 Apr;31(S1):S30–7.
14 Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol. 2016 Jan;69(1):16–40.
15 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. Eur Urol. 2015 Dec;68(6):927–36.
16 Feijoo ER, Sivaraman A, Barret E, Sanchez-Salas R, Galiano M, Rozet F, et al. Focal High-intensity Focused Ultrasound Targeted Hemiablation for Unilateral Prostate Cancer: A Prospective Evaluation of Oncologic and Functional Outcomes. Eur Urol. 2016 Feb;69(2):214–20.
17 Rischmann P, Gelet A, Riche B, Villers A, Pasticier G, Bondil P, et al. Focal High Intensity Focused Ultrasound of Unilateral Localized Prostate Cancer: A Prospective Multicentric Hemiablation Study of 111 Patients. Eur Urol. 2017 Feb;71(2):267–73.
18 Ganzer R, Hadaschik B, Pahernik S, Koch D, Baumunk D, Kuru T, et al. Prospective Multicenter Phase II Study on Focal Therapy (Hemiablation) of the Prostate with High Intensity Focused Ultrasound. J Urol. 2018 Apr;199(4):983–9.
19 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. Eur Urol. 2015 Apr;67(4):771–7.
20 Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Horie S. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol. 2008 Mar;38(3):192–9.
21 Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol. 2011 Apr;185(4):1246–54.
22 El Fegoun AB, Barret E, Prapotnich D, Soon S, Cathelineau X, Rozet F, et al. Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. Int Braz J Urol. 2011 Mar-Apr;37(2):213–9.
23 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 Jun;13(6):622–32.
24 Van Velthoven R, Aoun F, Limani K, Narahari K, Lemort M, Peltier A. Primary Zonal High Intensity Focused Ultrasound for Prostate Cancer: Results of a Prospective Phase IIa Feasibility Study. Prostate Cancer. 2014;2014:756189.
25 von Hardenberg J, Westhoff N, Baumunk D, Hausmann D, Martini T, Marx A, Porubsky S, Schostak M, Michel MS, Ritter M: Prostate cancer treatment by the latest focal HIFU device with MRI/TRUS-fusion control biopsies: A prospective evaluation. Urol Oncol 2018;36:401 e401-401.e409.
26 Stabile A, Orczyk C, Hosking-Jervis F, Giganti F, Arya M, Hindley RG, et al. Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer. BJU Int. 2019, Epub ahead of print.
27 Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. Eur Urol. 2018 Oct;74(4):422–9.
28 Kirkham AP, Emberton M, Hoh IM, Illing RO, Freeman AA, Allen C. MR imaging of prostate after treatment with high-intensity focused ultrasound. Radiology. 2008 Mar;246(3):833–44.
29 Rouvière O, Lyonnet D, Raudrant A, Colin-Pangaud C, Chapelon JY, Bouvier R, et al. MRI appearance of prostate following transrectal HIFU ablation of localized cancer. Eur Urol. 2001 Sep;40(3):265–74.
30 Rouvière O, Girouin N, Glas L, Ben Cheikh A, Gelet A, Mège-Lechevallier F, et al. Prostate cancer transrectal HIFU ablation: detection of local recurrences using T2-weighted and dynamic contrast-enhanced MRI. Eur Radiol. 2010 Jan;20(1):48–55.
31 Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019 Apr;4:CD012663.
32 Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al.; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017 Feb;389(10071):815–22.
33 Dickinson L, Ahmed HU, Hindley RG, McCartan N, Freeman A, Allen C, et al. Prostate-specific antigen vs. magnetic resonance imaging parameters for assessing oncological outcomes after high intensity-focused ultrasound focal therapy for localized prostate cancer. Urol Oncol. 2017 Jan;35(1):30.e9–15.