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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

MRI-guided focal laser ablation of prostate cancer: a prospective single-arm, single-center trial with 3 years of follow-up

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PURPOSE
We aimed to assess post-interventional and 36-month follow-up results of a single-center, single-arm, in-bore phase I trial of focal laser ablation (FLA) guided by multiparametric magnetic resonance imaging (mpMRI).

METHODS
FLA procedures were done in-bore MRI using a transperineal approach. Primary endpoints were feasibility and safety expressed as lack of grade 3 complications. Secondary endpoints were changes in international prostate symptom score (IPSS), sexual health inventory for men (SHIM), quality of life (QoL) scores, and serum prostate specific antigen (PSA) levels. Treatment outcomes were assessed by combined mpMRI-ultrasound fusion-guided and extended sextant systematic biopsy after 12, 24, and optionally after 36 months.

RESULTS
Fifteen participants were included. Seven patients (46.67%) had Gleason 3+3 and 8 patients (53.33%) had Gleason 3+4 cancer. All patients tolerated the procedure well, and no grade 3/4 complications occurred. All grade 1 and 2 complications were transient and resolved completely. There was no significant change in mean IPSS from baseline (-1, $p = 0.460$) and QoL (0, $p = 0.441$) scores following FLA but there was a significant drop in mean SHIM scores (-2, $p = 0.010$) compared to pretreatment baselines. Mean PSA significantly decreased after FLA (-2.5, $p < 0.001$). Seven out of 15 patients (46.67%) had residual cancer in, adjacent, or in close proximity to the treatment area (1 × 4+3=7, 1 × 3+4=7, and 5 × 3+3=6). Four out of 15 patients (26.67%) underwent salvage therapy (2 repeat FLA, 2 radical prostatectomy).

CONCLUSION
After 3 years of follow-up we conclude focal laser ablation is safe and feasible without significant complications.

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Since the introduction of population-based prostate specific antigen (PSA) screening, there has been an increase in the detection of prostate cancer (PCa) which is often low or intermediate grade (1). The proven benefit for PSA screening in improving cancer-specific survival comes at the cost of over-diagnosis and over-treatment of low-risk PCa, with significant treatment-related morbidity (2). To counteract this, active surveillance is becoming a widely practiced standard of care treatment option for certain low-risk PCa patients, with excellent long-term survival. Up to one-third of patients drop off active surveillance protocols because they are no longer comfortable with surveillance and opt for definitive treatment (3). Meanwhile, there is growing evidence that more patients with tumors deemed "intermediate-risk" receive unnecessary radical treatments based on the indolent biology of their tumors (4). Thus, there is a growing interest in alternatives to whole-gland definitive therapies for low-to-intermediate risk PCa.

PCa lesions can be visualized at mpMRI and targeted for biopsy (5, 6). Focal therapy with different ablative methods has the potential to be an alternative for low-risk and selected intermediate-risk patients (7, 8). mpMRI-guided focal laser ablation (FLA) in which thermal laser energy is applied to lesions to achieve coagulation necrosis has advantages such as having homogeneous tissue necrosis with sharp margins between dead and uninjured tissue, real-time MRI thermometry monitoring and rapid ablation times (9). Prior focal ther-

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apy trials demonstrated good functional outcomes for continence and potency, although longer follow-up data are still missing (10–13). In this study, we aimed to assess the feasibility, safety and efficacy of mpMRI-guided FLA, and report on 3-year functional and oncologic outcomes.

Methods

Study design

This is a prospective, non-randomized, unblinded, single-center, clinical trial (ClinicalTrials.gov identifier NCT01377753) with Institutional Review Board approval (approval number 11-C-0158) enrolling men with organ-confined PCa between August 2011 and May 2013. Fifteen patients were planned for trial enrollment. Informed consent was obtained from all patients. The primary objective was to assess the feasibility and safety of FLA for focal low-to-intermediate grade PCa. Secondary objectives included the assessment of functional outcomes via international prostate symptom score (IPSS), sexual health inventory for men (SHIM), international index of erectile function (IIEF-5), and quality of life (QoL) questionnaires and oncological outcomes measured by changes in PSA values and annual MRI-transrectal ultrasound (TRUS) fusion-targeted biopsies.

Inclusion criteria were organ-confined clinical stage T1c or T2a, 1 or 2 visible lesions on mpMRI, Gleason score ≤3+4=7 (Grade 2), ≤3 cores positive in a standard 12-core biopsy or ≤4 cores positive on mpMRI image-guided biopsy with 2 cores from each MRI-lesion, PSA<15 ng/mL or PSA density (defined as PSA/prostate volume) <0.15 in patients with PSA>15 ng/mL and negative metastatic workup as suggested by NCCN guidelines (14). In patients where standard biopsy cores were positive, these had to be from same sextant in the prostate as the MRI lesion(s). Exclusion criteria were the presence of >2 MRI-visible lesions, extracapsular extension, seminal vesicle invasion or metastatic disease, contraindications for MRI, acute urinary tract infection (UTI), severe lower urinary tract symptoms defined as an IPSS >20, estimated GFR ≤30 mL/min, uncontrolled coagulopathies, altered mental status, and other serious illnesses. Patients with a positive standard 12 core biopsy and no corresponding MRI targeted lesion were not eligible.

Main points

- In-bore MRI-guided focal laser ablation is a safe and feasible treatment method.
- Mid-term follow-up results indicate a residual or recurrent disease rate of 47% (7/15) in our series.
- Further research is needed to better understand the oncologic utility of MRI-guided focal laser ablation in prostate cancer.

Laboratory evaluations including serum PSA, complete blood count, urinalysis, urine culture, chemistry, coagulation profile and questionnaires were performed at 3, 6, 12, 18, 24, and 36 months. Repeat mpMRI was done for assessment of tissue changes as well as residual or recurrent disease at 6, 12, 18, 24, and 36 months. Pathologic evaluation of recurrent diseases with MRI-TRUS fusion-targeted, systematic biopsy was performed at 12, 24, and optional at 36 months (12/15). In case of residual cancer, defined as any cancer in the treatment area, a repeat salvage FLA was offered.

FLA procedures

The commercially available Visualase® platform was used in this study. A solid acrylic guide template (Visualase Inc, now owned by Medtronic) with 13 × 13 holes (spaced in a square grid with 5 mm center-to-center spacing) was placed against the patient's perineum. A 15 W 980 nm diode laser provided energy for the laser ablation which was monitored by magnetic resonance communication using the Visualase® MRI thermometry software. All cases were done in-bore MRI in lithotomy position after inserting a 16 F Foley catheter in the bladder. The first 5 patients were treated in a 1.5 T intraoperative scanner (Achieva, Philips). However, the fifth patient's lesion could not be well visualized on the 1.5 T scanner, and procedure was repeated on the following day with a 3 T magnet. Remaining 10 patients were treated in a 3 T scanner (Achieva, Philips). All ablation procedures were performed by a joint team of an interventional radiologist (>10 years of experience on image-guided ablation procedures and image-guided prostate interventions; e.g., biopsy) and a urologist (>10 years of experience on image-guided prostate interventions; e.g., biopsy).

Statistical analysis

Patient reported outcomes (IPSS, SHIM, and QoL) and PSA were measured at baseline and for each follow-up visit. To account for interpatient heterogeneity in the longitudinal profiles of these variables and to remove the influence of salvage treatment some patients received during the follow-up, estimators characterizing longitudinal changes prior to receipt of salvage treatment, or until the end of follow-up if there was no salvage treatment, were calculated for patient-reported outcomes. These per patient estimators were used to test against the null hypothesis of no change from baseline via the one-sample Wilcoxon rank test. All p values were two-sided and p values < 0.05 were considered statistically significant. All analyses were conducted using R.3.6.1 (R Foundation for Statistical Computing).

Results

Fifteen men were included in our study. Median age was 66 years (range, 47–75 years) and median PSA was 6.19 ng/mL (range, 2.16–14.5 ng/mL) prior to intervention. Gleason score was 3+3=6 (Grade 1) in 6 patients (40%) and 3+4=7 (Grade 2) in 9 patients (60%). Clinical stage assessed by digital rectal examination showed cT1c in 14 patients and cT2a in one patient. One patient had prior therapy for PCa (Patient 9, brachytherapy). Detailed patient demographics, baseline clinical data are summarized in Table 1.

Total ablation time per patient varied between 4 min and 36 min. The number of ablations performed depended on the size and location of the target lesions and varied between 3 and 14 per patient. Ablation power varied between 10.5 and 15 W. Maximum applied temperature varied between 50°C and 100°C. Mean overall procedure time from beginning to end of anesthesia was 4 h 43 min (range, 3 h 7 min to 7 h).

There were no serious complications during or after the procedure. Four patients had grade 1 adverse events: hematuria (n=2), urgency problems (n=1) and postoperative fever without proof of bacterial infection or sepsis (n=1). Two patients had more than one grade 1 adverse event: hematuria and bladder spasms (n=1), small transient pressure ulcer and a short episode of gross hematuria (n=1). Four patients had grade 2 adverse events: UTI with need for antibiotic therapy for 4 weeks (n=1), bilateral epididymitis and gross hematuria with 7 days of antibiotics and complete response (n=1), lower urinary tract symptoms with improvement after 3 weeks of tamsulosin (n=1), acute bacterial prostatitis and acute urinary retention with complete remission after catheterization and antibiotic course (n=1).

Table 1. Patient characteristics prior to treatment

Pt	Age	PSA (ng/mL)	Clinical stage	# of MRI lesions	Location of lesions	Gleason score	Tumor diameter (cm)	Tumor volume (cm^3)	Distance to urethra (cm)
1	58	14.5	cT1c	1	R mid-anterior TZ	3+3	1.3	0.77	1
2	71	9.2	cT1c	1	R mid-anterior TZ	3+4	1.7	1.14	1.5
3	65	7.6	cT1c	1	L apical anterior PZ	3+4	1.4	0.61	0.5
4	66	7.8	cT1c	1	R mid-anterior TZ	3+3	1.2	0.55	1.3
5	58	9	cT1c	1	R base PZ	3+4	0.7	0.19	2
6	47	4	cT1c	1	R mid TZ	3+3	0.7	0.54	0.8
7	66	4.5	cT1c	2	L apical anterior TZ & R apical anterior PZ	3+3	0.9 & 1	0.52 & 0.27	0.6 & 0.9
8	75	6.2	cT1c	1	L mid-base anterior TZ	3+4	2.6	2.7	2.4
9	62	2.2	cT1c	1	M mid-base TZ	3+3	1.2	0.44	0.2
10	62	14.5	cT1c	1	L apical PZ	3+4	0.6	0.48	0.3
11	62	5.3	cT2a	1	Left apical PZ	3+4	1.1	0.25	0.4
12	57	2.7	cT1c	1	M apical anterior PZ	3+3	1	0.63	0.2
13	71	5.8	cT1c	1	R apical anterior TZ	3+4	1.7	3.27	0.3
14	68	6.2	cT1c	1	R apical-mid anterior TZ	3+4	2.8	2.61	0.8
15	70	6.1	cT1c	1	R base PZ	3+3	1.1	0.31	1.2

Pt, patient; PSA, prostate specific antigen; MRI, magnetic resonance imaging; R, right; L, left; TZ, transition zone; PZ, peripheral zone; M, midline.

Table 2. Per patient mean change from baseline over follow-up visits* for all 3 questionnaire scores and PSA

Patient	Recurrence	Follow-up visit of reported recurrence (months)	Salvage/ additional treatment	Time to salvage treatment (months)	IPSS	SHIM	QoL	PSA
1	Yes	12	Yes	58	4.8	-0.2	0.5	-2.9
2	Yes	24	Yes	33	-0.2	-6	0.2	-1.8
3	No		No		-1.4	-1.2	0.2	-6.6
4	Yes	36	Yes	51	-3.8	-2.6	0	-4
5	No		No		2.6	-1	0.2	-3.1
6	Yes	12	Yes	25	-0.7	2.3	0.3	-1.9
7	Yes	12	No		-1.3	-5	-0.7	0.8
8	No		No		-2.3	0	NA	-2.7
9	No		No		-0.5	-0.3	0.5	-1.8
10	No		No		2	0	0.3	-2.7
11	No		No		-6	-1.2	0.8	0
12	Yes	36	No		0.8	-1.5	0.8	-0.9
13	No		No		-10.2	-4.6	-1.6	-5.1
14	No		No		1.3	-1.7	0.3	-4.8
15	Yes	12	Yes	20	0.3	-7.7	-1.3	0.9

IPSS, international prostate symptom score; SHIM, sexual health inventory for men; QoL, quality of life; PSA, prostate specific antigen.
*Mean change from baseline over follow-up visits prior to salvage treatment or across all follow-up visits if there was no salvage treatment.

No patient experienced incontinence after the procedure. Baseline measurements are given in Table 2 and Fig. 1. Per patient longitudinal changes from baseline of IPSS, SHIM, QoL, and PSA are given in Fig. 2 and exhibited large inter-patient variability. Seven patients had recurrence and two patients received salvage FLA treatments at 33 months and 20 months, respectively. Because no time trend was observed in the outcome variables, longitudinal changes for each patient were characterized by mean change from baseline. Per patient and overall mean change for each outcome measure demonstrated a large variability as displayed in Table 2 and plotted in Fig. 3. There was large variability in mean change. Notably, SHIM scores significantly decreased at follow-up

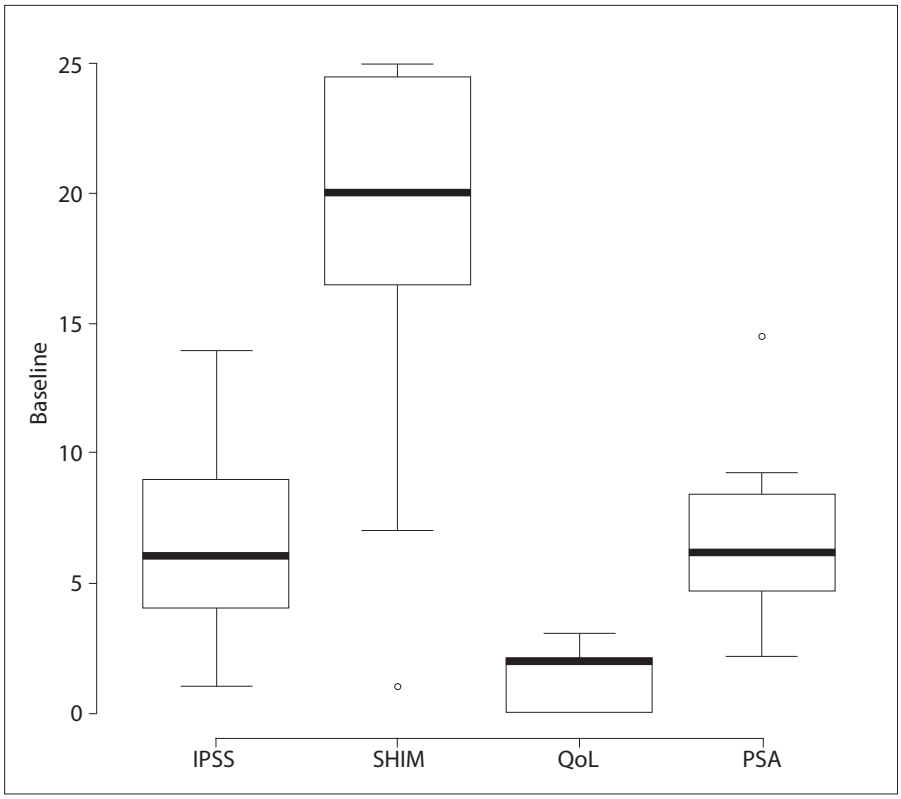

Figure 1. Box and whisker plots of IPSS, SHIM, QoL scores and PSA level at baseline. IPSS, international prostate symptom score; SHIM, sexual health inventory for men; QoL, quality of life; PSA, prostate specific antigen.

compared to baseline ($p = 0.010$). While PSA level was significantly lower at follow-up than at baseline ($p < 0.001$), change in PSA mainly occurred during the first 3 months after the focal therapy ($p < 0.001$). There was no significant difference in PSA at 3 months vs. after 3 months ($p = 0.653$).

Twelve patients (80%) opted to undergo another optional biopsy session 36 months after FLA (Fig. 4). Overall, 8 patients (53.33%) were cancer-free in the treatment area after FLA. However, two of these patients had Gleason 3+3 = 6 (Grade 1) diagnosed outside the treatment area including Patient 9 who was status post failed brachytherapy prior to study inclusion. Those patients were referred to their primary caregiver after their last biopsy for continuation of surveillance. Of the 7 patients with residual cancer (46.66%), 5 had Gleason 3+3=6 (Grade 1), one Gleason 3+4=7 (Grade 2) and one Gleason 4+3=7 (Grade 3). The patient with two treated lesions had residual Gleason 3+3=6 (Grade 1) PCa within both lesions. Furthermore, two patients had additional Gleason 3+3=6 (Grade 1) PCa outside the treatment area.

Patient 1 underwent holmium laser enucleation due to worsening lower urinary tract symptoms 58 months after FLA. Although he also had in-field residual disease he did not undergo salvage treatment and was placed on active surveillance. Patient 2 underwent salvage FLA for the right mid anterior transition zone lesion 33 months after the initial treatment. However, due to worsening lower urinary tract symptoms he underwent simple prostatectomy 8 months later. There was no PCa in his final histopathology specimen. Patient 4 had Gleason 4+3 (Grade 3) in 2 cores. This patient was included in a separate neoadjuvant vaccination trial (NCT02326805). After six vaccine injections the patient underwent robot-assisted radical prostatectomy (RARP) 53 months after his initial FLA treatment. Final histopathology was pT2c, N0, R0, Gleason 3+4 (Grade 2), with no Gleason 4+3 found. Patient 6 underwent RARP 25 months after his initial FLA treatment. Final histopathology was pT2c, N0, R1, Gleason 3+4 (Grade 2, 35% left, 8% right). Patient 15 had salvage FLA 20 months after his initial treatment. In two subsequent systematic and targeted biopsies there was no residual cancer in the field of treatment after 1 and 3 years, respectively. However, his first biopsy demonstrated one positive systematic core on the treated side remote from the target with minor Gleason 3+3=6 (Grade 1). Patient 7 had two FLA sessions for two different lesions since both lesions could not be ablated in one session. After both lesions proved positive for Gleason 3+3=6 (Grade 1) on post-FLA follow-up he was put on an active surveillance protocol. The remaining patient with in-field residual disease is also on active surveillance outside our institution.

Discussion

Several phase I and II studies have demonstrated early safety and feasibility of FLA with excellent functional results. However, these studies only report immediate post-interventional results or short-term follow-up (10, 13). The primary endpoint of our study was achieved since there were no more than grade 2 adverse events. No patient had postinterventional incontinence and there was no significant change in IPSS and QoL scores after 36 months of follow-up. However, there was a significant drop in SHIM scores and 7 out of 15 patients (46.66%) had residual cancer in the treatment area. One patient recurred with Gleason 4+3 (Grade 3) intermediate-risk disease. Four out of 15 patients (26.66%) needed salvage treatment because of residual/recurrent disease. Two patients underwent a second FLA session and 2 patients RARP with one patient being included in our neoadjuvant Enzalutamide-androgen deprivation therapy (ADT)-RARP trial. All other patients continue to be surveilled based on their low-risk profile.

While there were multiple in-field recurrences, several patients also had cancer detected in areas remote to the ablation. Most likely, these cancers correspond to incidental multifocal PCa lesions that were not detected prior to therapy. Although these are usually low risk cancers, surveillance of these patients is still necessary. Second, the goal of focal therapy of PCa is to treat the MRI visible lesions with Gleason score ≤3+4=7 (Grade 2). With up to 80% of PCa being multifocal, some argue that focal therapy of PCa is theoretically contraindicated since there is a high risk of leaving smaller tumors behind. However, with better understanding of PCa biology it is understood now that PCa metastases are typically

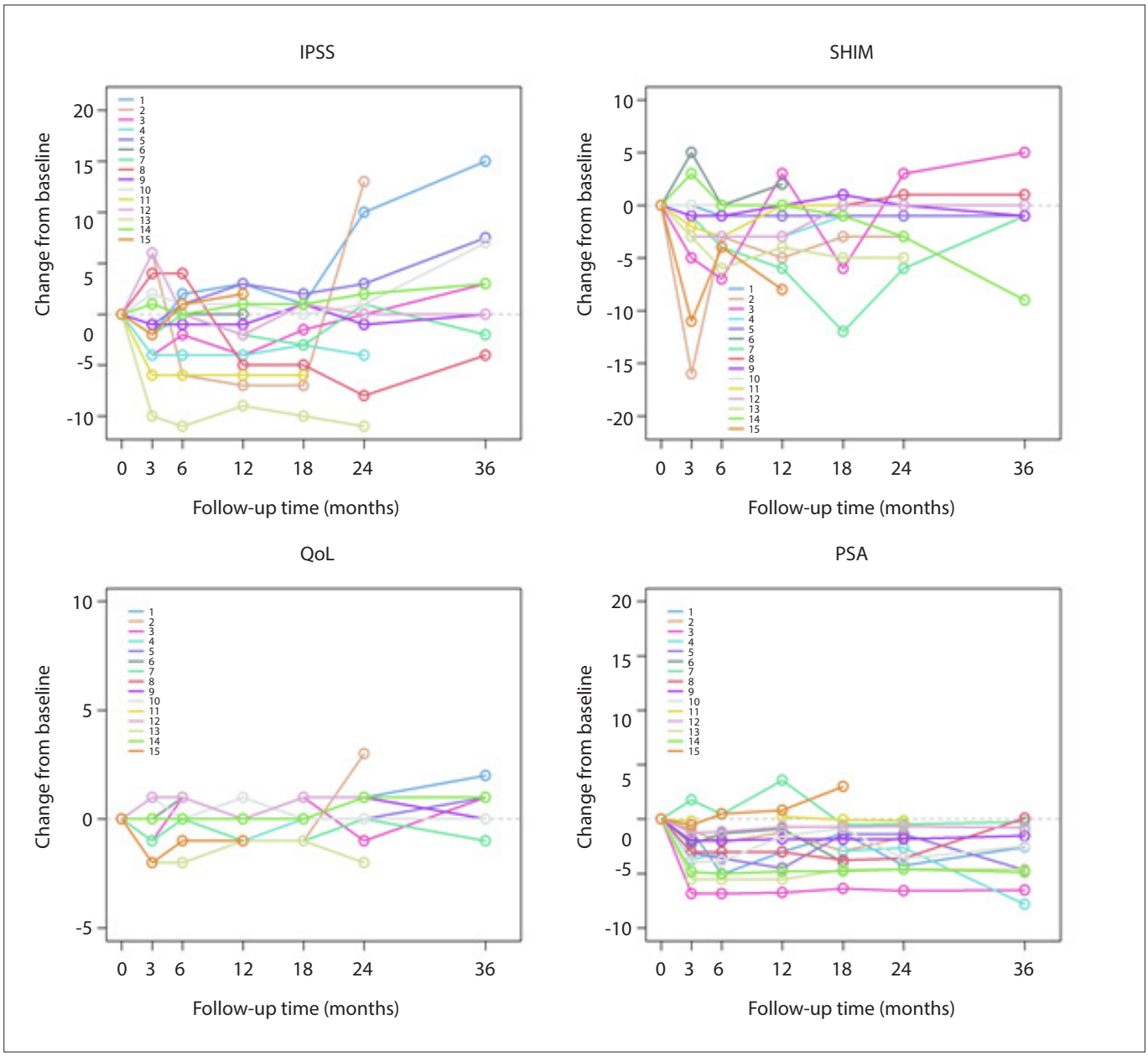

Figure 2. Change of IPSS, SHIM, QoL and PSA from baseline until receipt of salvage treatment or the end of follow-up if no salvage treatment was received. IPSS, international prostate symptom score; SHIM, sexual health inventory for men; QoL, quality of life; PSA, prostate specific antigen.

of monoclonal origin and originate from a single cell line in the largest lesion (15–17). In theory treating the visible lesions on MRI, some of which can sometimes be referred to the index lesion could prevent spread of the disease, while the nonsignificant lesions could be left behind without having the risk of metastases. However, identifying such index lesions remains the main challenge. Currently, there is not enough consensus on the definition of index lesion, and it is heavily based on visible lesion on MRI with a higher Gleason grade compared to other intraprostatic cancer foci. Furthermore, the index lesion hypothesis has been challenged by the highly heterogeneous genomic profile of multifocal PCa lesions. Further, in some studies, metastases do not appear to originate from index lesions, challenging the index lesion theory (18–20).

Our results are somewhat longer term than other studies investigating FLA. In a previous single center trial with similar methodology in 9 patients, 8 out of 9 had Gleason 3+3 (Grade 1) cancer and only one had Gleason 3+4=7 (Grade 2) (13). There were no complications or serious more than grade 2 adverse events and there was no significant difference in IPSS and SHIM scores after 6 months. Two out of 9 patients (22%) had residual Gleason 3+3=6 (Grade 1) disease located around the initial lesion. In the largest study group with 120 patients treated by FLA, pre-operative Gleason scores were 3+3=6 (Grade 1) in 37 (30.8%), 3+4=7 (Grade 2) in 56 (46.7%), and 4+3=7 (Grade 3) in 27 (22.5%) patients. One year after treatment, quality of life, sexual and urinary function did not change significantly. Twenty-two patients (18.3%) had residual cancer in the ablation zone with 4 patients (3.3%) having Glea-

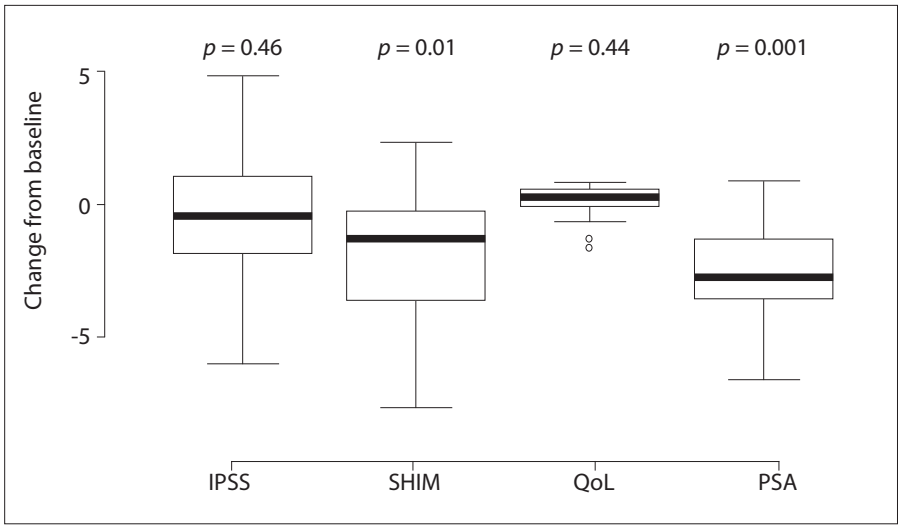

Figure 3. Change from baseline until receipt of salvage treatment or the end of follow-up if no salvage treatment was received. Per patient change of IPSS, SHIM, QoL and PSAS depicted in the boxplot was calculated as the average difference between outcomes measured at baseline and each follow-up visit. IPSS, international prostate symptom score; SHIM, sexual health inventory for men; QoL, quality of life; PSA, prostate specific antigen.

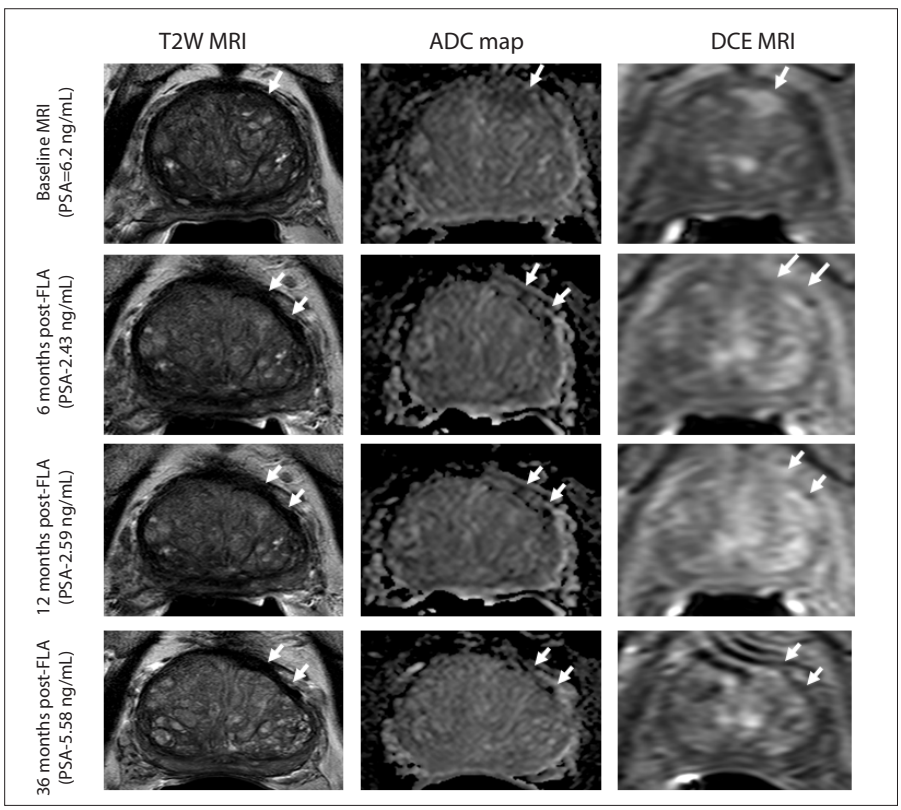

Figure 4. A 75-year-old male with a serum PSA of 6.2 ng/mL at the time of the baseline prostate MRI, which revealed a left mid anterior transition zone lesion with a resultant targeted biopsy indicating Gleason 3+4 prostate cancer *(arrows)*. MRI follow-up scans at 6 months, 12 months and 36 months after in-bore MRI-guided focal laser ablation demonstrate band-like appearance suggesting fibrosis on T2-weighted MRI and ADC map with no focal enhancement on DCE MRI *(arrows)*.

son 3+3=6 (Grade 1) and 18 patients (15%) having Gleason 3+4=7 (Grade 2). However, only patients with insignificant PSA drop or suspicious MRI lesions were biopsied which are controversial parameters for determining treatment success after focal therapy (21). As a consequence, the real recurrence rate might be underestimated.

Our study has some limitations. First, this was a small feasibility study. Furthermore, although a small patient population, the diversity and variability were immense. Studies with larger patient populations are needed to take this into account. Furthermore, improvements in localization, tracking, navigation, targeting, treatment planning software, and training are needed to decrease residual cancer in the ablated area, improve functional outcomes and reduce operation time. Finally, the procedure, although feasible, is still cumbersome due to long MRI scanner time. There is additional need for MRI-compatible equipment, surgeons or interventional physicians with special training. For such procedures to become a routine procedure, some simplification of the entire procedure flow, ergonomics, planning, verification, and equipment and software is needed. For example, using tracking-based MRI-TRUS fusion-targeted systems can be a potential solution and our institution is currently running such a study to explore use of transperineal MRI-TRUS fusion guidance for focal laser ablation (NCT02759744).

In conclusion, this study demonstrates feasibility of in-bore FLA with real-time MRI thermometry and reports similar medium-term success rates as other published experiences. Larger prospective and comparative studies are needed to evaluate long-term functional and oncological outcomes and determine clinical value and role within currently available portfolio of treatment options.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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