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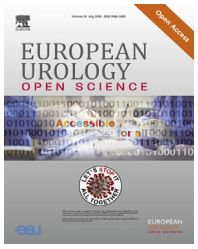

European Association of Urology

Prostate Cancer

Salvage Magnetic Resonance Imaging–guided Transurethral Ultrasound Ablation for Localized Radiorecurrent Prostate Cancer: 12-Month Functional and Oncological Results

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Abstract

Background: Up to half of all men who undergo primary radiotherapy for localized prostate cancer (PCa) experience local recurrence.
Objective: To evaluate the safety and early functional and oncological outcomes of salvage magnetic resonance imaging–guided transurethral ultrasound ablation (sTULSA) for men with localized radiorecurrent PCa.
Design, setting, and participants: This prospective, single-center phase 1 study (NCT03350529) enrolled men with biopsy-proven localized PCa recurrence after radiotherapy. Multiparametric magnetic resonance imaging (mpMRI) and ^{18}F prostate-specific membrane antigen-1007 (^{18}F PSMA-1007) positron emission tomography (PET)-computed tomography (CT) were used to confirm organ-confined disease localization. Patients underwent either whole-gland or partial sTULSA, depending on their individual tumor characteristics.
Outcome measurements and statistical analysis: Patients were followed at 3-mo intervals. Adverse events (AEs, Clavien-Dindo scale), functional status questionnaires (Expanded Prostate Cancer Index [EPIC]-26, International Prostate Symptom Score, International Index of Erectile Function-5), uroflowmetry, and prostate-specific antigen (PSA) were assessed at every visit. Disease control was assessed at 1 yr using mpMRI and ^{18}F-PSMA-1007 PET-CT, followed by prostate biopsies.
Results and limitations: Eleven patients (median age 69 yr, interquartile range [IQR] 68–74) underwent sTULSA (3 whole-gland, 8 partial sTULSA) and have completed 12-mo follow-up. Median PSA was 7.6 ng/ml (IQR 4.9–10) and the median time from initial PCa diagnosis to sTULSA was 11 yr (IQR 9.5–13). One grade 3 and three grade 2 AEs were reported, related to urinary retention and infection. Patients reported a modest degradation in functional status, most

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significantly a 20% decline in the EPIC-26 irritative/obstructive domain at 12 mo. A decline in maximum flow rate (24%) was also observed. At 1 yr, 10/11 patients were free of any PCa in the targeted ablation zone, with two out-of-field recurrences. Limitations include the nonrandomized design, limited sample size, and short-term oncological outcomes.

Conclusions: sTULSA appears to be safe and feasible for ablation of radiorecurrent PCa, offering encouraging preliminary oncological control.

Patient summary: We present safety and 1-yr functional and oncological outcomes of magnetic resonance imaging–guided transurethral ultrasound ablation (TULSA) as a salvage treatment for local prostate cancer recurrence after primary radiation. Salvage TULSA is safe and shows the ability to effectively ablate prostate cancer recurrence, with acceptable toxicity.

1. Introduction

Radiotherapy (RT), with or without androgen deprivation therapy (ADT), is a well-established primary treatment for localized prostate cancer (PCa) [1,2]. Recent technological advances have improved the safety and efficacy of RT, allowing an increase in radiation dose to the tumor while sparing critical surrounding structures [3]. However, up to half of all RT-treated men will still experience biochemical recurrence (BCR) [4], which is estimated to remain localized in the majority of cases [5]. Even if the recurrence remains local, 98% of patients will receive systemic ADT, which is noncurative and has potentially harmful side effects [6]. There is therefore a clear need for an effective treatment for localized radiorecurrent PCa that offers a chance of complete disease control and delays the adverse effects of systemic therapies or even avoids them altogether.

Several different salvage treatments have been investigated, including salvage prostatectomy [7], high-intensity focused ultrasound (HIFU) [8], cryoablation [9], and brachytherapy [10,11]. There have also been preliminary studies of reirradiation stereotactic body RT [12] and irreversible electroporation [13]. All of these approaches have their own shortcomings regarding oncological control and/or toxicity [14]. Salvage prostatectomy, a technically challenging procedure that is only offered at limited centers for carefully selected patients with favorable risk, has a high complication rate and a higher likelihood of adverse functional outcomes [7]. Owing to the invasiveness of the surgery, many patients are also ineligible because of comorbidities. Nonsurgical techniques such as HIFU, cryoablation, and brachytherapy have an estimated risk of BCR of between 31% and 42% and are associated with higher risks of complications and genitourinary and gastrointestinal toxicity [15].

With the onset of multiparametric magnetic resonance imaging (mpMRI) and prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and their ability to isolate recurrence, partial salvage therapy has gained in popularity, potentially offering a better compromise between disease control and toxicity [16,17]. However, a partial treatment approach is still controversial and typically applies to unilateral and well-confined dominant lesions, meaning that patients with diffuse and/or multifocal recurrence are likely to be poor candidates. An appealing way to overcome the challenges of disease localization and complications associated with nonsurgical techniques is to perform the intervention with advanced imaging guidance and real-time control of the ablation extent.

MRI-guided transurethral ultrasound ablation (TULSA) is a new treatment alternative that has been used for both whole-gland (WG) [18,19] and lesion-targeted [20,21] ablation of primary localized PCa. During TULSA the ablation is monitored and automatically controlled in real time under MRI thermometry for highly conformal ablation, while still allowing users the necessary control to intervene at their discretion to ensure that critical surrounding structures are spared. The rectum and urethra are also cooled during the procedure, which reduces the risk of injury.

The primary objectives of this study were to evaluate the safety and early functional and oncological outcomes of salvage TULSA (sTULSA) as an alternative treatment for localized radiorecurrent PCa.

2. Patients and methods

2.1. Study design

This was a prospective, nonrandomized, investigator-initiated, single-arm, single-center phase 1 study, registered as NCT03350529. It is the first TULSA study with salvage indication geared to evaluate safety and feasibility. For this reason, a limited number of patients were included and no comparative arm was used. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and written informed consent was obtained from all participants. The trial was performed in accordance with the principles of the Declaration of Helsinki.

2.2. Patient eligibility and selection

Men presenting with localized, histopathologically verified, radiorecurrent PCa were eligible and were included in the study. All study candidates had experienced BCR according to the Phoenix criteria, defined as a prostate-specific antigen (PSA) rise above the nadir of more

Table 1 – Patient characteristic and disease history before sTULSA

Patient	Characteristics at pTx			Year of diagnosis	RT parameters				aADT (mo)	Highest post-RT PSA (ng/ml)	Time from pTx to sTULSA (mo)	Age at sTULSA (yr)
	cT stage	ISUP GG	PSA (ng/ml)		Type	Technique	Total dose (Gy)	Fiducial seeds (*n*)				
1	T3	1	13	2006	EBRT	IMRT	78	3	6	15.2	147	69
2	T2	1	8.5	2005	EBRT	3D-CRT	72	0	12	5.5	157	69
3	T3	1	21	2007	EBRT	3D-CRT	72	0	Continuous	8.6	138	69
4	T2	5	10	2009	EBRT	3D-CRT	72	0	36	3.3	114	69
5	T1	1	13	1999	EBRT	3D-CRT	68	0	6	16	237	80
6	T1	1	9.5	2008	EBRT	IMRT	72	3	No ADT	11	130	77
7	T1	2	14	2008	EBRT	IMRT	76	3	6	4.7	129	70
8	T2	1	9.4	2015	HDR	HDR	27	0	No ADT	8.3	48	66
9	T1	5	37	2004	EBRT[a]	IMRT	72	3	36	13	175	67
10	T1	1	13	2007	EBRT	3D-CRT	72	0	No ADT	9.5	144	81
11	T3	3	22	2010	EBRT	IMRT	72	3	36	2.15	109	62

aADT = adjuvant androgen deprivation therapy; EBRT = external beam RT; HDR = high dose rate brachytherapy; IMRT = intensity-modulated radiation therapy; ISUP GG = International Society of Urological Pathology grade group; PSA = prostate-specific antigen; pTx = primary treatment; RT = radiation therapy; sTULSA = salvage magnetic resonance imaging–guided transurethral ultrasound ablation; 3D-CRT = three-dimensional conformal RT.

[a] The patient received salvage HDR brachytherapy (3 × 9 Gy) in 2011 for histologically verified localized radiorecurrent prostate cancer after EBRT.

than 2 ng/ml. Each patient underwent pelvic 3-T mpMRI and ^{18}F-labeled PSMA ligand 1007 (^{18}F-PSMA-1007) PET-computed tomography (CT) within 3 mo before sTULSA to confirm disease was organ-confined. After imaging, each patient also underwent pre-TULSA biopsy. MRI-targeted biopsies were taken from all prostatic lesions suspicious for malignancy on MRI and/or ^{18}F-PSMA-1007 PET-CT. In the absence of a visible lesion, systematic biopsies were taken; otherwise, systematic biopsies were not mandatory but highly recommended. To confirm sufficient urethra patency for the device instrumentation, all participants underwent cystoscopy before sTULSA. Exclusion criteria included evidence of extraprostatic disease on restaging, including seminal vesicle (SV) invasion, contraindications for MRI (eg, cardiac pacemaker, intracranial clips), hip replacement surgery or other metal in the pelvic area, and claustrophobia. Patients with prostate calcifications and/or cysts with a largest diameter >1 cm in the anticipated line of sight of the treatment region were also excluded.

2.3. Intervention

Treatment was delivered using TULSA (TULSA-PRO, Profound Medical Inc., Mississauga, Canada). A detailed description of the technology is provided in our earlier paper [20]. The TULSA technique and study intervention are described in detail in the Supplementary material. Patients received either WG or partial treatment, which was decided in advance of the therapy according to the dominant disease location(s), disease diffusivity, lesion size, and overall disease burden. The ablative effect covered all areas deemed suspicious on imaging (PSMA PET and/or MRI) and/or containing cancer in biopsies, and, if applicable, with a 5-mm margin of the visible tumor up to the prostate capsule. With this treatment strategy, angular arc-like ablation patterns varied between segmental, hemiablation, and WG ablation. Partial ablation was only performed if the lesion(s) was unilateral, well confined, and concordant on screening biopsy and imaging. Most patients were not catheterized during the procedure, and a transurethral catheter was inserted immediately after treatment.

2.4. Follow-up and assessment

Follow-up visits were scheduled at 1–2 wk and 3, 6, 9, and 12 mo. A catheter removal trial was performed at the first follow-up visit. mpMRI was performed at 3 mo. Adverse events were recorded at every follow-up visit using the Clavien-Dindo classification for surgical complications [22], as well as PSA, uroflowmetry (postvoid residual volume [PVR], average flow rate, maximum flow rate [Qmax], voided volume), and functional questionnaires (Expanded Prostate Cancer Index [EPIC]-26, International Prostate Symptom Score [IPSS], IPSS quality of life, International Index of Erectile Function [IIEF]-5). At 12 mo, patients underwent ^{18}F-PSMA-1007 PET-CT and pelvic 3-T mpMRI, followed by a transrectal ultrasound-guided biopsy. The biopsy protocol included two to four in-field biopsies and additional biopsies from any other regions deemed suspicious on imaging. BCR was assessed using the Phoenix criteria. Patients underwent cystoscopy at 12 mo to assess the effect of treatment.

3. Results

3.1. Patient characteristics

Eleven patients were treated with TULSA between April 2018 and June 2019. Baseline characteristics for these 11 participants are presented in Tables 1 and 2 . Additional baseline information is presented in Supplementary Table 1. At the time of sTULSA, the median patient age was 69 yr (interquartile range [IQR] 68–74), median prostate volume was 21 cm^3 (IQR 18–24), median PSA was 7.6 ng/ml (IQR 4.9–10), and the median time from initial PCa diagnosis was 11 yr (IQR 9.5–13). Ten patients had received external beam RT and one patient high dose rate (HDR) brachytherapy as primary treatment. One patient also received second-line salvage HDR brachytherapy before sTULSA. Four of the 11 patients had ongoing ADT at enrollment, which was discontinued after TULSA.

Ten patients had histopathologically verified local PCa recurrence at enrollment. One consenting patient refused his screening biopsy, but had a rising PSA of 9.5 ng/ml and a Likert 5 MRI lesion concordant with ^{18}F-PSMA-1007 PET-CT (maximum standardized uptake value 49.6 for the tumor), and no signs of extraprostatic disease on imaging. The pre-

Table 2 – Radiorecurrent disease characteristics before salvage MRI-guided transurethral ultrasound ablation. Bold entries indicate patients with multifocal disease

Pt	ADT at enrolment, duration	MRI T stage	PSA (ng/ml)	Prostate volume (cm^3)	Positive Bx/Bx taken	Total length (mm)		ISUP GG[d]	Likert score[e]	TD (mm)[e]	SUV_{max}[e]	Treatment coverage (% TPV)	Ablation pattern
						Bx	Cancer						
1	BIC 37 mo	2c	1.9	18	**4/6**[a] **3/6**	**NA**[c] **75**	**NA**[c] **27**	**3** **3**	**4** **4**	**13** **15**	**7.2** **11.3**	75	Subtotal, posterobasal region untreated
2	–	2a	5.5	37	3/8[b]	70	12	5	4	8	6.8	25	Right apex to midgland quadrant
3	BIC 37 mo	2c	7.5	14	**6/6**[a] **4/6**	**96** **75**	**45** **27**	**3** **3**	**4** **4**	**19** **19**	**48.1** **48.1**	100	Whole gland
4	–	2b	3.3	18	4/6[b]	84	8	5	5	11	44.6	50	RL hemiablation
5	–	2b	16	24	3/3[b]	32	22	3	5	20	23.3	50	LL hemiablation
6	–	2b	11	21	5/6[b]	59	28	3	5	17	5.4	50	RL hemiablation
7	–	2c	4.7	33	**3/4**[b] **4/4**	**70** **50**	**21** **25**	**4** **2**	**4** **4**	**16** **9**	**17.7** **8.1**	75	Anterior and LL hemiablation
8	DGX + BIC 19 mo	2b	0.1	24	1/3[b]	33	1.5	4	5	12	7.4	50	RL hemiablation
9	–	2c	13	21	7/9[b]	101	33	5	5	20	10.7	100	Whole gland
10	–	2c	9.5	20	Refused Bx	–	–	–	5	18	49.6	75	Anterior and LL hemiablation
11	BIC 19 mo	NLD	0.1	16	1/12[a]	165	8	3	NLD	NLD	NLD	100	Whole gland

ADT = androgen deprivation therapy; BIC = bicalutamide; Bx = biopsy; DGX = degarelix; ISUP GG = International Society of Urological Pathology grade group; LL = left lobe; MRI = magnetic resonance imaging; NA = not available; NLD = no lesion detected; PSA = prostate-specific antigen; Pt = patient; RL = right lobe; SUV_{max} = maximum standardized uptake value; TD = tumor diameter; TPV = total prostate volume.

[a] The patient underwent systematic biopsies.

[b] The patient underwent MRI-targeted biopsies.

[c] The percentage of prostate cancer in the biopsy material was 40%.

[d] Pathological determination of ISUP GG for salvage patients is not standardized because of radiation-induced changes.

[e] The exact location of all recurrent tumors on MRI and prostate-specific membrane antigen positron emission tomography/computed tomography is shown in Supplementary Figure 1.

sTULSA locations of the recurrent tumors on MRI and ^{18}F-PSMA-1007 PET-CT are presented in Supplementary Figure 1. In ten patients the MRI-visible radiorecurrence was spatially concordant with ^{18}F-PSMA-1007 PET-CT. One patient receiving ongoing ADT at enrollment showed no radiologically verified recurrence, but had recurrence in systematic biopsies.

All patients had severe erectile dysfunction according to IIEF-5 at the time of enrollment.

3.2. *Study intervention*

sTULSA was feasible in every study patient, with a median ablation time of 49 min (IQR 39–50) and ablation volume of 14 cm^3 (IQR 13–17). Three patients received WG ablation, while eight patients underwent partial ablation. The patient-specific ablation patterns are shown in Supplementary Figure 2. The only patient with a lesion not visible on imaging but with biopsy-proven recurrence was one of those three patients undergoing WG ablation. Nine patients did not have urinary drainage during the procedure and a transurethral catheter was inserted afterwards, while a suprapubic catheter (SPC) was inserted before treatment in the other two patients. All patients were under general anesthesia during the intervention and were discharged on the first postoperative day, with median of post-treatment catheterization duration of 7 d (IQR 1–14). Immediate postoperative recovery was relatively painless, with a mean

Table 3 – Functional results before and after salvage MRI-guided transurethral ultrasound ablation

Functional status questionnaire	Median score (interquartile range)			
	Baseline	3 mo	6 mo	12 mo
IPSS urinary symptom score	8 (4–10)	12 (8–23)	10 (8–14)	7 (5–18)
IPSS quality of life	1 (0–3)	3 (2–4)	3 (1–4)	2 (1–3)
IIEF-5 erectile function	0 (0–3)	0 (0–1)	0 (0–2)	2 (0–3)
EPIC-26 urinary incontinence domain	100 (100–100)	54 (36–100)	86 (47–100)	96 (46–100)
EPIC-26 irritative/obstructive domain	94 (88–94)	81 (60–88)	75 (59–94)	75 (72–100)
EPIC-26 bowel domain	100 (88–100)	96 (88–100)	96 (81–100)	96 (90–100)
EPIC-26 sexual domain	18 (17–33)	17 (10–24)	15 (9–18)	15 (13–36)

EPIC = Expanded Prostate Cancer Index; IPSS = International Prostate Symptom Score; IIEF = International Index of Erectile Function; MRI = magnetic resonance imaging.

Table 4 – Oncological outcomes at 12 mo after sTULSA

Patient	Biopsy					Imaging		PSA (ng/ml)		
	Positive cores/total cores		Total length (mm)		ISUP GG	mpMRI	PSMA PET	Baseline	1 yr after sTULSA	BCF
	In-field	Out-of-field[a]	Biopsy	Cancer						
1	0/4	1/4	87	1.0	4	Negative	Right, SV	1.9[b]	0.7[c]	No
2	0/4	–	60	–	–	Negative	Negative	5.5	1.4	No
3	0/4	–	69	–	–	Negative	Negative	7.5[b]	0.2[c]	No
4	0/4	–	48	–	–	Negative	Negative	3.3	0.3	No
5	1/2	0/2	20	1.5	2	Negative	Left, lobe	16	1.4	No
6	0/4	–	43	–	–	Negative	Negative	11	0.2	No
7	0/6	–	53	–	–	Negative	Negative	4.7	0.2	No
8	0/5	–	75	–	–	Negative	Negative	0.1[b]	0.1[c]	No
9	0/4	1/2	75	4.0	4	Positive	Right, SV	13	1.1	Yes
10	0/2	0/4	90	–	–	Negative	Negative	9.5	0.2	No
11	0/6	–	68	–	NA	Negative	Negative	0.1[b]	0.2[c]	No

BCF = biochemical failure; ISUP GG = International Society of Urological Pathology grade group; mpMRI = multiparametric magnetic resonance imaging; NA = not applicable; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; PSA = prostate-specific antigen; sTULSA = salvage MRI-guided transurethral ultrasound ablation; SV = seminal vesicles.

[a] Out-of-field biopsies were only performed if imaging findings revealed anything suspicious.

[b] Patient received androgen deprivation therapy.

[c] Androgen deprivation therapy was discontinued after sTULSA.

visual analog scale score for pain of 1 (range 0–1) during hospitalization. At discharge, patients were prescribed paracetamol and/or nonsteroidal anti-inflammatory analgesics for use as needed. None of the patients needed stronger analgesics.

3.3. Toxicity outcomes

Adverse events attributable to the intervention included one grade 3 and three grade 2 events among four separate patients (3 WG, 1 partial). Three patients had simultaneous urinary infection and urinary retention, while the fourth had only infection, all of which resolved with antibiotics. One patient who underwent WG treatment had his retention treated with SPC and 6-mo application of 2 J stents (grade 3) because of upper urinary tract dilatation, while the other two patients (1 WG, 1 partial) received SPC due to urinary retention (grade 2). Ten patients were free of catheterization at 1 yr, while one patient who had received prior salvage brachytherapy remained on intermittent catheterization. No bowel-related adverse events of any grade were observed.

3.4. Uroflowmetry outcomes

The median uroflowmetry results at baseline were: PVR 57 ml (IQR 0–122), average flow rate 5.9 ml/s (IQR 4.2–8.2), Qmax 12 ml/s (IQR 11–16), and voided volume 433 ml (IQR 265–449). Results for PVR, average flow rate, Qmax, and voided volume at baseline and 3, 6, and 12 mo are shown in Supplementary Figure 3. Compared to baseline, the declines in average flow rate and Qmax at 12 mo were 27% and 24%, respectively. The median decrease in voided volume from baseline to 12 mo was 54%. One patient had an increase in PVR (from 143 to 250 ml) after sTULSA, although this patient was the only one who had received a prior salvage treatment; otherwise, the median PVR improved threefold at 12 mo.

3.5. Functional outcomes

A summary of patient-reported functional questionnaire responses at baseline and 3, 6, and 12 mo is presented in Table 3. A minimal overall decrease was observed at 12 mo. The EPIC-26 irritative/obstructive domain was most affected, decreasing from a median score of 94 (IQR 88–94) at baseline to 75 (IQR 72–100) at 12 mo. During 1-yr follow-up, three patients received mirabegron for urinary urgency; otherwise, no new medications that affected urinary or sexual function were needed.

3.6. Histological, imaging, and PSA outcomes

The 1-yr biopsy and imaging outcomes are presented in Table 4. No lesion was observed at 3 mo on mpMRI. At 12 mo, 10/11 patients were free of any PCa in the targeted ablation zone, confirmed with biopsy and imaging, and had low and stable PSA. The immediate treatment outcome on MRI thermometry for all study participants is shown in Supplementary Figure 2. Baseline and 12-mo mpMRI and ^{18}F-PSMA-1007 PET-CT images for all study participants are shown in Supplementary Figure 1.

There were one in-field and two out-of-field histopathologically verified recurrences at 1 yr, all detected by ^{18}F-PSMA-1007 PET-CT. Only one of the three recurrences was detected by MRI. The only in-field recurrence occurred during partial treatment, characterized by 1.5 mm of vital cancerous tissue (International Society of Urological Pathology grade group 2) in the tip of one biopsy core. Recurrence was visible only on ^{18}F-PSMA-1007 PET-CT, and appeared at the periphery of the ablated region. This patient underwent active monitoring because of low and stable PSA

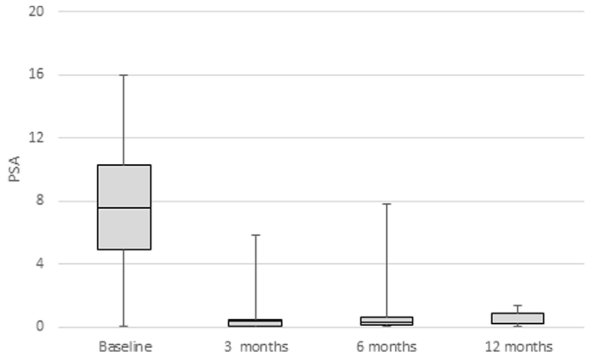

Fig. 1 – Temporal distribution of median prostate specific antigen (PSA) after salvage magnetic resonance imaging–guided transurethral ultrasound ablation. Boxes denote the interquartile range.

(1.4 ng/ml) at 18 mo after sTULSA. Two patients (one WG, one partial) had out-of-field recurrences on biopsies, which were also detected by ^{18}F-PSMA-1007 PET-CT. The patient who underwent partial sTULSA was successfully retreated 12 mo later, and had low and stable PSA of 0.89 ng/ml at 12 mo after the second procedure. No significant deterioration in uroflowmetry or functional outcomes was observed after the second sTULSA. The patient who underwent WG sTULSA experienced BCR at 6 mo and PSMA PET revealed extraprostatic involvement with new SV tumor and two new lymph node metastases that were not visible during screening. This patient received ADT.

The median PSA decreased from 7.6 ng/ml (IQR 4.9–10) at baseline to a nadir value of 0.2 ng/ml (IQR 0.1–0.4) and was 0.23 ng/ml (IQR 0.2–0.9) at 12 mo, corresponding to a decrease of 97%, despite discontinuation of ADT after TULSA in all patients ($n = 4$) receiving ADT before TULSA. The median prostate volume reduction was 55% (IQR 44–63%) at 12 mo. The temporal distribution of PSA is shown in Figure 1.

A patient case is presented in Figure 2 for a 69-yr-old male with a radiorecurrent, histopathologically proven, left-lobe unifocal tumor concordant on MRI and ^{18}F-PSMA-1007 PET-CT. The patient underwent hemiablation (Fig. 2D), with the acute effect observed on contrast-enhanced MRI as a nonperfused volume (Fig. 2E). At 12 mo there was no detectable carcinoma on MRI or ^{18}F-PSMA-1007 PET-CT (Fig. 2F–H) or in targeted biopsies.

4. Discussion

This is the first study evaluating TULSA as a salvage therapy for localized radiorecurrent PCa. sTULSA was technically feasible for all patients and showed encouraging early-stage oncological control and low toxicity.

One grade 3 and three grade 2 adverse events were reported, which compares favorably with other salvage interventions. Importantly, there were no urethral strictures, rectal injuries, or fistulas after sTULSA. Although rare, these complications have been reported after other salvage interventions [7–9,14]. Patients receiving sTULSA experienced minor impacts on functional outcomes, the most significant of which was a modest 20% worsening of irritative/obstructive symptom scores. This observation was also supported by declines in Qmax and average flow rate at 12 mo. In contrast to our study, previous experience with WG TULSA for primary treatment of localized PCa showed improvement in flow rates, presumably due to downsizing of the benign prostatic hyperplasia component [19,23]. This difference in flow rates is probably explained by the significantly different disease history and the ablation of previously irradiated prostate tissue.

Owing to anticipated postprocedural edema as a result of thermal injury, catheterization time of at least 1 wk was preplanned in our study protocol and suggested for each patient. Factors that influenced catheter selection (SPC or transurethral catheter) and catheterization duration included the extent of treatment, patient desire, logistical factors, how well the bladder emptied before treatment, and the type of catheter treatment chosen. Here we are reporting on our initial experience with TULSA in the treatment of radiorecurrent PCa, and therefore no conclusion can be drawn regarding catheterization duration after sTULSA. One patient who received previous salvage brachytherapy fared worse, with prolonged SPC for 9 mo before progressing to intermittent catheterization. In this patient, cystoscopy at 9 mo showed an open urethra and bladder neck, a large cavity within the prostate, and no stricture.

Ten of 11 patients were free of any cancer in the targeted ablation volume at their 1-yr follow-up, while two of 11 patients had an out-of-field recurrence. Of the three patients with biopsy-proven local recurrence, one patient, who had undergone partial sTULSA, underwent a second partial sTULSA targeted at the biopsy-proven out-of-field recurrence in the base of the SV. The second sTULSA treatment was well tolerated.

Treatment monitoring after nonsurgical salvage therapies is challenging, particularly after partial treatment. In this study we used PSA, ^{18}F-PSMA-1007 PET-CT, mpMRI, and 12-mo biopsies for monitoring of oncological outcomes. ^{18}F-PSMA-1007 PET-CT detected all three biopsy-proven recurrences, in contrast to mpMRI, which only detected one. There was no histologically verified recurrence within the prostate or BCR for the patients with negative ^{18}F-PSMA-1007 PET-CT.

TULSA has several potential advantages compared to existing nonsurgical salvage interventions in terms of patient selection, ablation patterns, and ablation time. Cryoablation is primarily used for recurrent anterior tumors because it offers less spatial control. Owing to organ-protective warming tools, cryoablation can be also less effective for apical and periurethral tumors [16,24]. Meanwhile, HIFU offers high spatial control but requires a longer time to complete the ablation and is more restrictive regarding prostate size, which is why it is used more often for posterior tumors [15]. Since HIFU is delivered transrectally, anterior tumors may be challenging to treat with this modality. By contrast, TULSA is delivered transurethrally and offers both high spatial

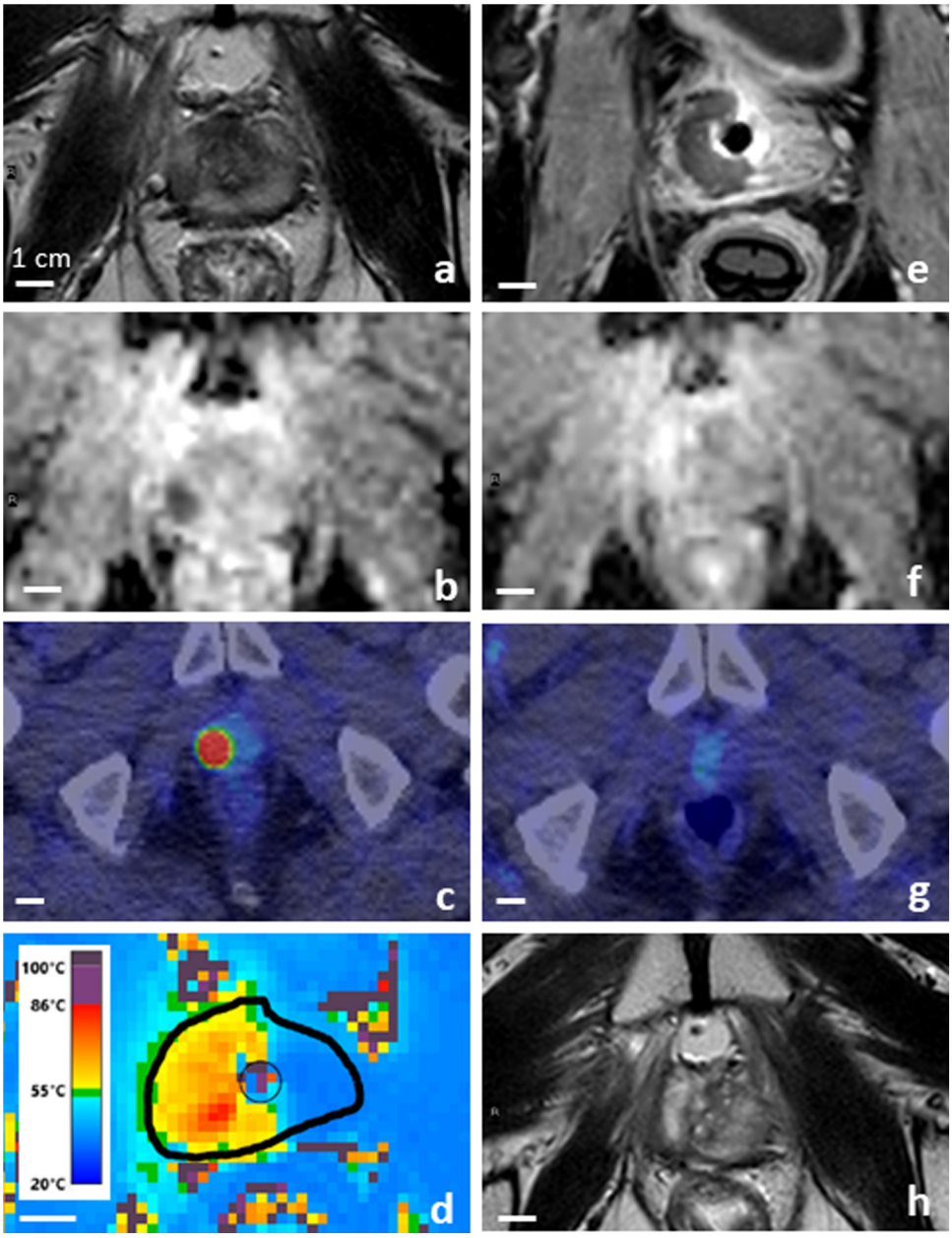

Fig. 2 – Example of a patient case. (A,B) Screening T2-weighted and diffusion-weighted MRI revealed a distinct focus graded as a Likert 5 lesion, which was also present on (C) ^{18}F-PSMA-1007 PET-CT (maximum standardized uptake value 44.6) (c). The patient underwent (D) targeted hemiablation, during which the targeted prostate region reached a lethal minimum temperature of 55 °C. (E) The nonperfused volume can be visualized immediately after treatment, which demonstrates the acute ablation effect. At 12 mo the patient underwent additional follow-up imaging. (F,H) Multiparametric MRI and (G) ^{18}F-PSMA-1007 PET-CT were both negative. The prostate volume decreased from 18 to 10 cm^3 (56%) at 12 mo. The imaging findings agree with a post-sTULSA biopsy, which showed no vital cancer. MRI = magnetic resonance imaging; PSMA-1007 = prostate-specific membrane antigen ligand 1007; PET = positron emission tomography; CT = computed tomography; sTULSA = salvage MRI-guided transurethral ultrasound ablation.

control by combining the precision of the ultrasound heat source and thermometry monitoring, and can treat large volumes in a relatively short amount of time. This means that TULSA can be used anywhere in the prostate, for either WG or partial ablation.

This study has several limitations, including the small sample size, the nonrandomized trial design, short-term oncological outcomes, and a patient population with relatively heterogeneous PCa disease history, including patients with ongoing ADT at enrollment. Even though one patient was treated without histopathological proof of local recurrence, the authors would like to reaffirm the need for histopathological proof of local recurrence before proceeding with any local salvage treatment. Another limitation of TULSA is the relatively complex technical requirements of the device, including the prolonged magnet occupation time and MR-compatible anesthesia equipment, which in turn carry additional costs.

5. Conclusions

sTULSA appears to be safe and feasible for salvage ablation of radiorecurrent PCa, but additional studies with larger populations and longer follow-up are needed to validate the efficacy of this treatment.

Data sharing statement: All the data collected for the study, including the deidentified individual participant data, the study protocol, and informed consent forms (in Finnish), will be available for anyone who wishes to access the data for a period commencing with publication and ending 5 yr later. Proposals for access to the data should be directed to sara.karnell@tyks.fi. Requestors will need to sign a data access agreement.

Author contributions: Mikael Anttinen 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*: Anttinen, Blanco Sequeiros, Boström.
Acquisition of data: Anttinen, Mäkelä, Nurminen, Sainio.
Analysis and interpretation of data: Anttinen, Viitala.
Drafting of the manuscript: Anttinen, Viitala.
Critical revision of the manuscript for important intellectual content: Boström, Blanco Sequeiros, Taimen, Saunavaara.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.euros.2020.10.007.

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