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## Platinum Priority – Prostate Cancer Editorial by Herbert Lepor on pp. 456–457 of this issue

# Magnetic Resonance Imaging–Guided Transurethral Ultrasound Ablation of Prostate Tissue in Patients with Localized Prostate Cancer: A Prospective Phase 1 Clinical Trial

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### Abstract

**Background:** Magnetic resonance imaging–guided transurethral ultrasound ablation (MRI-TULSA) is a novel minimally invasive technology for ablating prostate tissue, potentially offering good disease control of localized cancer and low morbidity. **Objective:** To determine the clinical safety and feasibility of MRI-TULSA for whole-gland prostate ablation in a primary treatment setting of localized prostate cancer (PCa).

**Design, setting, and participants:** A single-arm prospective phase 1 study was performed at three tertiary referral centers in Canada, Germany, and the United States. Thirty patients (median age: 69 yr; interquartile range [IQR]: 67–71 yr) with biopsy-proven low-risk (80%) and intermediate-risk (20%) PCa were treated and followed for 12 mo.

*Intervention:* MRI-TULSA treatment was delivered with the therapeutic intent of conservative whole-gland ablation including 3-mm safety margins and 10% residual viable prostate expected around the capsule.

**Outcome measurements and statistical analysis:** Primary end points were safety (adverse events) and feasibility (technical accuracy and precision of conformal thermal ablation). Exploratory outcomes included quality of life, prostate-specific antigen (PSA), and biopsy at 12 mo.

**Results and limitations:** Median treatment time was 36 min (IQR: 26–44) and prostate volume was 44 ml (IQR: 38–48). Spatial control of thermal ablation was  $\pm 1.3$  mm on MRI thermometry. Common Terminology Criteria for Adverse Events included hematuria (43% grade [G] 1; 6.7% G2), urinary tract infections (33% G2), acute urinary retention (10% G1; 17% G2), and epididymitis (3.3% G3). There were no rectal injuries. Median pretreatment International Prostate Symptom Score 8 (IQR: 5–13) returned to 6 (IQR: 4–10) at 3 mo (mean change: -2; 95% confidence interval [CI], -4 to 1). Median pretreatment International Index of Erectile Function 13 (IQR: 6–28) recovered to 13 (IQR: 5–25) at 12 mo (mean change: -1; 95% CI, -5 to 3). Median PSA decreased 87% at 1 mo and was stable at 0.8 ng/ml (IQR: 0.6–1.1) to 12 mo. Positive biopsies showed 61% reduction in total cancer length, clinically significant disease in 9 of 29 patients (31%; 95% CI, 15–51), and any disease in 16 of 29 patients (55%; 95% CI, 36–74).

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**Conclusions:** MRI-TULSA was feasible, safe, and technically precise for whole-gland prostate ablation in patients with localized PCa. Phase 1 data are sufficiently compelling to study MRI-TULSA further in a larger prospective trial with reduced safety margins. **Patient summary:** We used magnetic resonance imaging–guided transurethral ultrasound to heat and ablate the prostate in men with prostate cancer. We showed that the treatment can be targeted within a narrow range (1 mm) and has a well-tolerated side effect profile. A larger study is under way.

Trial registration: NCT01686958, DRKS00005311.

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### 1. Introduction

The widespread use of prostate-specific antigen (PSA) for prostate cancer (PCa) screening has led to a stage, grade, and risk migration of the disease, resulting in increased diagnosis of organ-confined low-risk and intermediate-risk tumors [1]. Although low-risk disease is increasingly being managed with active surveillance [2,3], definite intervention is eventually warranted in a significant number of these patients [4,5]. Most newly diagnosed intermediate-risk PCa patients are receiving active treatment with curative intent [3]. Although current definitive treatments provide good oncologic outcomes, they can be associated with long-term erectile, urinary, and bowel complications that may significantly compromise patients' quality of life [6,7].

The ultimate goal of treatment of clinically significant organ-confined PCa is to obtain local cancer control with a low morbidity profile. To this end, there has been growing enthusiasm for minimally invasive ablative therapies.

Magnetic resonance imaging (MRI)-guided transurethral ultrasound ablation (TULSA) is a novel minimally invasive technology that integrates quantitative image-based planning, monitoring, and treatment control with transurethral delivery of therapeutic ultrasound to ablate prostate tissue (both benign and malignant) through thermal coagulation [8]. The entire procedure is conducted within an MRI unit, offering high-resolution planning images that are registered naturally to real-time quantitative thermometry images acquired during treatment. A closed-loop temperature feedback control algorithm modulates the intensity, frequency, and rotation rate of the ultrasound, shaping the ablation volume precisely to individual prostate anatomy and reducing the risk of possible damage to periprostatic structures (rectum, urinary sphincter, neurovascular bundles, and pelvic bone) [9]. Multiparametric MRI techniques have also shown promise to detect and spatially localize PCa within the gland, facilitating treatment planning [10]. By combining the diagnostic, visualization, and real-time thermal dosimetry capabilities of MRI with the accuracy of feedback-controlled ultrasound ablation, MRI-TULSA could provide spatially precise treatment tailored to patientspecific anatomy and pathology.

Comprehensive studies in computer simulations [9,11,12], tissue-mimicking gel phantoms [12–14], and an in vivo canine model [15–19] have demonstrated the feasibility and safety of MRI-TULSA in the preclinical setting. More recently, a proof-of-concept clinical study demonstrated the ability of MRI-TULSA to wholly ablate a

small region within the prostate prior to radical prostatectomy (RP) [8]. While permitting histologic analysis of whole-mount tissue sections registered to MRI thermometry data, the timing of surgery precluded assessment of treatment safety. We report the first experience of a multicenter prospective phase 1 clinical trial, with the a priori objective of establishing safety and feasibility of MRI-TULSA for whole-gland prostate ablation in the primary treatment setting of patients with organ-confined PCa.

### 2. Patients and methods

A prospective multicenter single-arm phase 1 clinical safety and feasibility trial was designed for MRI-TULSA in patients with localized PCa (NCT01686958, DRKS00005311). The study was performed at three tertiary referral urology centers in London, Ontario, Canada; Heidelberg, Germany; and Royal Oak, Michigan, USA. The trial was approved by the respective research ethics boards, and written informed consent was obtained from all study participants.

Thirty treatment-naive men aged  $\geq$ 65 yr with biopsy-proven organconfined PCa (clinical stage T1c–T2a, N0, M0), PSA  $\leq$ 10 ng/ml, and Gleason score (GS) 3 + 3 or 3 + 4 were enrolled between March 2013 and March 2014. Recruitment of patients with GS 3 + 4 was allowed in Canada only.

### 2.1. MRI-TULSA system

MRI-TULSA was performed using the TULSA-PRO investigational device (Profound Medical Inc., Toronto, Canada), and the entire procedure was conducted within a 3-T MRI (Magnetom Trio, Siemens, Munich, Germany) with posterior and anterior multichannel phased-array coils. As illustrated in Figure 1, a rigid ultrasound applicator (UA) incorporates a linear array of 10 independent ultrasound transducers that emit directional (but not focused) high-intensity ultrasound energy directly into the adjacent prostate. In this configuration, the ultrasound beams expose a large volume of tissue, resulting in short treatment times and creating a continuous region of thermal ablation without risk of cold spots [20]. A fluid circuit flows water through the UA, providing 1–2 mm of urethral tissue preservation [18] and a passive endorectal cooling device (ECD). The UA is held in situ with a positioning system (PS) that also provides remote linear and rotational motion of the device within the prostatic urethra. A treatment delivery console (TDC) includes customized software to outline the target prostate boundary during planning, monitor the thermal therapy delivery in real time during treatment, and implement the proprietary temperature feedback control algorithm.

### 2.2. MRI-TULSA procedure

Patients were induced with general endotracheal anesthesia, followed by insertion of a suprapubic catheter (SPC) and transurethrally inserted



Fig. 1 – Treatment with magnetic resonance imaging–guided transurethral ultrasound ablation. ECD = endorectal cooling device; UA = ultrasound applicator.

nitinol guidewire. The SPC was left open throughout the procedure to avoid prostate displacement between the treatment plan and real-time MRI thermometry images. The patient was then moved onto the MRI bed, and the UA was inserted manually over the guidewire followed by the ECD.

Under MRI guidance and remote operation of the PS, the UA was positioned precisely within the prostatic urethra with a 3-mm safety margin between the ultrasound transducers and sphincter plane at the prostate apex. High-resolution prostate MR images were then acquired for treatment planning (T2-weighted turbo spin echo, echo/repetition time 52/3000 ms, 26-cm field of view,  $1 \times 1 \times 2.5$  mm<sup>3</sup> voxels). Using the TDC, the physician traced the outer prostate boundary on oblique-axial images acquired transverse to the UA and aligned with each transducer element. Diagnostic MRI information was not incorporated into treatment planning, and the outer prostate boundary was not modified near cancer foci or the neurovascular bundles. No boundary was drawn on images outside the prostate with the corresponding transducer remaining off during treatment. The attending urologist and radiologist arrived at a consensus regarding the outer prostate boundary.

Within the design of this phase 1 safety and feasibility study, treatment was delivered with intent of conservative whole-gland ablation. The target prostate volume was defined with a 3-mm safety margin from the outer prostate boundary drawn by the physicians, and heated to  $\geq$ 55 °C representative of complete acute thermal coagulation [8,16,17]. Based on preclinical data, delayed cell kill was anticipated to migrate an additional 1.3 ± 0.5 mm (maximum: 3 mm) toward the prostate capsule [15], in accordance with a lethal thermal dose of 240 CEM43 (cumulative equivalent minutes at 43 °C) [19]. Using treatment simulations and realistic patient models [12], a residual viable prostate tissue volume of approximately 10% ± 3% was expected around the gland periphery.

Treatment began with high-intensity ultrasound energy delivered to the prostate in one complete rotation of the UA under active MRI thermometry feedback control (proton resonance frequency shift method [21], echo planar imaging, oblique-axial aligned with planning images, echo/repetition time 8/350 ms, 26-cm field of view,  $2 \times 2 \times 4 \text{ mm}^3$  voxels, 0.8 °C average precision in vivo human prostate, 0.11 ± 0.33 °C accuracy and precision validated by a fiberoptic temperature sensor in a tissue-mimicking gel phantom). Real-time MRI thermometry images were acquired every 5.9 s, providing continuous assessment of a three-dimensional temperature volume during treatment. Administration of a gastrointestinal antispasmodic (hyoscine butylbromide or glucagon) minimized peristalsis that can cause MRI thermometry artifacts. Maximum prostate temperatures were maintained <100 °C by the feedback controller to avoid tissue carbonization and boiling, both undesirable during ultrasound therapy.

After treatment, contrast-enhanced (CE) MRI was acquired after weight-adjusted intravenous injection of a gadolinium-based contrast agent (0.1 mmol/kg) to assess the nonperfused volume (NPV). The SPC was left in place for 2 wk to avoid acute urinary retention due to thermo-induced edema. Prophylactic antibiotics were prescribed as per standard of care, and patients were admitted overnight if deemed appropriate by the investigator.

### 2.3. End points and follow-up

Primary end points were safety and feasibility, evaluated to 12 mo. Safety was assessed independently by either a study nurse or urologist, using Common Terminology Criteria for Adverse Events v.4. Feasibility was evaluated quantitatively because the accuracy and precision of generating a thermal volume of acute ablation (55 °C on MRI thermometry) conformed to the planned target prostate volume. In this context, treatment accuracy and precision refer, respectively, to the average and standard deviation of the spatial distance between the 55 °C isotherm generated during treatment and the target prostate boundary defined during treatment planning.

Follow-up visits were at 2 wk, 1, 3, 6, and 12 mo. SPC was removed at 2 wk, following a successful trial of voiding. Exploratory end points included PSA, quality-of-life questionnaires (International Prostate Symptom Score [IPSS], erectile function domain of International Index of Erectile Function [IIEF]-15, bowel habits domain of University of California, Los Angeles Prostate Cancer Index-Short Form [UCLA-PCI-SF],

Table 1 – Baseline patient demographics and prostate cancer disease characteristics

Characteristics	Frequency $(n = 30)$	Percentage						
Age, yr; median: 69 yr (IQR: 67–71)								
60–65 <sup>a</sup>	2	6.7						
65-70	16	53.3						
70–75	11	36.7						
75-80	1	3.3						
BMI, kg/m <sup>2</sup> ; median: 27.1 (IQR: 24.6–29.1)								
<18.5	0	0						
18.5-25.0	9	30.0						
25.0-30.0	14	46.7						
$\leq$ 30.0	7	23.3						
Race								
Multiracial	1	3.3						
White	29	96.7						
Prostate cancer risk (D'Amico)								
Low risk	24	80.0						
Intermediate risk	6	20.0						
Gleason score								
6 (3 + 3)	24	80.0						
7 (3 + 4)	6	20.0						
Pretreatment PSA, ng/ml <sup>b</sup> ; median (IQR): 5.8 ng/ml (IQR: 3.8-8.0)								
0-5.0	12	40.0						
5.0-10.0	17	56.7						
10.0-15.0	0	0						
15.0–20.0 <sup>c</sup>	1	3.3						

BMI = body mass index; IQR = interquartile range; PSA = prostate-specific antigen.

<sup>a</sup> The first two patients were recruited under the first revision of the protocol, which allowed age 45–75 yr.

<sup>b</sup> Pretreatment PSA is equal to the average of the baseline and treatment day PSA values. If the treatment day PSA is missing, the pretreatment PSA equals the baseline value.

<sup>c</sup> Clinical protocol deviation: Baseline PSA was 12.2 ng/ml and treatment day PSA was 19.4 ng/ml, although the result was not received until after the patient was treated.

Eastern Cooperative Oncology Group [ECOG] performance status), MRI at 12 mo, and 12-core (minimum) transrectal ultrasound (TRUS) prostate biopsy at 12 mo. Cystoscopy was performed in all patients at 12 mo and additionally, if indicated, at the investigators' discretion.

### 3. Results

Table 1 lists the baseline characteristics of the 30 participants. Mean pretreatment PSA was 6.0 ng/ml, with 24 (80%) and 6 (20%) participants having low- and intermediate-risk PCa (D'Amico [22]), respectively.

### 3.1. Feasibility

MRI-TULSA was successful and well tolerated by all study participants, with average prostate volume of 48 ml (range: 21–95) and ultrasound treatment time of 36 min (range: 24–61) (Table 2). Maximum temperature distribution measured during treatment depicted a continuous region of thermal ablation shaped to the target prostate volume with spatial accuracy and precision of  $0.1 \pm 1.3$  mm (Fig. 2a). There were no observations of ablative heating on MRI thermometry of the external urinary sphincter or rectal wall. Immediate post-treatment necrosis, as visualized by the peripheral region of enhancement surrounding the NPV on CE-MRI [15], correlated well with the thermal pattern measured by MRI thermometry (Fig. 2b).

### 3.2. Safety

There was no intraoperative complication, no rectal injury or fistula, and no severe urinary incontinence. There were no G4 or higher adverse events and only one attributable G3 event (epididymitis, requiring intravenous antibiotics). Most attributable events were acute G1 and G2, related to the genitourinary system, occurring and resolving within 3 mo of treatment (Table 2). Incontinence concerns resolved by 12 mo except one patient with ongoing G1 (no pads) downgraded from G2 (pads). Figure 3 illustrates temporal changes in continence, showing a "pad-free, leak-free continence" rate of 97% (95% CI, 83–100) and a "pad-free continence" rate of 100% (95% CI, 91–100) at 12 mo. Gastrointestinal events were rare and minor.

Overall, 29 of 30 patients (97%) were discharged within 24 h of the procedure. One patient stayed 2 nights in the hospital for psychosocial reasons. Median SPC catheterization was 2.2 wk(IQR: 2.0–3.3) as per protocol, with prolonged catheterization in eight patients for up to 1 mo and in one patient with history of poorly controlled insulin-dependent diabetes for 10.8 mo due to urinary retention. He resumed normal micturition after SPC removal, with uroflowmetry and IPSS values returning to baseline by 18 mo.

Cystoscopy was performed at the 12-mo visit specifically to assess urethral strictures. There was an incidental finding of an asymptomatic urethral stricture G1 in one patient requiring no action. There was a G2 stricture resolved with a urethral dilator in the patient with poorly controlled diabetes who had several Foley catheters and cystoscopies during the management of his retention. No sloughing was noted.

### 3.3. Exploratory outcomes

Table 2 summarizes the patient-reported quality-of-life outcomes. Median (IQR) IPSS values increased at 1 mo and returned to pretreatment baseline by 3 mo, with a mean change of -2 (95% CI, -4 to 1), and symptom improvement in 17 patients (57%). Median (IQR) IIEF-15 erectile function decreased initially and returned to pretreatment values by 12 mo, with a mean change of -1 (95% CI, -5 to 3). ECOG performance status increased by 1 point in two patients (6.7%) at 1 mo and returned to baseline by 3 mo, meaning that all patients were able to perform all predisease physical activities without restriction.

Erectile dysfunction was defined as a score of 0–1 for question 2 of the IIEF-15 [23]. Accordingly, the proportion of patients with erections sufficient for penetration remained relatively unchanged from 21 of 30 (70%; 95% CI, 51–85) at baseline to 20 of 29 (69%; 95% CI, 49–85) at 12 mo (Fig. 3, solid line). Of 20 participants with erections sufficient for penetration at baseline, 17 (85%; 95% CI, 62–97) remained so at 12 mo (Fig. 3, dashed line).

Postoperative PSA decreased, consistent with the conservative whole-gland treatment plan and 10% residual

### Table 2 - Magnetic resonance imaging-guided transurethral ultrasound ablation phase 1 study outcomes

Feasibility						
Parameter ( $n = 30$ )	Ν	Nean $\pm$ SD	Median (I	Range		
Prostate volume Ultrasound treatment time Thermal ablation accuracy Thermal ablation precision	44 30 0. 1.	$8 \pm 17 \text{ ml}$ $6 \pm 10 \text{ min}$ $1 \pm 0.4 \text{ mm}$ $3 \pm 0.4 \text{ mm}$	44 ml (38–48) 36 min (26–44 0.1 mm (–0.3 1.3 mm (1.0–1	21–95 ml 24–61 min –0.6 to 1.1 mm 0.7–2.4 mm		
Safety						
Adverse event, G <sup>a</sup>	Patients, <i>n</i> (%; 95%	GCI)	Comment			
GU, common and significant	events					
Hematuria,	12/20 (12: 25 62	)	Asymptomatic			
GI G2	2/30 (67.08-2)	) 2)	Symptomatic			
Urinary tract infection	2/30 (0.7, 0.0 2.	2)	Symptomatic			
G2	10/30 (33; 17-53	)	Oral antibiotics			
Epididymitis,		,				
G3	1/30 (3.3; 0.1-1	7)	IV antibiotics			
Urinary retention,						
G1	3/30 (10; 2.1–27	3/30 (10; 2.1–27) Blocked SPC				
G2	5/30 (17; 5.6–35	5)	Prolonged catheterization			
Obstructive micturition,	2/20 (10, 2.1. 25	7)	Declar and anth staringtion			
G2	3/30 (10; 2.1-27	')	Profoliged Catheterization			
G1	1/30 (3 3 0 1-1	7)	Occasional: pads not indicated			
62	3/30 (10: 2.1–27	7)	Spontaneous: pads indicated 1/3	30 ongoing at 12 mo althou	igh downgraded to G1	
02	3,330 (10, 211 2)	,	(no pads)		ign donnigraded to er	
Urinary stricture,						
G1	1/30 (3.3; 0.1–1	7)	Incidental finding, asymptomatic, no action			
G2	1/30 (3.3; 0.1–1	7)	Resolved with urethral dilator			
GI, all events						
Rectal pain, G1	1/30 (3.3; 0.1–17	)	No action			
Fecal straining, G1	1/30 (3.3; 0.1-17	)	No action			
Bloating, G1	3/30 (10; 2.1–27)	)	No action; may be related to GI antispasmodic			
Quality of life						
Median (IQR)	Baseline	1 mo	3 mo	6 mo	12 mo	
IPSS	8 (5-13)	14 (11-19)	6 (4–10)	5 (3-8)	5 (4-7)	
IIEF-EF-15	13 (6–28)	7 (2–12)	11 (4–18)	11 (4–19)	13 (5–25)	
UCLA-PCI-SF-BH	100 (90-100)	100 (80-100)	100 (89–100)	100 (89-100)	100 (100-100)	
ECOG status, $n$ (%)	Baseline	1 mo	3 mo	6 mo	12 mo	
Grade 0	30/30 (100)	28/30 (93)	28/28 (100)	30/30 (100)	29/29 (100)	
Oncologic control						
Median (IQR)	Baseline	1 mo	3 mo	6 mo	12 mo	
PSA, ng/ml	5.8 (3.8-8.0)	0.8 (0.5–1.1)	0.9 (0.4–1.7)	0.8 (0.4–1.1)	0.8 (0.6-1.1)	
Parameter			Patients, <i>n</i> (%; 95% CI)			
Positive biopsy (any disease) Positive biopsy (clinically significant disease) <sup>b</sup> Overall absence of clinically significant disease <sup>c</sup>			16/29 (55; 36–74) 9/29 (31; 15–51) 20/29 (69; 49–85)			

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group performance status; G = grade; GI = gastrointestinal; GS = Gleason score; GU = genitourinary; IIEF-EF = International Index of Erectile Function-Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; IV = intravenous; PSA = prostate-specific antigen; SD = standard deviation; SPC = suprapubic catheter; TCL = total cancer length; UCLA-PCI-SF-BH = University of California, Los Angeles Prostate Cancer Index-Short Form-Bowel Habits.

<sup>a</sup> Attributable adverse events of the same name are reported once per patient using the highest attributable grade.

<sup>b</sup> Clinically significant biopsy outcome is based on the highest GS in all cores and TCL (the cumulative sum of all cancer in all cores) and is defined as GS 3 + 3 TCL >10 mm, GS 3 + 4 TCL >3 mm, any GS  $\geq 4 + 3$ , or increased TCL from baseline biopsy. Definition is adapted from Donaldson et al [25], using a median agreement score  $\geq 5$  for residual cancer in untreated tissue. Median agreement score  $\geq 5$  was considered acceptable because this analysis examines TCL from a 12-core biopsy compared with the maximum cancer core length used in the consensus paper.

<sup>c</sup> Defined as absence of clinically significant disease on 12-mo biopsy and absence of Phoenix biochemical failure.



Fig. 2 – (a) Maximum temperature distribution measured during treatment; (b) Visualization of the peripheral region of enhancement surrounding the non-perfused volume on CE-MRI acquired immediately after treatment. Images are oblique-axial transverse to the UA. CE-MRI = contrast-enhanced magnetic resonance imaging; MRI = magnetic resonance imaging.

viable prostate tissue (Table 2). Median PSA decreased 87% from 5.8 ng/ml (IQR: 3.8–8.0) to 0.8 ng/ml (IQR: 0.5–1.1) at 1 mo, remaining stable at 0.8 ng/ml (IQR: 0.6–1.1) to 12 mo. Median PSA nadir was 0.6 ng/ml (IQR: 0.3–0.8). One patient experienced Phoenix biochemical failure [24] at 12 mo.

MRI and TRUS prostate biopsy at 12 mo showed diminished prostate volumes, averaging 51% fibrosis. Biopsies were positive for clinically significant disease in 9 of 29 patients (31%; 95% CI, 15–51) (defined in Table 2 [25]).



Functional outcome Patients, n (%; 95% Cl)	Baseline (0 mo)	1 mo	3 mo	6 mo	12 mo
Pad-free continence	30/30 (100; 91– 100)	27/30 (90; 73–98)	29/30 (97; 83–100)	29/30 (97; 83–100)	30/30 (100; 91– 100)
Leak-free, pad-free continence	30/30 (100; 91– 100)	27/30 (90; 73–98)	27/30 (90; 73–98)	29/30 (97; 83–100)	29/30 (97; 83–100)
Erections sufficient for penetration (all patients)	21/30 (70; 51–85)	10/28 (36; 19–56)	14/29 (48; 29–67)	17/30 (57; 37–75)	20/29 (69; 49–85)
Erections sufficient for penetration (only patients potent at baseline)	21/21 (100; 87– 100)	10/19 (53; 29–76)	13/20 (65; 41–85)	15/21 (71; 48–89)	17/20 (85; 62–97)

Fig. 3 – Temporal change in continence and erectile function. CI = confidence interval; G = grade; IIEF = International Index of Erectile Function.

Positive biopsies for *any* disease were obtained in 16 of 29 patients (55%; 95% CI, 36–74), although they demonstrated a 61% reduction in total cancer length. One patient with a stable 12-mo PSA 0.4 ng/ml refused follow-up biopsy and withdrew from the study.

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Two patients underwent salvage prostatectomy after 12 mo. Although whole-mount sections were not done, the pathologist specifically commented on the first RP specimen that "tumour was mostly peripheral, with extensive extra-prostatic extension, and it was at the margin in multiple areas including right posterior and bladder neck." For the second specimen, "the tumour was localized to the posterior/lateral peripheral area (1 mm subcapsular)."

All other participants remain on active surveillance with per protocol clinical monitoring to 5 yr.

### 4. Discussion

MRI-TULSA is a novel technology that integrates superior intra- and periprostatic details provided by MRI for treatment planning, intraoperative thermal monitoring, and active temperature feedback control, with the capability to ablate prostate tissue transurethrally. This technology differs from other ablative therapies such as cryotherapy, laser interstitial thermal therapy, and high-intensity focused ultrasound because the thermal energy is delivered directly to the prostate without traversing and potentially damaging normal tissue. By directly measuring the thermal response during treatment and actively adjusting the therapy accordingly, MRI-TULSA automatically compensates for inter- and intrapatient variability in stromal epithelial ratio and dynamic vascularity. Most importantly, the rectum and external urinary sphincter can be spared with accuracy, optimizing the therapeutic risk-benefit ratio with complete prostate ablation and minimal side effects.

Short ultrasound ablation times were demonstrated for prostate volumes up to 95 ml, which is important when considering integration into the MRI suite. Total procedure time was not formally recorded but was typically 4–6 h with this first-generation MRI-TULSA device; later cases were shorter than earlier ones. Usability feedback from this phase 1 study will be integrated into future generations of the device to improve workflow, streamline treatment, and minimize procedure time in the MRI.

### 4.1. Clinical implications

This phase 1 study achieved its feasibility and safety objectives, demonstrating the ability to thermally ablate target tissues to within  $\pm 1.3$  mm and a well-tolerated side-effect profile with minor or no impact on urinary, erectile, and bowel function at 12 mo. There were no G4 or higher adverse events, one transient attributable G3 event, and notably no injury to rectal or periprostatic structures. The relatively high rate of genitourinary tract infection is a concern and could have been related to the cystoscopy or suprapubic cystostomy performed outside of the traditional endoscopy or surgical suite, or possible cross-contamination from ECD insertion and manipulation. Functional outcomes, IPSS and IIEF-15, both showed a favorable anticipated trend of initial deterioration with subsequent gradual improvement toward baseline levels.

A 3-mm circumferential margin between the prostate capsule and target acute ablation volume was mandated by this first-in-human safety study, regardless of tumor location, which was deliberately conservative based on preclinical data [15]. The obvious concern was that this margin, even accounting for 1-3 mm of additional delayed cell kill, translated to a substantial and clinically significant residual viable prostate volume (10% of pretreatment volume) with both benign and malignant tissue left untreated. The residual tissue is located at the prostate periphery where many cancers are located. Building on the favorable safety and morbidity profile from this phase 1 study, subsequent iterations of this technology and clinical study will include a larger patient population and reduced safety margins. In light of the spatial tolerance of thermal ablation confirmed by MRI thermometry, it is hypothesized that the planning perimeter can be extended with predictable targeting and precise controlled ablation. Treatment-related safety and morbidity will be reassessed accordingly.

Oncologic outcomes were not the primary or secondary end point of this phase 1 study, and thus no meaningful conclusion can be derived. The limited data from the two RP specimens, showing only viable tissue at the periphery, are encouraging. The observed rate of positive biopsies could partly be attributed to the previously mentioned safety margin and smaller treatment target. The potential source of undertreatment could have been compounded by subjective manual prostate delineations by the urologists and radiologists. The PSA and biopsy data, however, provide supportive evidence of safe and feasible conservative whole-gland ablation. Although some patients had residual cancer on follow-up biopsy, the proportion with leak-free, pad-free urinary continence, maintenance of erectile function sufficient for penetration, and negative biopsy or biopsy with clinically meaningful reduction in overall disease burden was noteworthy.

### 4.2. Study limitations

Obvious limitations of the study include the small sample size and short follow-up, although the phase 1 safety, feasibility, and exploratory clinical end points were achieved. Concerns regarding the peripheral location of many PCas within the imposed safety treatment margin can be viewed as limitations, although the obligation was to satisfy safety requirements.

### 4.3. Context and future directions

The ultimate treatment goal for clinically significant organconfined PCa is to obtain local cancer control with minimal morbidity, avoiding treatment-related effects including urinary, erectile, and bowel dysfunction. Current management approaches are polarized between aggressive definitive whole-gland treatment and active surveillance. MRI-TULSA offers the potential to tailor ablation and its extent to individual patient disease characteristics and treatment expectations.

Focal therapy also attempts to provide a good riskbenefit ratio by targeting treatment only to primary index lesions. Although MRI-TULSA meets all requirements set out by an international task force on focal therapy [26], reliable imaging of all clinically significant lesions and the multifocal nature of PCa remain important challenges [27].

Considering the spatial ablation precision demonstrated in this phase 1 study and that most adverse events were related to infection and short-term prostate edema, it is conceivable the 3-mm safety margin can be reduced while maintaining a good safety profile with improved oncologic outcomes. Incorporating diagnostic MRI information into the treatment planning workflow may be the key to ensure complete ablation of MRI-visible index lesions while delivering significant therapeutic effect to most of the prostate and minimizing damage to periprostatic tissue.

Based on the safety profile and promising oncologic outcomes obtained in this phase 1 study using a firstgeneration device, plans for a larger multicenter pivotal clinical trial are under way, with special attention to reduce the safety margins and increase the cytocidal effects of the treatment to the prostate capsule.

### 5. Conclusions

MRI-TULSA is a novel minimally invasive procedure that provides detailed treatment planning, real-time thermal dosimetry, and precise closed-loop feedback control of prostate ablation, with a well-tolerated side-effect profile. This study demonstrates the clinical safety and feasibility of MRI-TULSA for whole-gland prostate ablation in the primary treatment setting of patients with localized PCa. Although the risk-benefit ratio achieved in this study is promising for conservative management of this disease, MRI-TULSA offers the flexibility to further tailor treatments on a patient-specific basis. Data from this phase 1 clinical trial are sufficiently compelling for further study of MRI-TULSA in a wider PCa patient population, with reduced safety margins.

*Author contributions:* Joseph L. Chin 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: Chin, Pahernik, Roethke, Relle, Burtnyk. Acquisition of data: Chin, Billia, Relle, Roethke, Popeneciu, Kuru, Hatiboglu, Mueller-Wolf, Romagnoli, Kassam, Hafron, Nandalur, Chronik, Burtnyk, Pahernik. Analysis and interpretation of data: Chin, Billia, Relle, Roethke, Popeneciu, Kuru, Mueller-Wolf, Romagnoli, Kassam, Hafron, Nandalur, Burtnyk, Pahernik. Drafting of the manuscript: Chin, Billia, Burtnyk. Critical revision of the manuscript for important intellectual content: Pahernik, Relle. Statistical analysis: Burtnyk. Obtaining funding: None. Administrative, technical, or material support: Chronik. Supervision: Motsch, Harle, Schlemmer. Other (specify): None.

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