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Magnetic Resonance Imaging-Guided Transurethral Ultrasound Ablation of Prostate Cancer

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Purpose: Magnetic resonance imaging-guided transurethral ultrasound ablation uses directional thermal ultrasound under magnetic resonance imaging thermometry feedback control for prostatic ablation. We report 12-month outcomes from a prospective multicenter trial (TACT).

Materials and Methods: A total of 115 men with favorable to intermediate risk prostate cancer across 13 centers were treated with whole gland ablation sparing the urethra and apical sphincter. The co-primary 12-month endpoints were safety and efficacy.

Results: In all, 72 (63%) had grade group 2 and 77 (67%) had NCCN® intermediate risk disease. Median treatment delivery time was 51 minutes with 98% (IQR 95–99) thermal coverage of target volume and spatial ablation precision of ±1.4 mm on magnetic resonance imaging thermometry. Grade 3 adverse events occurred in 9 (8%) men. The primary endpoint (U.S. Food and Drug Administration mandated) of prostate specific antigen reduction ≥75% was achieved in 110 of 115 (96%) with median prostate specific antigen reduction of 95% and nadir of 0.34 ng/ml. Median prostate volume decreased from 37 to 3 cc. Among 68 men with pretreatment grade group 2 disease, 52 (79%) were free of grade group 2 disease on 12-month biopsy. Of 111 men with 12-month biopsy data, 72 (65%) had no evidence of cancer. Erections (International Index of Erectile Function question 2 score 2 or greater) were maintained/regained in 69 of 92 (75%). Multivariate predictors of persistent grade group 2 at 12 months included intraprostatic calcifications at screening, suboptimal magnetic resonance imaging thermal coverage of target volume and a PI-RADS™ 3 or greater lesion at 12-month magnetic resonance imaging ($p < 0.05$).

Conclusions: The TACT study of magnetic resonance imaging-guided transurethral ultrasound whole gland ablation in men with localized prostate cancer

Abbreviations and Acronyms

ED = erectile dysfunction
GG = grade group
IIEF-15 = International Index of Erectile Function
IPSS = International Prostate Symptom Score
MID = minimally important difference
MRI = magnetic resonance imaging
PSA = prostate specific antigen
TACT = TULSA-PRO Ablation Clinical Trial
TULSA = transurethral ultrasound ablation

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demonstrated effective tissue ablation and prostate specific antigen reduction with low rates of toxicity and residual disease.

Key Words: prostatic neoplasms; radiotherapy, image guided; minimally invasive surgical procedures; transurethral resection of prostate; magnetic resonance imaging

MEN with early stage prostate cancer are faced with a choice between active surveillance or radical therapy (surgery or radiation). Emerging image-guided minimally invasive ablative treatments offer an appealing alternative with potential benefits of a relatively nonmorbid intervention and cancer eradication.

Multiparametric magnetic resonance imaging directs targeted therapy and enables real-time mapping of tissue temperature during ablation. MRI-guided transurethral ultrasound ablation is a novel ablation procedure using the TULSA-PRO® device, which leverages MRI thermometry and disease localization to ablate via transurethral thermal ultrasound.1–8 TULSA differs from transrectal high intensity focused ultrasound by use of a continuous sweeping directional ultrasound beam delivered from the prostatic urethra (rather than discrete spots transrectally), real-time MRI for planning and thermometry, and cooling of the urethra and rectum.

Treat-and-resect studies confirmed feasibility of thermally ablating prostate tissue under magnetic resonance thermometry with an accuracy of 1 to 3 mm. Heating 55C or greater achieved 100% cell kill in the treatment zone.[8,9] A phase I study of whole gland treatment in men with predominately low risk prostate cancer demonstrated an acceptable safety profile and quality of life outcomes at 12 months[10] but intentionally left 10% of the peripheral prostate untreated. The multicenter prospective trial described here evaluates the safety and efficacy of ablating to the prostate capsule.

MATERIALS AND METHODS

Patients

TULSA-PRO Ablation Clinical Trial is a prospective, multi-center, single-arm pivotal study in patients with localized prostate cancer (NCT02766543). The protocol was designed in conjunction with the U.S. Food and Drug Administration towards 510(k) clearance as a prostate ablation device and received IRB approval at 13 centers in the U.S.A., Europe and Canada. Informed consent was obtained from all participants.

Inclusion criteria were age 45 to 80 years old, Gleason Grade Group 1 to 2 prostate cancer, clinical stage T2b or less, PSA 15 ng/ml or less, minimum 10-core biopsy, no previous treatment and could undergo MRI.

Exclusion criteria were prostate greater than 90 cc, width greater than 6 cm or length greater than 5 cm; nonMRI compatible implants, active infection, suspected tumor within 3 mm of the prostate apical plane on MRI, intraprostatic cysts or calcifications greater than 1 cm.

TULSA Procedure

Whole gland TULSA sparing the urethra and a 3 mm margin of prostate tissue at the apical sphincter was performed within 3T MRI (Skyra/Prisma, Siemens, Germany; Achieva/Ingenia, Philips, Netherlands). The device consists of a rigid ultrasound applicator which incorporates a linear array of 10 ultrasound transducers that emit directional (focused to a blade) energy into the prostate (fig. 1). This results in a continuous region of thermal ablation to the prostate capsule. Water pumped through the applicator and an endorectal cooling device provides 1 to 2 mm of periurethral and rectal preservation.[10] The applicator is secured with a MRI compatible robot that provides remote linear and rotational motion of the device within the prostatic urethra. A treatment delivery console includes software to outline the target prostate boundary, monitors thermal therapy and implements temperature feedback.

The TULSA outpatient procedure was performed as a collaboration between a urologist and radiologist as previously described.[8–10] Prophylactic antibiotics were administered before and for several days after treatment. General anesthesia, cystoscopy and suprapubic catheter placement were performed outside the MRI suite. Treatment planning images were acquired and used to register the ultrasound applicator location, guide adjustments and define target ablation area. In the context of a safety and efficacy study, ablation plans were set with a small margin from the apical plane to avoid incontinence. During treatment, images from magnetic resonance thermometry are displayed every 5 to 6 seconds to determine the amount of energy delivered by each transducer. The ultrasound frequency, applied power and device rotation are automatically modulated to achieve an ablative temperature of 55C within the treatment target.

Patient Assessment and Endpoints

Primary objectives were safety and efficacy. Primary safety endpoint was frequency and severity of adverse events, documented at each visit according to the Common Terminology Criteria for Adverse Events. Primary efficacy endpoint for prostate tissue ablation was proportion of men achieving a PSA reduction $\geq$75% of baseline, defined to meet regulatory requirements rather than oncological control.

Secondary endpoints were: early oncological efficacy defined as the proportion of patients with no cancer or reduced grade and extent of cancer on 12-month 10-core biopsy, prostate volume reduction assessed by central radiology, patient reported changes in quality-of-life, and evaluation of post treatment multiparametric MRI.

Urinary symptoms were assessed based on a minimally important difference of 5 in the International Prostate Symptom Score[11] and a MID of 1 for the IPSS quality of life item. MIDs for voiding and storage subscores were half the standard deviation of baseline values.[12] Voiding function was assessed by the number of men with postvoid residual less than 100 ml, and number of

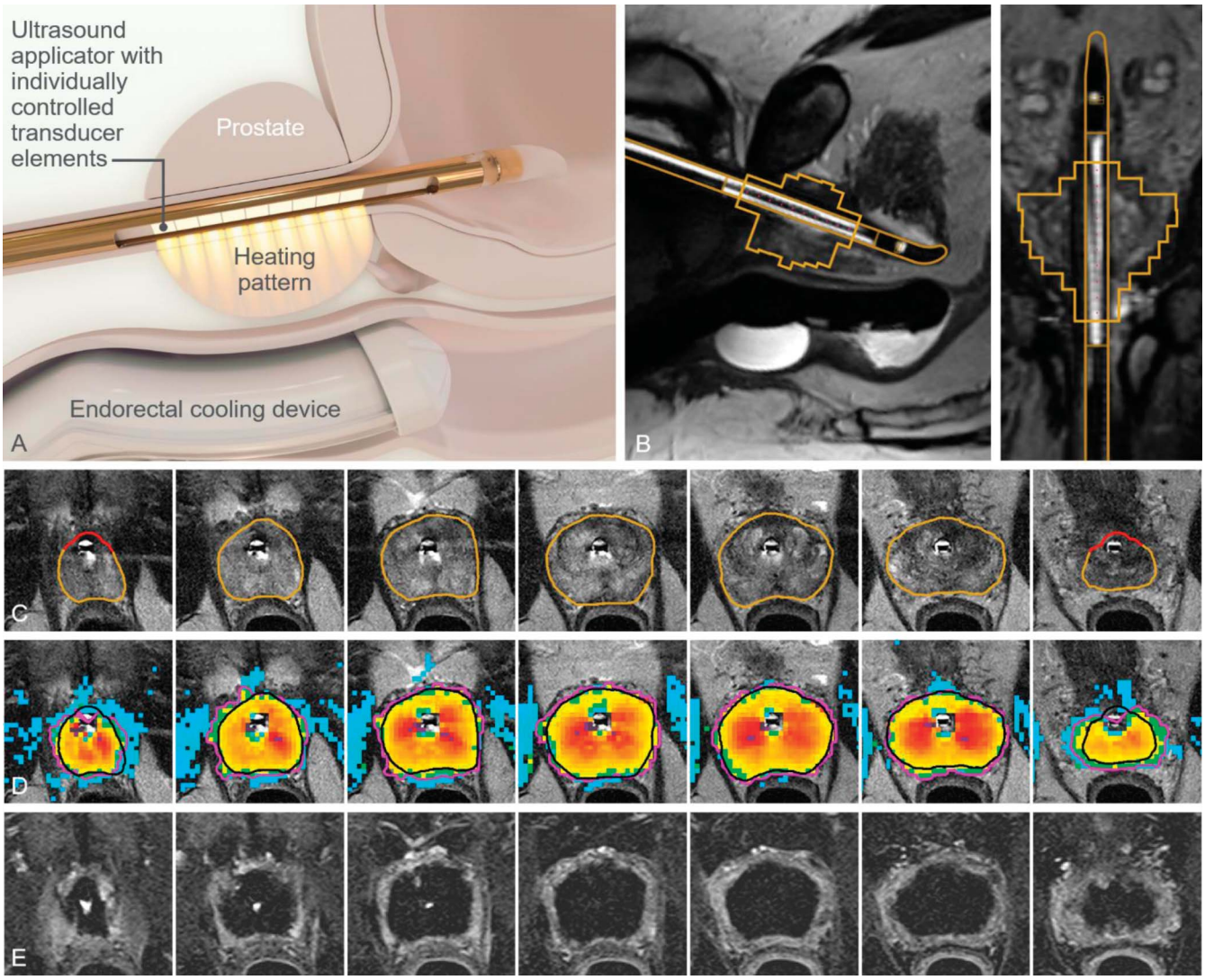


Figure 1. TULSA procedure. *A,* rendering of ultrasound applicator and endorectal cooling device. *B,* sagittal and coronal views of 3D T2-weighted image of ultrasound applicator and planned ablation zone. *C,* ablation zone prescribed on intraoperative axial T2-weighted images from prostate apex to base. *D,* MRI temperature map depicting maximum temperatures achieved during treatment. *E,* enhancement defect confirms ablation extent on posttreatment contrast enhanced T1 weighted images.

men with peak urinary flow rate 15 ml/sec or greater. Erectile function was assessed using International Index of Erectile Function questionnaire with a MID of 4.[13] Potency was evaluated by IIEF-15 question 2, similar to analyses in focal therapy trials.[14] Other quality of life domains, daily pad use and urine leakage were assessed with the EPIC-50 questionnaire.[15] Missing IPSS, IIEF, EPIC and ECOG scores were not interpolated.

Statistical Methods

The predefined primary efficacy endpoint was the proportion of men achieving a prostate specific antigen reduction 75% or more of baseline. With a success threshold of 50% of patients, a 1-sided exact test ($\alpha = 0.025$) was expected to reach 80% power with 90 patients. For accurate estimation of safety and secondary outcomes and to account for dropout, 110 patients were targeted.

Continuous variables describing PSA, prostate volume and quality of life scores were summarized by median and interquartile range and compared to baseline using paired 2-sided Wilcoxon signed rank tests or Friedman tests with significance of $p < 0.05$. Dichotomous variables describing the number of patients who experienced a gain or loss of function, or moderate change in quality of life 2 or more times MID were summarized as proportions and compared to baseline using exact tests.

Multivariate logistic regression assessed the relative odds of having GG2 on 12-month biopsy, adjusting for baseline characteristics, treatment day parameters and 12-month MRI. Analyses were performed using R (R Foundation for Statistical Computing, Austria).

RESULTS

Patients

Among 115 men, median age was 65 (IQR 59–69) years, PSA 6.3 (4.6–7.9) ng/ml; 77 (67%) and 38 (33%)

Table 1. *Baseline patient demographics and clinical characteristics of 115 patients*

Median age (IQR, range)	65.0	(59–69, 46–79)
Median body mass index, kg/m^2 (IQR, range)	27.7	(24–30, 20–43)
No. race (%):		
White/Caucasian	99	(86)
Hispanic	9	(8)
Black	5	(4)
Asian	2	(2)
No. Grade Group (%):		
Low volume GG1 (2 or fewer cores and less than 50% in any core)	17	(15)
High volume GG1	26	(23)
GG2	69	(60)
GG3	3	(3)
No. biopsy cores positive (%):		
1 to 2 cores	33	(29)
3 to 4 cores	36	(31)
5 or more cores	46	(40)
No. disease laterality (%):		
Unilateral GG1	28	(24)
Bilateral GG1	15	(13)
Unilateral GG2	36	(31)
GG2 with contralateral GG1	18	(16)
Bilateral GG2	18	(16)
Median PSA, ng/ml (IQR, range)	6.3 (4.6–7.9, 0.9–17.1)	
No. clinical stage (%):		
T1c	89	(77)
T2a	20	(17)
T2b	1	(1)
T2, unspecified substage	5	(4)
No. prostate volume (%):*		
Less than 20 cc (minimum 15 cc)	5	(4)
20 to 40 cc	51	(44)
40 to 60 cc	48	(42)
60 to 80 cc	7	(6)
80 cc or more (maximum 125 cc)	4	(3)
No. baseline PI-RADS^{TM} (%):*		
2 or less	17	(15)
3	21	(18)
4	60	(52)
5	17	(15)
No. prostatic calcifications (%):		
No	101	(88)
Yes (max less than 10 mm)	14	(12)

* Assessed by site

patients had NCCN intermediate and low risk disease, respectively (table 1). Seventy-two patients (63%) had ≥GG2 (3 had GG3 and were granted protocol deviations due to having only slightly more than 50% Gleason pattern 4 cancer with otherwise favorable characteristics), 26 (23%) had high volume GG1 (3 or more cores or 50% or greater in a core) and 17 (15%) had low volume GG1.

TULSA Procedure

Median procedure time from positioning the anesthetized patient in the MRI to recovery was 243 (IQR 201–281) minutes. Median ablation time was 51 (IQR 39–66, range 21–112) minutes. Median targeted prostate volume was 40 (IQR 31–51) cc, with 98% of the prescribed target prostate volume heated to ablative temperatures (thermal dose greater than 240 equivalent minutes at 43C)[16] and spatial accuracy/ablation precision of 0.1±1.4 mm measured on MRI thermometry.

Patients were discharged the same day (55%) or admitted overnight (45%), per protocol and physician's discretion. Median time to successful voiding and removal of suprapubic catheter was 17 (IQR 11–24) days.

Safety

A total of 12 Grade 3 (severe) adverse events occurred in 9 (8%) men, including genitourinary infection (4%), urethral stricture (2%), urinary retention (1.7%), urethral calculus and pain (1%) and urinoma (1%), all resolved by the 12-month visit (table 2). There were no Grade 4 events, rectal injuries, severe incontinence requiring surgical intervention or severe erectile dysfunction unresponsive to medication.

At 12 months, 27 men (23%) had moderate ED (Grade 2, managed by oral medication with no new use of vacuum pump or penile injections), and 3 (2.6%) had moderate urinary incontinence (Grade 2, pad use). The majority of other attributable Grade 1 and 2 (mild to moderate) adverse events occurred and resolved within 3 months of treatment. Urinary tract infections (25% Grade 2 including asymptomatic positive culture at 1-month urine analysis) resolved with oral antibiotics, and 2 (1.8%) had recurrent infections ongoing at 12 months. Urethral stricture occurred in 3 men (2.6%) and resolved with a transurethral procedure. Urinary retention in 10 men (9%) resolved within 3 months with medication and/or catheterization. Moderate abdominal or rectal discomfort was experienced by 4 men (3.5%) and resolved with ibuprofen/acetaminophen in the first month.

Efficacy

PSA reduction 75% or greater as achieved in 110 (96%) men. Median PSA reduction was 95% (IQR 91–98) to a median nadir of 0.34 (IQR 0.12–0.56) ng/ml. Median (IQR) PSA decreased from 6.3 (4.6–7.9) ng/ml to 0.5 (0.3–1.2) ng/ml at 1 month. At 12 months, median PSA was stable at 0.5 (0.3–1.2) ng/ml with biochemical failure (PSA nadir + 2 ng/ml) in 3 men (2.6%; table 3). Two of 115 patients had missing 12-month PSA values, which were interpolated from the 6-month visit.

Median decrease in perfused prostate volume as assessed by a central radiologist using 12-month MRI was 91%, from a median 37 (IQR 27–48) cc to 2.8 (IQR 1.7–4.7) cc. At 12 months, 111 (97%) men underwent prostate biopsy (fig. 2), the remaining 4 men refused. A median of 10 (IQR 10–12) cores sampled the diminished prostate volume, for an increased sampling density of 3.5 (IQR 2.1–5.7) cores per cc of prostate compared to 0.4 (IQR 0.3–0.5) cores per cc at baseline. There was no evidence of cancer in 72 (65%) men and 16 (14%)

Table 2. *Adverse events reported according to Common Terminology Criteria for Adverse Events as total number of attributable events occurring at any time (and proportion of study participants experiencing those events), and subset of those events that were ongoing at 12-month visit.*

Attributable Adverse Events Description	Any Occurrence			Ongoing at 12 Months		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
No. genitourinary (%):						
Erectile dysfunction	16 (14)	33 (29)	—	14 (12)	27 (23)	—
Hematuria	43 (35)	2 (2)	—	—	—	—
Urinary incontinence	21 (17)	7 (6)	—	9 (8)	3 (3)	—
Pain/discomfort (pelvic/genital/treatment area)	21 (15)	8 (7)	—	2 (2)	—	—
Urinary urgency	24 (18)	5 (4)	—	3 (3)	—	—
Edema	25 (17)	4 (4)	—	—	—	—
Dysuria	13 (11)	11 (7)	—	2 (2)	—	—
Urinary frequency	14 (12)	2 (2)	—	4 (3)	—	—
Ejaculation disorder	12 (10)	3 (3)	—	6 (5)	3 (3)	—
Bladder spasm	1 (1)	12 (10)	—	—	—	—
Urethral bleeding	13 (11)	—	—	—	—	—
Urethral discharge	10 (9)	1 (1)	—	—	—	—
Urinary retention	—	9 (7)	2 (2)	—	—	—
Weak urinary stream	9 (6)	4 (3)	—	2 (2)	3 (3)	—
Nondescriptive lower urinary tract symptoms	6 (5)	4 (3)	—	3 (3)	—	—
Pain/discomfort (bladder/urinary tract)	4 (3)	4 (3)	1 (1)	1 (1)	—	—
Debris in urine	5 (3)	1 (1)	—	—	—	—
Urethral stricture	—	1 (1)	2 (2)	—	—	—
Urethral calculus	—	—	1 (1)	—	—	—
Urinoma	—	—	1 (1)	—	—	—
No. infections (%):						
Urinary tract infection	—	40 (25)	3 (3)	—	2 (2)	—
Epididymitis	—	6 (5)	2 (1)	—	—	—
No. gastrointestinal pain/discomfort (abdominal/anorectal) (%)	10 (9)	4 (3)	—	—	—	—
No. general pain/discomfort (hip/back) (%)	5 (3)	5 (4)	—	—	—	—
No. deep vein thrombosis (%)	—	1 (1)	—	—	—	—

Grade 1 to 2 events occurring in 3% or more of patients and all serious (requiring hospital stay) or severe (grade 3) events are listed, with worst grade reported for each patient. There were no attributable Grade 4 to 5 events. Includes 10 attributable serious adverse events (requiring hospital stay) occurring in 7 (6%) men, all resolved by 12 months: infection (4%), urinary retention (1%), urethral stricture (1%), urinoma (1%), and deep vein thrombosis (1%).

had low volume GG1. Among the 68 men with GG2 or greater at baseline, 54 (79%) were free of GG2 or greater at 12 months. Similarly, 20 of 26 (77%) men with high volume GG1 at baseline had either no cancer or low volume GG1 (fewer than 3 cores and less than 50% per core) at 12 months. In men with low volume GG1 at baseline, 13 of 17 (77%) were free of any disease at 12 months. Overall, histological improvement (eradication of GG2, shift from high to low volume GG1, or eradication of GG1 disease) occurred in 7% to 80% of men across all risk subgroups.

On multivariable analysis (supplementary table, https://www.jurology.com), predictors of GG2 or greater at 12-month biopsy included presence of intraprostatic calcifications at screening (OR 11.4, 95% CI 1.8–73, p=0.01), failure to achieve thermal dose coverage 96% or greater (OR 4.34, CI 1.1–18, p=0.04) and presence of PI-RADS version 2 score 3 or greater lesion at 12-month MRI (OR 8.79, CI 1.8–44, p=0.008). Baseline tumor grade, bilaterality, baseline MRI findings, prostate volume and PSA were not associated with presence of GG2 or greater at 12-month biopsy. Results of the model did not change significantly upon removal of MRI after treatment or addition of pre-treatment apical disease.

Based on 12-month assessment, 8 (7%) men sought additional treatment, while 11 (10%) men with GG2 or biochemical failure had thus far refused further therapy. Repeat TULSA was not permitted per protocol, and patients opted for radical prostatectomy (4) or radiation (4), for which detailed outcomes are not currently available.

Quality of Life

Patient reported measures of erectile function (IIEF-15) and overall sexual function and satisfaction (EPIC-50 sexual domain score) indicated an initial decline followed by gradual recovery, with a third experiencing moderately decreased sexual function at 12 months (table 3). Of the 92 men who were potent at baseline (IIEF-15 question 2 score 2 or greater indicating erection firmness sufficient for penetration at least some of the time), 69 (75%) maintained or regained potency by 12 months (fig. 3).

EPIC-50 urinary incontinence domain scores declined at 1 to 3 months and recovered to baseline by 6 months. At 12 months, less than 1% of patients were incontinent (more than 1 pad/day on EPIC-50 item 5), 7% wore 1 pad/day and 4% reported more daily leakage than baseline.

Table 3. *Clinical outcomes*

Efficacy Outcomes (Median and interquartile range)	Baseline	1 month	3 months	6 months	12 months	MID	Moderate Decline 2 or greater × MID (% men at 1 year)	Moderate Improvement 2 or more × MID (% men at 1 year)	Loss of Function (% Men at 1 yr)	Gain of Function (% Men at 1 yr)
Efficacy outcomes:										
Median PSA,* ng/ml (IQR)	6.3 (4.6—7.9)	**0.5 (0.3—1.2)**	**0.5 (0.2—0.9)**	**0.5 (0.2—1.0)**	**0.5 (0.3—1.2)**	—	—	—	—	—
Median prostate volume,†, ‡ cc (IQR)	37 (27—48)	—	—	—	**2.8 (1.7—4.7)**	—	—	—	—	—
MRI lesion,† PI-RADS™ 3 or greater (%)	84/114 (74)	—	—	—	**31/104 (30)**	—	—	—	—	—
Median quality of life questionnaires (IQR):										
IPSS Urinary Symptom Score	7 (3—10)	**14 (7—21)**	8 (4—12)	6 (2—12)	6 (3—9)	5	8/112 (7)	7/112 (6)	—	—
IPSS Quality of Life	1 (0—3)	**3 (1—5)**	2 (1—3)	1 (0—2)	1 (0—2)	1	15/113 (13)	21/113 (19)	—	—
IPSS Voiding Subscore	2 (0—6)	**5 (2—10)**	2 (0—5)	2 (0—6)	2 (0—6)	1.9	20/113 (18)	20/113 (18)	—	—
IPSS Storage Subscore	3 (2—6)	**7 (4—11)**	**5 (3—7)**	3 (2—7)	3 (2—5)	1.4	19/112 (17)	16/112 (14)	—	—
IIEF-15 Erectile Function Domain	26 (17—29)	**5 (2—8)**	**6 (3—21)**	**8 (4—24)**	**14 (5—26)**	4	**38/109 (35)**	6/109 (6)	—	—
EPIC Urinary Incontinence Domain	100 (92—100)	**84 (54—100)**	**84 (65—100)**	100 (79—100)	100 (86—100)	9	16/112 (14)	8/112 (7)	—	—
EPIC Irritative/Obstructive Domain	93 (86—97)	**54 (32—75)**	86 (75—96)	93 (79—100)	93 (82—100)	7	9/110 (8)	6/110 (5)	—	—
EPIC Bowel Domain	96 (93—100)	**95 (88—98)**	98 (93—100)	98 (93—100)	97 (93—100)	6	6/110 (5)	2/110 (2)	—	—
EPIC Sexual Domain	67 (52—75)	**21 (10—39)**	**31 (17—50)**	**37 (18—58)**	**44 (19—63)**	12	**35/108 (32)**	1/108 (1)	—	—
Functional outcomes:										
Median peak urine flow§ (QMax), ml/s	17 (12—22)	—	—	—	16 (12—22)	—	—	—	7/37 (19)	7/25 (28)
Postvoid residual,‖ ml	30 (9—67)	—	—	—	**14 (0—50)**	—	—	—	6/78 (8)	**11/15 (73)**
ECOG Performance Status¶ (% men)	**112/114 (98)**	95/110 (86)	90/94 (96)	104/107 (97)	105/107 (98)	—	—	—	2/112 (2)	**2/2 (100)**

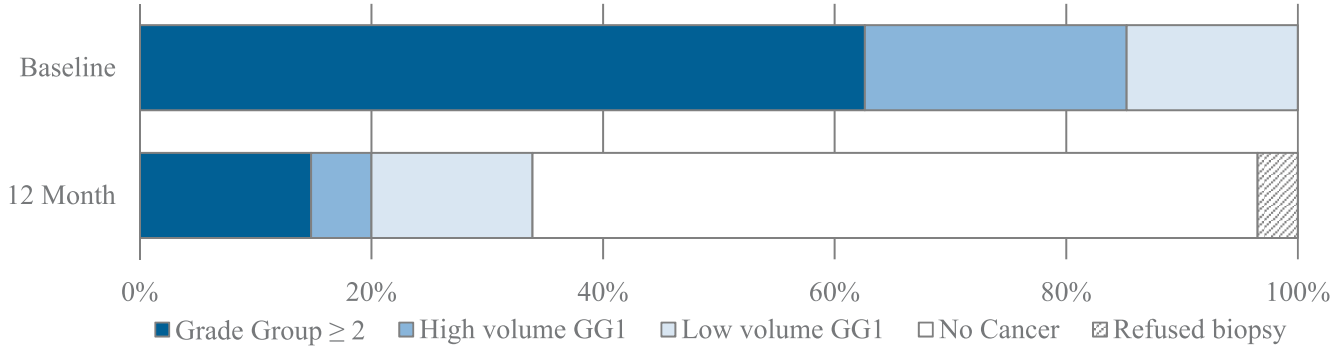
Bolded values have a statistically significant difference from baseline. MID for IPSS subscores defined as 0.5 SD from baseline.
* Nadir 0.34 (0.1—0.6); reduction 95% (91—98); proportion with PSA reduction greater than 75%: 110/115 (96%).
† Assessed by central radiology laboratory.
‡ Reduction 91% (87—96).
§ Uroflowmetry included only if voided volume 150 ml or more, reference 15 ml/s or more.
‖ Ref. more than 100 ml.
¶ Ref. 1 or more.

IPSS urinary symptom score, quality of life score and voiding/storage subscores recovered to baseline by 3 months and were unchanged at 12 months, with similar numbers of men experiencing moderate improvements or declines in symptoms. At 12 months, EPIC-50 urinary irritative/obstructive domain scores had recovered, peak urine flow rate was unchanged and nearly all men with high postvoid residual at baseline experienced a significant improvement. EPIC-50 bowel domain scores and ECOG performance status recovered by the 3-month visit.

DISCUSSION

In a large, multicenter prospective study in men with predominately intermediate risk prostate cancer, whole gland ablation sparing the urethra and apical sphincter with MRI-guided transurethral ultrasound ablation met its primary regulatory endpoint of PSA reduction and had a low rate of morbidity. At 12 months extensive biopsy sampling of the markedly reduced prostate volume demonstrated a benefit for nearly 80% of men. TULSA also had a relatively low risk of functional decline. No men had a rectal injury, 96% returned to baseline urinary continence and 75% of potent men maintained or returned to erections sufficient for penetration.

The primary PSA endpoint was met, defined by regulators to assess the efficacy of TULSA as a prostate tissue ablation device. This is an early report from a single-arm study. The patient population allowed for evaluation of oncologically relevant secondary outcomes including PSA stability, posttreatment biopsy and salvage treatment.



Baseline biopsy Median sampling density: 0.35 cores/ml	**12-month biopsy** Median sampling density: 3.5 cores/ml				
	No cancer	**Low-Volume GG1**	**High-Volume GG1**	**GG ≥2**	**Clinical Benefit**
Low-Volume Grade Group 1 (GG1) (n=17; 1-2 positive cores and < 50% per core)	13/17 (76%)	3/17 (18%)	0/17 (0%)	1/17 (6%)	13/17 (76%) No cancer
High Volume GG 1 (n=26; ≥ 3 positive cores or ≥ 50% per core)	16/26 (62%)	4/26 (15%)	4/26 (15%)	2/26 (8%)	20/26 (77%) No cancer or low-volume GG1
GG ≥2 (n=68; includes 3 men with GG3)	43/68 (63%)	9/68 (13%)	2/68 (3%)	14/68 (21%)[1]	54/68 (79%) No cancer or only GG1
Overall (n=111; excludes 4 with baseline GG2 who refused biopsy at 12 months)	72/111 (65%)	16/111 (14%)	6/111 (5%)	17/111 (15%)	87/111 (78%) No cancer or reduced volume/grade

[1] Includes 8 men with GG2, 3 GG3, 2 GG4, and 1 GG5.

Figure 2. Histological outcomes stratified by grade and volume at baseline and 12 months. Of 68 men with GG2 or greater disease on baseline biopsy 79% experienced clinical benefit of either no cancer or only GG1 upon 12-month systematic 10-core biopsy of their residual prostate tissue. Likewise, of 26 men with high volume GG1 (3 or more positive cores or 50% or more per core) at baseline 77% experienced the clinical benefit of either no cancer or only low volume GG1 at 12 months. Overall, 65% of 111 men who underwent biopsy after TULSA had no evidence of cancer at 12 months.

Notwithstanding the limitations of comparisons between ablative and extirpative therapies, the 7% rate of salvage treatment and 20% rate of residual clinically significant prostate cancer in intermediate risk patients (two-thirds of those with GG2 or greater having either bilateral disease or at least 5 positive cores) are in line with accepted rates of early failure or additional intervention after standard treatments[17,18] and goals for retreatment after ablative therapies.[19] The inclusion of men with low risk disease reflects guidelines at the time the protocol was designed. However, the majority of these patients enrolled with suspicious MRI lesions and either bilateral disease or 3 or more positive cores.

TULSA was associated with a high degree of safety and maintenance of quality of life. Moderate urinary incontinence (Grade 2, pads indicated) was experienced by 2.6% of men, with 7% wearing 1 pad per day and 1 (0.9%) wearing more than 1 pad per day. ED was experienced by 23% to 35% while erection sufficient for penetration was preserved in 75% of potent men. These compare favorably to radical prostatectomy[20,21] and other whole gland ablation techniques.[22,23] We did not observe any bowel toxicity, an important concern for patients undergoing radiation therapy or transrectal high intensity focused ultrasound.[24] An appeal of the transurethral approach is that energy is not directed through the rectum. Therefore, the risk of rectal injury is less than a transrectal approach. This also means that the entire prostate gland can be treated, without limitations related to prostate volume, or distance from the anterior prostate to the rectum.

Limitations of this report include the relatively short duration of followup and reliance on post-ablation systematic biopsy for evaluating local histological control. While level 1 evidence supporting MRI-targeted biopsy emerged after the

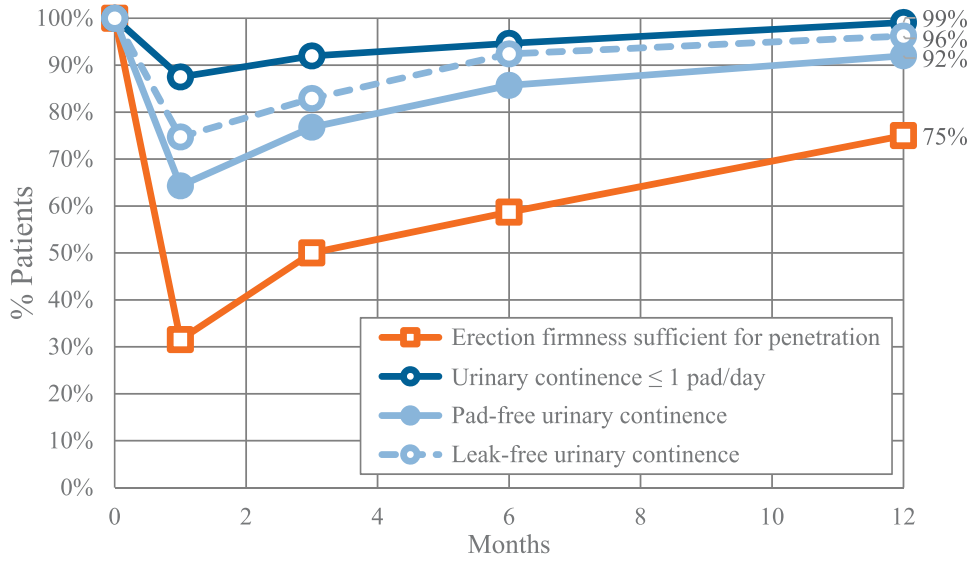


Figure 3. Functional outcomes. Erection sufficient for penetration (IIEF question 2 score 2 or greater) assessed among 92 men who had adequate function at baseline. Urinary continence reported as normalized proportion of patients free of daily leakage or pad use defined using EPIC questions 1 and 5, respectively.

study was designed, the median of 10 systematic posttreatment biopsy cores from small prostates (median 3 cc) represents a high sampling density compared to typical 1 core/cc saturation template mapping biopsy[25] and is unlikely to miss significant residual cancers. Thermally fixed nonviable cells can retain their apparently malignant tissue morphology, confounding Gleason grading and potentially introducing false positives.[26] This is a limitation of relying on postablation biopsies to define oncologic outcome, analogous to early postirradiation biopsies.[27] The relationship between early postTULSA outcomes and traditional endpoints such as clinical recurrence, need for salvage therapy or metastasis-free survival is unknown and will become available with ongoing 5-year followup. A recent publication indicates that salvage prostatectomy after TULSA is safe.[28]

Our study represents the initial learning curve at 13 academic sites with a first generation commercial device for which experienced clinical proctors were not yet available. The small number of subjects at each site demonstrated the ability for new teams to adopt the technique but was reflected in the overall anesthesia durations that were long compared to the approximately 1-hour ablation times. Outcomes may improve with more aggressive screening for intraprostatic calcifications, re-treatment of under-heated regions based on magnetic resonance thermometry, and further experience. Despite excluding patients with calcifications greater than 1 cm, some calcifications less than 1 cm caused acoustic shadowing and were associated with a higher likelihood of residual GG2 or greater disease, indicating the need for more strict limitation of calcification size in future studies. Excluding the 14 patients with calcifications identified at screening, GG2 disease was eliminated in 51 of 60 (85%) men. Early indicators of residual disease such as inadequate thermal coverage on intraoperative maps (observed in 33 patients, of whom 27% had residual GG2), inappropriate PSA response, or suspicious lesion on postTULSA MRI may identify men who might benefit from more rigorous followup or a repeat procedure. Since completion of this study, TULSA has been used primarily for customized partial gland ablation with urethral rather than suprapubic catheterization.[29,30] This has decreased the relatively long posttreatment catheterization period and is likely to reduce the likelihood of urinary complications, ED, incontinence and infections. The data in this study are significantly improved compared to the phase 1 study[10] suggesting that algorithm modifications and local experience improves the efficacy and safety of TULSA.

CONCLUSIONS

TULSA is a minimally invasive procedure that employs planar ultrasound energy with customized MRI based treatment planning, real-time thermal dosimetry and closed loop temperature feedback control for effective prostate cancer ablation with a favorable side effect profile and minimal impact on quality of life. Further studies are warranted and ongoing.

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EDITORIAL COMMENTS

The authors, an impressive group of experienced clinician-scientists, evaluated a relatively new device to treat early stage prostate cancer using MRI guided transurethral ultrasound ablation (TULSA). The protocol was designed to gain U.S. Food and Drug Administration 510(k) clearance as a prostate tissue ablation device. A more vigorous trial will be necessary to gain clearance as a device to specifically treat prostate cancer, a goal of a variety of devices.

The study was comprised of 115 men recruited from 13 centers. Although 63% had GG2 cancers it

is important to note that GG2 alone may add very limited risk. The cut point for high volume disease may easily be exceeded with systematic and targeted biopsy. It appears that the study population was carefully selected and represented a generally lower risk population. The fact that PI-RADS™ 3 or greater predicted residual disease supports this notion.

Although the device described uses a transurethral approach, patients underwent general anesthesia (243 minutes) and had a suprapubic catheter placed (17 days). Treatment was delivered in a MRI unit and was directed by both a urologist and a radiologist. Other devices may have advantages when judged by these criteria. The authors mention that focal therapy is possible with this device and it is likely that this will be pursued, a similar path compared to other ablation strategies which started out as whole gland treatments.

In summary, the authors are to be congratulated for a well-done initial study of a new approach to prostate tissue ablation. How it will compare to the long list of competing approaches remains to be seen. When evaluating all such approaches, urologists have to commit to careful patient selection (avoiding treatment of men who may need no treatment) and designing and completing randomized trials that more critically assess their value in cancer control and avoidance of morbidity.[1]

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Klotz et al present 12-month data on 115 men with low intermediate risk prostate cancer undergoing transurethral ultrasound ablation (TULSA) in 13 centres. This novel minimally invasive procedure applies energy using a rotational device placed in the prostatic urethra (reference 10 in article). Real time thermal dosimetry aims for whole gland ablation up to the capsula at around 55C while a water cooling system spares urethra and rectum. The treatment is given under anesthesia with the patient in the magnetic resonance imaging (MRI) scanner (median total procedure 243 minutes; ablation time only 51 minutes).

Main endpoints were established in collaboration with the U.S. Food and Drug Administration. Grade 3 adverse events were seen in 8%. Of preprocedure potent men, many (75%) maintained or regained potency by 12 months. Incontinence rates were also very favorable. The mandated endpoint of greater than 75% prostate specific antigen (PSA) reduction was reached in 96%. Biochemical failure was seen in only 3%. In 35% however cancer was still found in followup biopsies after 1 year. Long-term oncological endpoints were not the objective of this trial.

As applicable to many novel ablative (focal) therapies,[1] many questions remain including position of TULSA between active surveillance or radical therapies; learning curve; patient-selection using MRI and targeted/systematic biopsies; followup regimen of small remaining gland using posttreatment low PSA, MRI, and/or biopsies; indication for and complications and oncological outcomes of re-intervention or salvage therapy (reference 28 in article). Still, TULSA may prove to be a valuable addition to our treatment arsenal, providing cancer control with low toxicity. Prospective analysis from properly conducted studies and open presentation of the results of all these new techniques should be encouraged.

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REPLY BY AUTHORS

We agree with the comments expressed in these editorials. Our publication represents an early experience (incorporating the learning curve) with this novel technology. It reports endpoints mandated by the U.S. Food and Drug Administration (FDA) geared toward regulatory approval. Patient selection was designed pragmatically to enhance study accrual. Ultimately, we believe the primary role for this technology will be hemiablation for patients with unilateral intermediate risk cancers not interested in active surveillance.

We agree with Drs. van den Bergh and Vis that many questions about the role and limitations of focal therapy remain, including patient selection, systematic vs targeted biopsies, followup strategies and success of retreatment/salvage therapies. Ongoing trials and the incipient international registry of focal therapy outcomes (Focal Therapy Society) will help answer these important questions.

Dr. Carroll comments that FDA approval was for ablation and not prostate cancer treatment. No device has received FDA approval for prostate cancer treatment since the Medical Device Regulation Act of 1976. Pre-1976 treatments such as radiation, prostatectomy and cryotherapy were all grandfathered. Robotic surgical devices have also not received FDA indication to treat cancer. For example, "the FDA's evaluation of robotically-assisted surgical devices has generally focused on determining whether the complication rate at 30 days is clinically comparable to other surgical techniques… for use in the prevention or treatment of cancer, the FDA anticipates these uses would be supported by specific clinical outcomes, such as local cancer recurrence, disease-free survival, or overall survival."[1] Therefore, TULSA for tissue ablation is in a similar regulatory position as the Da Vinci robot.

The conceptual appeal of TULSA is the modifiable closed loop system, whereby energy delivered can be tailored based on the anatomical temperature map. Our data suggest functional outcome and elimination of high grade cancer are promising. With increased experience, iterative selection and treatment modifications, and requisite longer-term followup, we anticipate that TULSA will have a place in the treatment landscape for localized prostate cancer.

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