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ARTICLE

Salvage open radical prostatectomy for recurrent prostate cancer following MRI-guided transurethral ultrasound ablation (TULSA) of the prostate: feasibility and efficacy

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ABSTRACT

Introduction: MRI-guided transurethral ultrasound ablation (TULSA) is a novel modality for minimally invasive ablation in patients with localised prostate cancer (PCa). A multi-national Phase 1 (30 patients) and subsequent Phase 2 (115 patients) study showed TULSA to be feasible, safe and well tolerated. However, technical viability and safety of salvage prostatectomy for those who failed TULSA is unclear. Herein, we report the feasibility and morbidity of salvage radical prostatectomy (sRP) post-TULSA.

Methods: Four patients with biopsy-proven residual cancer following TULSA underwent open retropubic sRP within 39 months of TULSA. Peri-and post-operative morbidity were reported. Detailed histopathologic assessment is reported.

Results: Median follow-up was 43 months after sRP. Mean operating times, blood loss, and length of stay were 210 min, 866 ml, and 3.5 days, respectively. Intraoperative finding of some fibrotic reaction of endopelvic and Denonvilliers fascia was characteristic. There were no perioperative complications. Whole-mount pathology sections showed one pT2b and three pT3a, suggesting under-staging pre-TULSA. Location of disease was compatible with persistent cancer mostly in the untreated peripheral safety region. One man received an artificial urinary sphincter. All men experienced erectile dysfunction responsive to treatment. Two patients with positive surgical margins had PSA progression requiring salvage radiation, with one requiring long-term androgen deprivation therapy.

Conclusions: RP is a viable and safe salvage option if TULSA fails. Technical difficulty and perioperative morbidity were negligible and attributable to minimal peri-prostatic reaction from TULSA.

Abbreviation: IIEF: International index for erectile function; IPSS: International prostate symptom score; IQR: Interquartile range; MRI: Magnetic resonance imaging; PCa: Prostate cancer; PS: Positioning system; QoL: Quality of life; sRP: Salvage radical prostatectomy; TACT: TULSA-PRO Ablation Clinical Trial; TULSA: Transurethral ultrasound ablation; UA: Ultrasound applicator

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Salvage prostatectomy; MRI guided; TULSA; localised prostate cancer

Introduction

Magnetic resonance image (MRI) guided transurethral ultrasound ablation (TULSA) is a novel technology for ablation of organ-confined prostate cancer (PCa). TULSA combines real-time MRI guidance and closed-loop temperature feedback control to provide customised patient-specific targeted ablative therapy with minimal impact to adjacent peri-prostatic structures (Figure 1) [1]. An initial Phase-I (NCT01686958, DRKS00005311) clinical trial of MRI-guided TULSA included treatment-naïve men aged ≥65 years with biopsy-proven low or intermediate risk prostate cancer demonstrated effective ablation of prostatic tissue with a favourable safety profile [2,3].

The Phase-1 study mandated a safety margin of 3 mm within the prostate capsule, resulting in an anticipated 10% of peripheral prostate tissue untreated [3]. Clinical efficacy was confirmed with a Phase 2 trial in 115 patients [4]. The ablation volume was increased from 90% to 98% with the safety margin changed to 2 mm from the prostate capsule and a higher target temperature at the margin (57 C from 55 C) [5].

Patients and methods

Patients with residual clinically significant disease and negative metastatic workup were offered salvage therapy. Herein, we explore the feasibility and morbidity of salvage radical prostatectomy (sRP) following TULSA and report our experience including surgical, histologic and functional outcomes.

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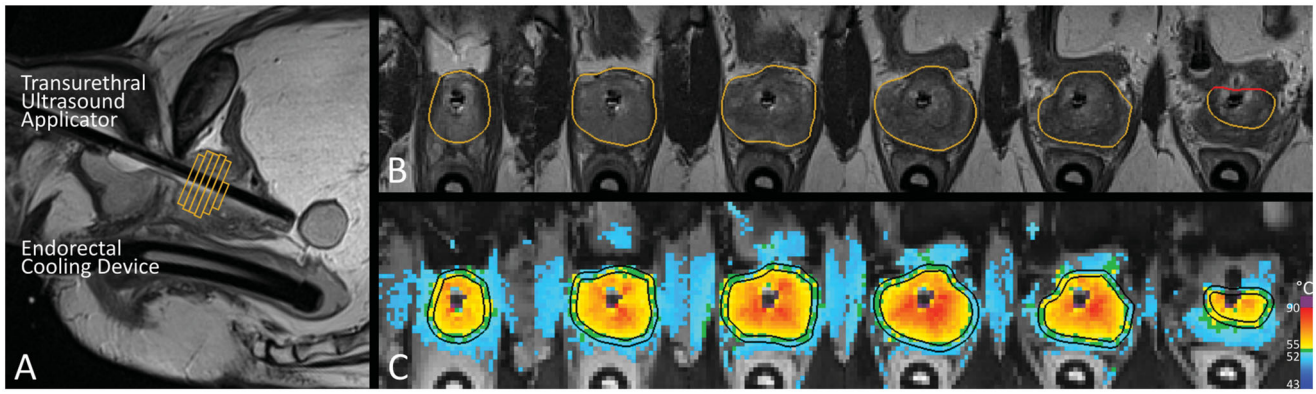

Figure 1. Magnetic resonance imaging-guided transurethral ultrasound ablation of the prostate (TULSA). (A) Sagittal T2-weighted image depicts placement of ultrasound applicator and endorectal cooling device. (B) Overlays indicate locations of target boundaries defined on transverse T2-weighted images from apex (left) to base (right). (C) The physician monitors temperature images acquired dynamically during ablation, which are used by the software to automatically adjust treatment parameters to ensure that thermal necrosis reaches the planned target boundary. In this Phase-I study, ablation extent was limited to a safety margin (inner black contour) set 3 mm inside the prostate capsule (outer contour).

Clinical pathway

The clinical pathway for patients in the Phase-I study included the following visits: A screening visit, confirming Gleason $\leq 3+4$ disease (minimum 12-core Transrectal Ultrasound-guided biopsy acquired $\geq$6 weeks but $\leq$6 months before treatment), Prostate-specific antigen (PSA) $\leq$10 ng/ml. A pre-treatment baseline visit for inclusion/exclusion assessment including detailed medical history and physical examination, PSA, Electrocardiography, cystoscopy, blood and urine analysis, uroflowmetry, and quality-of-life questionnaires (IPSS, IIEF-15, UCLA-PCI-SF). Treatment day included PSA, supra-pubic (SP) catheter placement, MRI-guided planning and ablation, adverse events assessment, and overnight admission only when necessary. The 2-week follow-up visit was comprised of SP catheter removal following clamping for 24 h to ensure successful trial of voiding and post-void residual volume $<$100 cc, physical examination, urine culture and analysis, medication review and adverse events assessment. Subsequent follow-up visits at 1, 3, 6, 12, 24, 36, 48, and 60 months thereafter included physical examination, PSA, blood and urine analysis, uroflowmetry, medication review, adverse events assessment, and quality-of-life questionnaires. Follow-up prostate MRI was acquired at 1 year, and systematic 12-core TRUS-guided biopsy was acquired at 1 and 3 years.

Surgical technique

Salvage surgery was performed with modifications to the open retropubic radical prostatectomy technique with the retrograde Campbell approach as described previously [6]. The open approach was opted over the robotic approach to allow easy intraoperative access to the perineum and rectum, and because of the uncertainty of the degree of operative difficulty. Patients were placed in a modified Lloyd-Davies position with the table flexed at 15 degrees just below the waist. Bilateral pelvic lymphadenectomy was performed. Special attention was paid to the posterior dissection with an assistant placing a finger in the rectum to help provide tactile feedback in proximity to the rectum.

Histological examination

Prostatectomy specimens, including seminal vesicles, were submitted en bloc, and all lymph node dissection specimens including perinodal fat tissue, were submitted for histopathological assessment. The Genito-urinary pathologists were alerted to and familiarised with the pre-operative TULSA procedure. Sectioning of the prostate for pathology followed a standard protocol that optimizes assessment of tumour distribution, resection margins, and any possible areas of extraprostatic tumour extension.

Results

Twelve patients in this Centre were part of the Phase-I study, of which four underwent sRP. Pre-TULSA characteristics showed 3 low risk and 1 intermediate risk prostate cancer (Table 1). The median interval to sRP from TULSA was 21 (15–39) months. Intraoperative dissection in the periprostatic and pre-rectal area was somewhat more difficult than with primary RP due to some increase in tissue reaction and neovascularity. No rectal injury occurred. One patient received a blood transfusion (2 units). Mean blood loss was 1000 cc.

One of four patients had upgrading of GS from post-TULSA biopsies to sRP. Residual viable cancer was primarily located in the periphery, as anticipated due to the deliberate capsular tissue sparing (Figure 2). Three of the four cases showed extra-prostatic extension. Surgical margin status was positive for two patients. There were no cases of lymph node metastasis, with median node yield of 10. All four patients had unilateral nerve sparing.

With a median follow-up of 34 months after sRP, two patients with negative margins have not had biochemical recurrence (Table 1). No patients developed metastatic disease. Functionally, one patient received an artificial urinary sphincter for stress urinary incontinence. All four patients had erectile dysfunction after sRP, but all responded to pharmacologic treatment.

Table 1. Summary of outcomes following sRP post-TULSA treatment.

	Patient 1	Patient 2	Patient 3	Patient 4
Primary TULSA Characteristics				
Pre TULSA Prostate Vol (cc)	32.5	38.9	40.5	46.4
Pre TULSA PSA (ng/mL)	1.2	19.4	4.8	8.0
Pre TULSA Stage	1c	1c	1c	1c
Pre TULSA Gleason Score	3 + 3	3 + 4	3 + 3	3 + 3
sRP Characteristics				
Pre-sRP Age (years)	69	70	70	67
Pre-sRP Prostate Vol (cc)	17.3	21.5	19.9	24.4
Pre-sRP PSA (ng/mL)	1.72	5.29	1.10	9.3
Pre-sRP Gleason Score	3 + 4	3 + 4	3 + 4	3 + 4
Estimated Blood Loss (mL)	700	1000	1000	900
Post-operative length of stay	6	3	3	2
Clavien-Dindo classification	II (ileus)	0	0	0
sRP Histological Features				
Gleason Score	3 + 4	3 + 4	3 + 4	4 + 3+5
Tumour volume	5%	10%	10%	15%
Tumour Stage	3a	3a	2b	3a
Extraprostatic extension	Yes	Yes	No	Yes
Cancer location	R post periphery	L base, bladder neck	Most of L side	Multifocal
Nodal count	14	10	10	9
Surgical margin status	Negative	Positive	Negative	Positive
Short term oncological outcomes				
Follow duration since sRP (mon)	29	46	54	39
Biochemical recurrence (PSA > 0.4)	No	Yes	No	Yes
Salvage treatments	Nil	EBRT	Nil	EBRT, ADT
Short-term functional outcomes				
Urinary function post-sRP	Mild SUI	Continent	SUI – Implant	Mild SUI
Erectile dysfunction pre-sRP	Yes	No	No	No
Erectile dysfunction post-sRP	Yes	Yes	Yes	Yes
Erectile dysfunction treatment	PDE5i	ICI	PDE5i	MUSE
Other complications	Nil	Nil	Urethral stricture – dilated once	Radiation cystitis

ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; ICI: intracavernosal injections; MUSE: medicated urethral system for erectile dysfunction; PDE5i: PDE-5 inhibitors; SUI: stress urinary incontinence. Mild SUI – 1 or less pads/day.

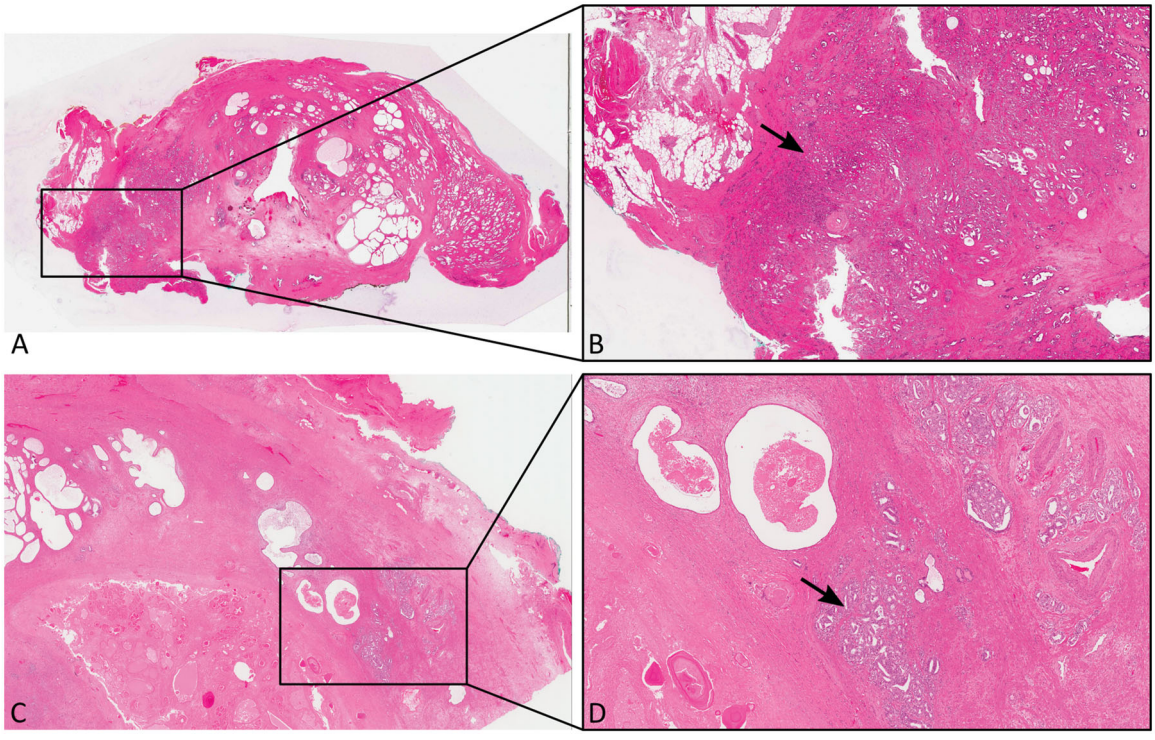

Figure 2. Histological results from two patients showing tumour recurrence towards periphery, outside the ablation zone. H and E stained whole mount for patient 2 (A) and patient 4 (C). A magnified view with arrow showing location of tumour recurrence (B,D).

Discussion

MRI-guided TULSA has been shown to be a safe, feasible, and well-tolerated procedure for prostate cancer tissue ablation [3]. Experience with these four cases illustrates the technical feasibility, and safety of salvage RP after TULSA. For

all patients, the ablative therapy resulted in some tissue reaction and neovascularity, resulting in higher than average blood loss. There were no serious surgical adverse events, and fibrosis was less extensive than usually seen after radiation therapy. Careful and deliberate dissection was essential, and intraoperative access to the rectum was invaluable in avoiding inadvertent proctotomy.

Prior studies have performed treat and resect approach in TULSA patients [7,8]. The initial study, performed to correlate histological changes post-TULSA, was performed in an open approach immediately post-ablation [7]. The second study focused on delayed resection 3 weeks post-TULSA using robot-assisted laparoscopic prostatectomy. Both groups of investigators found the surgical resection uncomplicated. We report similar outcomes for sRP, when performed at a median 21 months. The open surgical approach for sRP was chosen at our institution, with our preference to gain ready access to the rectum intraoperatively if necessary.

All four prostatectomy specimens showed viable disease in the prostate periphery (outside the area of ablation) in addition to one prostate showing multifocal involvement. The peripheral disease could be attributed, for the most part, to the protocol-mandated sparing of the peripheral margin in the Phase-I TULSA trial [9]. It should be noted that the Phase-I trial with the deliberate tissue sparing was not an efficacy study but rather a 'safety and feasibility' trial and thus a conclusion on the effectiveness of TULSA as an ablative modality for cancer could not be drawn. Three of the four patients turned out to have pT3 disease, highlighting suboptimal preoperative staging in this study, where pre-TULSA MRI was not mandatory, (nor was it prevalent in the trial period of 2013–2014), resulting in pre-treatment understaging in these men. More rigorous screening, e.g. with mandatory pre-operative MRI, would have rendered some candidates ineligible for the study due to pre-existing extraprostatic disease.

The histological ablated tissue volume was not correlated with planned ablation area specifically for these patients. The correlation of 12-month prostate volume reduction to non-perfused volume on immediate post-treatment contrast-enhanced T1-weighted MRI has been assessed in patients from this Phase-I trial by Bonekamp et al [2]. This analysis concluded that the non-perfused volume acquired immediately after treatment correlated with but under-estimated the eventual prostate volume reduction, likely due to the effects of delayed cell death. Interestingly, measures of thermal ablation coverage derived from intra-procedural MRI temperature images were found to be in excellent agreement with prostate volume reduction at 12 months.

Oncological, safety, and functional outcomes shown are comparable with sRP post-radiation therapy. There were no instances of anastomotic stricture or rectal injury, major complications that may be encountered in post-radiation sRP [10]. Functional outcomes have also been adequate, with one of the four patients requiring surgical intervention for incontinence. While erectile dysfunction rates have been high, patients have had reasonable success with PDE5 inhibitors or intracavernosal injections. Most importantly, these cases illustrated that salvage prostatectomy is a viable option for patient who fail TULSA.

The major limitations of this study include small sample size, single surgeon experience and short follow up, due to this being the first opportunity to study salvage therapy post-TULSA.

Conclusions

Post-TULSA sRP is both safe and feasible, although technically challenging, with acceptable morbidity.

Acknowledgements

Profound Medical Inc. approved the manuscript.

Research involving human subjects and informed consent

The Phase I clinical trial was approved by local ethics boards as well as registered in USA (NCT01686958) and Europe, (DRKS00005311). Informed consent was obtained from all participating individuals.

Disclosure statement

Joseph L. Chin certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g. employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Joseph L. Chin is a consultant for Profound Medical Inc. Shiva M Nair received honorarium for participating in a user feasibility study for Profound Medical Inc. The remaining authors have nothing to disclose.

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