Personalized Treatment for Patients with Prostate Cancer Using MRI-guided Transurethral Ultrasound Ablation (TULSA)

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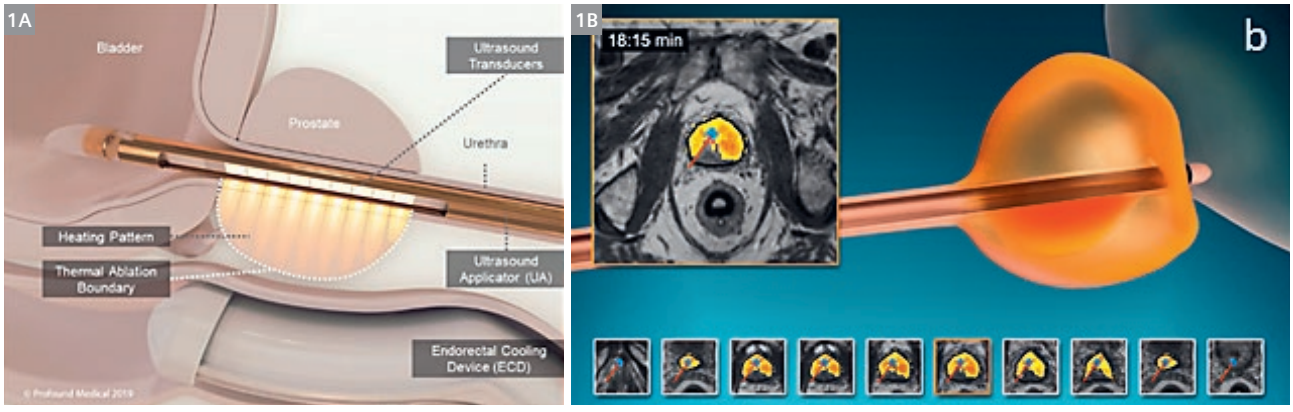
Background

The lifetime risk of being diagnosed with prostate cancer (PCa) is one in six [1]. Although PCa can be lethal, most men who are diagnosed with PCa will not suffer clinically significant consequences from the disease during their lifetime. According to (inter)national guidelines, when a patient has localized PCa treatment the conventional treatment options include radical prostatectomy (RP) and radiation therapy (RT), which treat the whole prostate regardless where the underlying pathology is located. The comorbidity associated with this type of treatment in combination with a relatively high cancer specific survival (92%) has a tremendous impact on quality of life and cost. Approximately 15–20% of the patients who undergo prostatectomy will suffer from treatment-induced urinary dysfunction and 8–36% will have to live with erectile dysfunction [2, 3].

Several new interventions have been developed hoping to offer non-inferior oncological control with an improved safety profile, including minimally invasive modalities such as high-intensity focused ultrasound, cryoablation, and laser ablation [4]. At their inception these technologies performed whole-gland ablation, but as PCa screening and disease localization have improved primarily due to the advent of mpMRI [5], there has been a shift to targeted treatment. Targeted therapy treats the dominant lesion plus an additional thermal safety margin, with the rationale this should offer the best compromise between oncological control and morbidity.

The concept of targeted therapy is still relatively new and therefore controversial, and has stricter inclusion requirements, meaning patients with multi-focal and / or diffuse disease are likely not ideal candidates. This underscores the need for a modality that can delivery safely and effectively both whole-gland and targeted treatment.

MRI-guided transurethral ultrasound ablation (TULSA) has been used as a primary treatment for whole-gland treatment [6, 7] as well as targeted treatment [8, 9] and will be explored in more detail.



1 MRI-guided transurethral ultrasound (TULSA) procedure. **(1A)** Rendering of ultrasound applicator and endorectal cooling device. **(1B)** Ablation zone is prescribed on intraoperative transverse T2-weighted images from prostate apex to base, and the ablation is observed in real-time with thermometry.

TULSA overview

TULSA is a newer technology which uses high-intensity thermal ultrasound to destroy prostate tissue by treating the prescribed boundary to an ablative temperature of 55 °C. The procedure takes place entirely in the MRI suite with the patient under general anesthesia or regional block. A rigid transurethral ultrasound catheter is guided into the prostate and then secured with an MRI-compatible robot that provides linear and rotational motion of the device within the prostatic urethra during treatment planning and the ablation. The ultrasound catheter has ten separate elements, each which are independently controlled for acoustic power and frequency. A rectal device is inserted which cools the rectum with cold water (Fig. 1A).

Device localization is performed with a high-resolution sagittal 3D T2-weighted SPACE sequence (TR 1700 ms; TE 97 ms; Slice thickness 1 mm; FOV 256 mm; Resolution 1 x 1 x 1 mm). Treatment planning is performed with transverse T2-weighted images (qtse: TR 7500 ms; TE 101 ms; Slice thickness 3 mm; FOV 260 mm; Resolution 1 x 1 x 3 mm) and monitored in real-time with a segmented EPI MRI thermometry sequence (TR 45 ms; TE 8 ms; Slice thickness 4 mm; FOV 256 mm; Resolution 2 x 2 x 4 mm) (Fig. 1B).

One of TULSA's distinguishing features that allows it to ablate large volumes of tissue yet still offer conformal ablation is the automated controller. During the ablation real-time thermometry images acquired by the MRI are sent to the TULSA software every ~6 s. These images are processed immediately upon arrival, and the controller in turn calculates the optimal device rotation rate, acoustic power and acoustic frequency for all active ultrasound elements. This process repeats itself indefinitely until the ablation is completed. The control parameters are adjusted to achieve the fine balance of reaching the 55 °C temperature at the prescribed boundary in the shortest possible treatment time, but not overshooting into surrounding structures. Over time (~50 minutes for a whole-gland ablation) the ultrasound catheter is rotated through the prostate via the robotic arm, delivering a consistent thermal dose to the targeted volume.

Whole-gland TACT trial

The most extensive and up-to-date clinical data regarding TULSA comes from the TACT trial (NCT02766543). This was a multi-center, prospective, single-arm clinical trial where patients with low- to intermediate-risk, biopsy-proven, localized PCa (Table 1) were treated with TULSA as a first-line therapy. From September 2016 until February 2018 115 men were enrolled across 13 different institutions in 5 different countries. The main objectives of the study were safety and early oncological control at one year as determined by PSA, biopsy, and mpMRI. Every patient regardless of their specific disease characteristic received whole-gland ablation but with sparing to the urethra and apical sphincter. Repeat TULSA was not allowed. At the time of writing 2-year follow-up is available for 48 / 115 patients (42%).

Procedural outcomes

The median (IQR) ablation time was 51 minutes (39–66), achieving 98% thermal coverage. The spatial precision of the TULSA ablation was 1.4 mm. Patients were discharged the same day (55%) or admitted overnight (45%), mostly depending on the local hospital protocol.

Safety outcomes

No ≥ Grade 4 adverse events, no intraoperative complications, no rectal injury, and no rectal fistula were observed. A total of 12 Grade 3 (severe) adverse events occurred in 9 (8%) men, including genitourinary infection (4%), urethral stricture (2%), urinary retention (2%), urethral calculus and pain (1%), and urinoma (1%), all resolved by the 12-month visit.

No patient had severe erectile dysfunction. Of the 92 patients at baseline who had erections sufficient for penetration, 75% maintained this at one year, and this increased to 83% in those patients with two-year follow-up, indicating a continued recovery. Moderate urinary incontinence (Grade 2, pads) was reported by 3 patients (2.6%), with no new incontinence at 2 years. The patient-reported IPSS (International Prostate Symptom Score) questionnaire was used to quantify urinary symptoms after the intervention, where a score 1–7 represents mild, 8–19 moderate and 20–35 severe symptoms. The median IPSS was unchanged from 7 at baseline to 6 at one year and 5 at two years after TULSA.

Oncological outcomes

Median (IQR) PSA reduction at one year was 95% (91–98%) with a median nadir of 0.3 ng/ml and was stable at two years. Median decrease in perfused prostate volume changed by 91% at 12 months, decreasing from a median of 37 cc at baseline to 3 cc.

Median age, age	65 (59–69)
PSA, ng/ml	6.3 (4.6–7.9)
Grade Group Distribution, n (%)	72 with GG2 (63%) 43 with GG1 (37%)
Targeted prostate volume, cc	40 (32–50)

Table 1: Patient characteristics at baseline for whole-gland TACT trial.

From biopsy results there was no evidence of cancer in 72 (65%) men and 16 (14%) had low-volume GG1. Among the 68 men with GG ≥ 2 at baseline, 54 (79%) were free of GG ≥ 2 at 12 months. Similarly, 20 of 26 (77%) men with high-volume GG1 at baseline had either no cancer or low-volume GG1 (< 3 cores and < 50% per core) at 12 months. Overall, histological improvement (eradication of GG2, shift from high to low-volume GG1, or eradication of GG1 disease) occurred in 75–80% of men across all risk subgroups.

12-month MRI showed a 96% negative predictive value for absence of GG2 disease on 1-year biopsy.

TULSA case example: whole-gland ablation

A 68-year-old male arrived in our clinic in 2017 with suspicion of localized PCa in the left midgland peripheral zone based on elevated PSA and mpMRI findings (PSA 6.9 ng/ml, PI-RADS 5, prostate volume 52 cc). Baseline mpMRI findings were concordant with the MRI-targeted biopsy, revealing 2 positive cores with a total cancer core length of 12 mm (Grade Group 2).

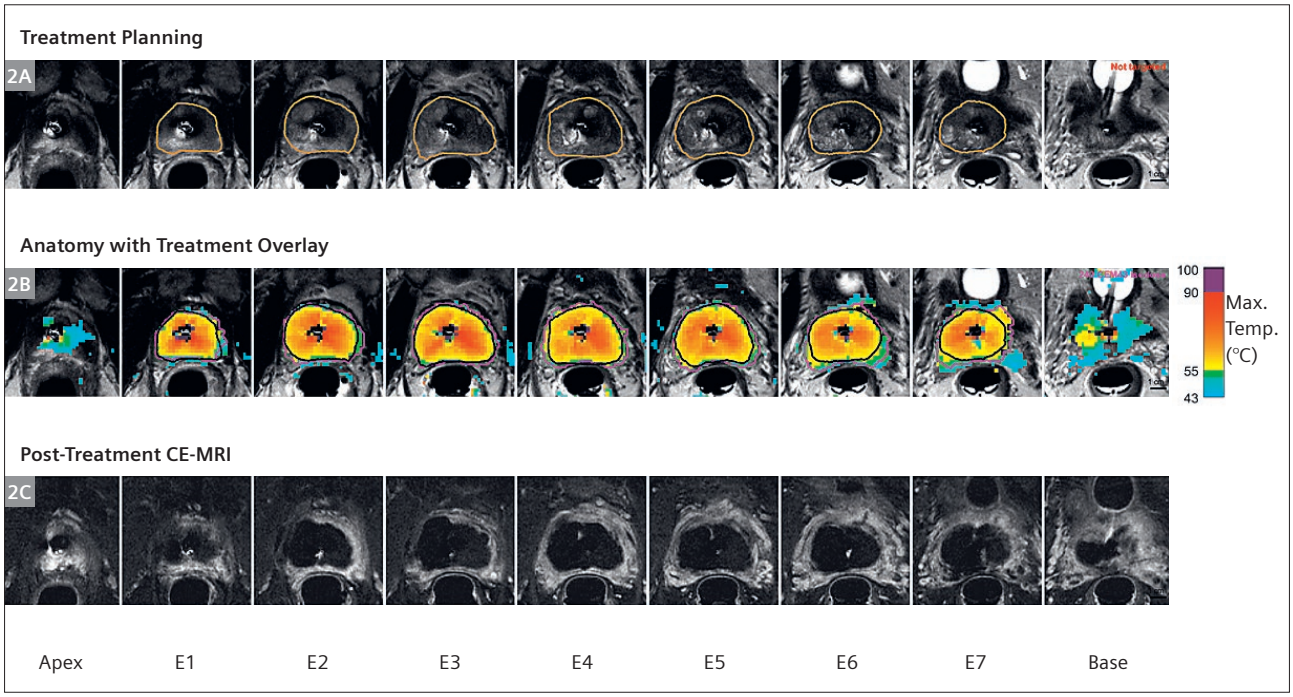
The patient underwent whole-gland TULSA with urethra and apical sphincter sparing, with the treatment plan show in Figure 2A. The total ablation time lasted 42 minutes, with the patient discharged the following day. The maximum heat deposition at the end of treatment (Fig. 2B) and the corresponding immediate post-ablation contrast scan revealing immediate cell kill can be seen in Figure 2C.

One-year follow-up visit was promising, with the patient experiencing no urinary incontinence, no rectal injuries, and an IPSS improvement from 14 to 8. Oncological control at 12 months was demonstrated by a low and stable PSA of 0.41 ng/ml, negative mpMRI and a negative 12-core biopsy.

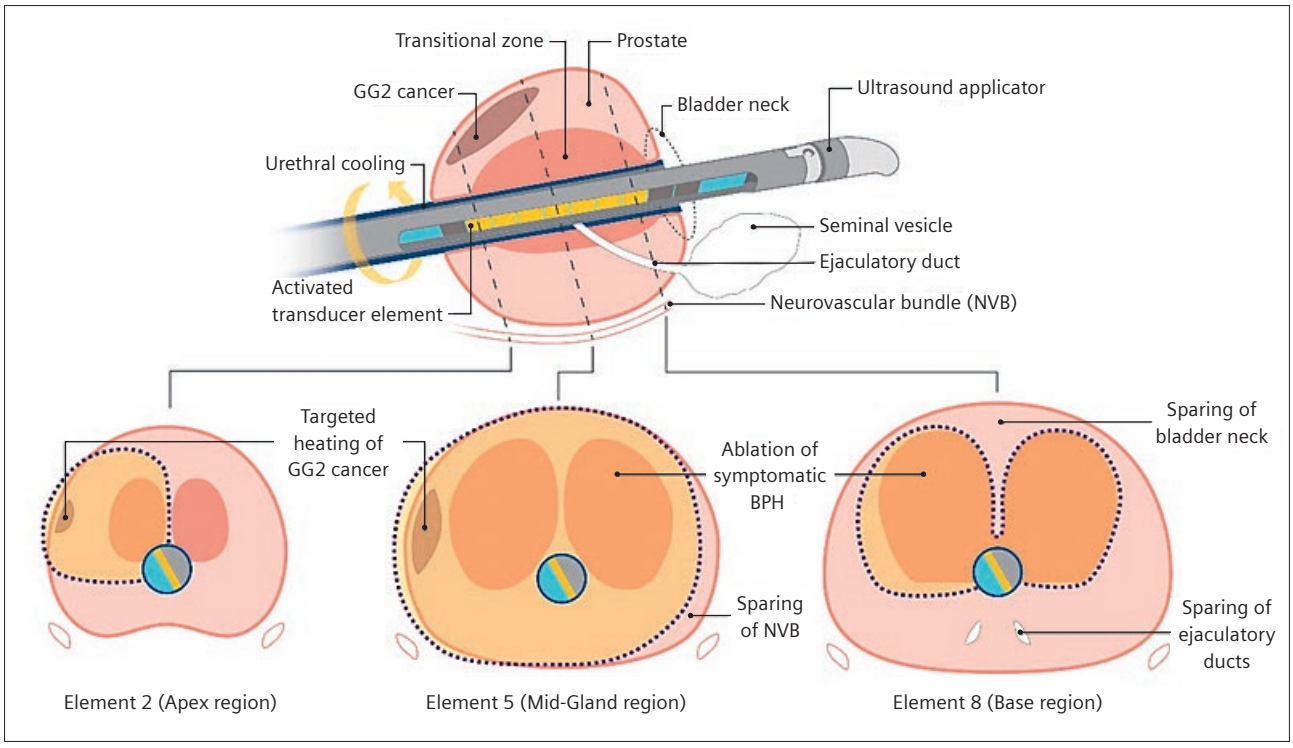
TULSA personalized care

As discussed earlier, in the last decade PCa disease localization has greatly improved. This has given treating physicians the option to spare viable prostate tissue and treat only the source of tumor. Opting for targeted therapy is not solely a clinical decision however, as the patient's wishes and underlying health conditions must also be considered, providing a better platform for the patient to control their own care. Possible treatment options with TULSA include whole-gland, whole-gland with nerve sparing, hemi-ablation, or quadrant ablation. Figure 3 illustrates a hypothetical custom treatment plan with TULSA.

If one considers the TACT trial as 'worst-case' for safety and morbidity as the ablation was performed on the whole gland without nerve sparing, it is reasonable to expect a safety improvement moving to partial ablation, although this must be still be confirmed through more extensive clinical trials.



2 **(2A)** Treatment plan outlined on transverse T2w planning sequence. **(2B)** Maximum heat deposition in temperature at the end of treatment. **(2C)** Post-ablation contrast scan showing immediate cell kill based on non-perfused volume.



3 Personalized TULSA treatment. A patient presents with both localized intermediate-risk prostate cancer and urinary symptoms prior to treatment. A treatment plan is devised to target only the dominant lesion with a thermal safety margin, as well as the source of adenoma causing urinary obstruction. The apical sphincter, the left side of the neurovascular bundle, the ejaculatory ducts, and the bladder neck are spared from the ablation volume, in order to offer the best compromise between oncological control and function.

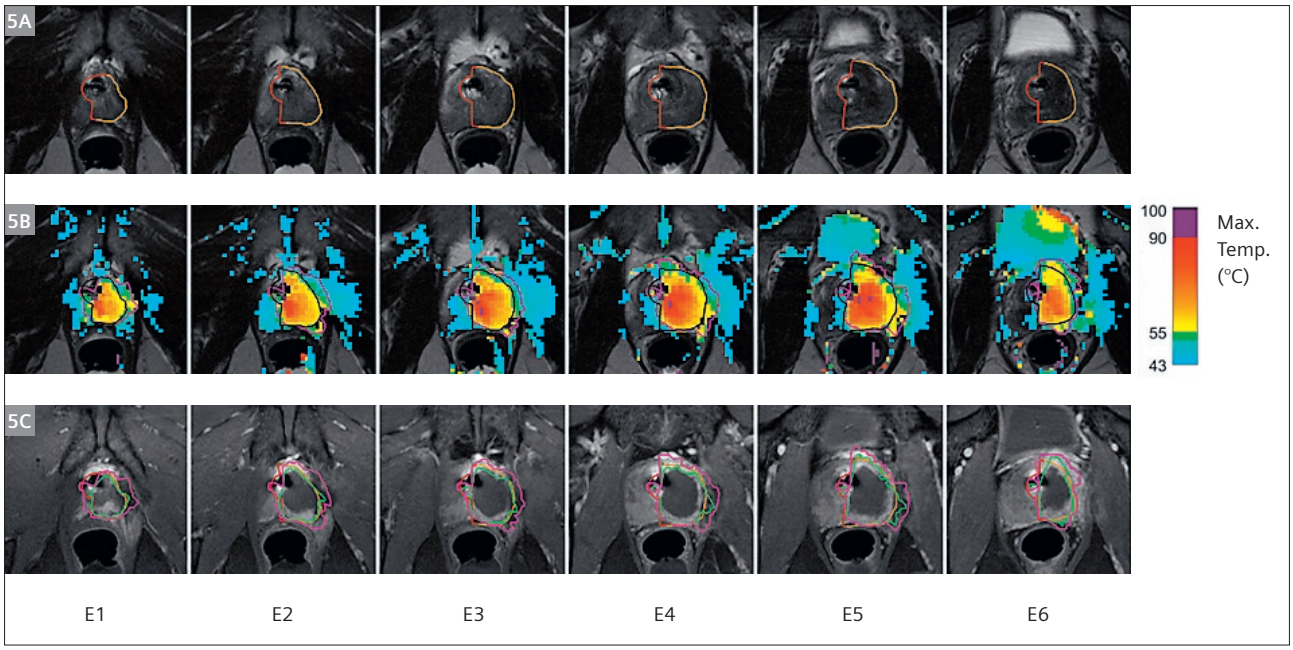
TULSA case example: hemi-ablation

A 60-year-old male with intermediate-risk, unilateral, localized PCa (PSA 15 ng/ml, Grade Group 2, PI-RADS 4) arrived at our clinic in 2018. mpMRI findings were concordant with positive biopsy location with the lesion apparent on DWI, outlined in yellow (Fig. 4).

The individualized treatment plan was developed by a multi-disciplinary team including urologists and radiologists, and presented to the patient before the treatment. It was determined the patient would undergo hemi-gland ablation, which would spare one side of the neurovascular bundle, while still targeting the dominant lesion (Fig. 5). The ablation time lasted 35 minutes, with the patient discharged the following day.

At 2 years post-TULSA the patient underwent mpMRI which revealed no suspicions and the PSA was stable at 3.9 ng/ml, a decrease of 74% from baseline which is expected for a focal treatment. No changes to urinary, bowel, or sexual function were noted.

4 Screening image for patient who underwent targeted TULSA treatment. Biopsy showed single lesion Grade Group 2 which was concordant on mpMRI (PI-RADS 4). The lesion is outlined in yellow. Based on the tumor characteristics it was decided the patient would undergo a hemi-ablation on the left side.



5 Hemi-ablation treatment with TULSA. Elements E1–E6 were enabled on the left lobe to deliver spatially precise ablation in order to reduce toxicity. The treatment plan **(5A)** was determined in advance of the therapy. The ablation lasted only 35 minutes **(5B)** and the immediate treatment effects can be visualized on contrast MRI with the non-perfused volume.

Conclusion

TULSA is a new technology which has demonstrated promising early oncological results with a well-tolerated safety profile. As PCa disease localization continues to improve, it is expected that targeted treatment will become increasingly part of localized PCa management. As MRI is already embedded within TULSA, used both to guide, plan, and monitor treatment, TULSA is well-positioned to address the changing landscape of PCa disease management.

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