

Whole-gland MRI-guided transurethral ultrasound ablation of low-risk prostate cancer: preliminary results from a multi-center phase I clinical trial

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TARGET AUDIENCE: Radiologists and physicists involved in image-guided therapy, specifically MR-guided treatment of prostate cancer.

PURPOSE: Minimally-invasive, image-guided therapies for localised prostate cancer (PCa) are emerging as alternative treatments to active surveillance and radical treatments (surgery, radiation), with the aim of providing good local disease control and low morbidity¹. MRI-guided transurethral ultrasound ablation (TULSA) uses high intensity ultrasound delivered from a transurethral device to generate a continuous volume of thermal coagulation that is shaped precisely to the prostate using real-time MR-thermometry and active temperature feedback control^{2,3}. A phase I clinical trial of MRI-guided TULSA was initiated with the world's first primary-care patient treatment in March 2013. The aim of this prospective, multi-institutional study is to determine the safety and feasibility of MRI-guided TULSA and to assess its efficacy for treatment of PCa.

METHODS: Men with biopsy-proven, low-risk prostate cancer (age ≥ 65 y, T1c/T2a, PSA ≤ 10 ng/ml, Gleason 6 [3+3]) were enrolled into this ethics-approved study. The whole prostate gland was targeted for treatment with MRI-guided TULSA (PAD-105, Profound Medical Inc., Canada). MR imaging was performed using a 3 Tesla clinical magnet (Magnetom Trio, Siemens Healthcare, Germany) and a 16-channel phased-array coil. The transurethral device was inserted under general anaesthesia and positioned precisely in the prostatic urethra using an MRI-compatible positioning system and MR image guidance. Treatment planning was performed by tracing the outer prostate boundary on oblique-axial T2-weighted images acquired transverse to the ultrasound device and aligned with each transducer element (Fig. 1). The "acute ablation boundary" was defined 3mm inside the prostate and targeted to 55°C^{2,3}, with late cell kill expected to migrate an additional 1-3mm towards the prostate capsule⁴ (Fig. 1). Ultrasound treatment was delivered in one session under active MR-thermometry feedback control: EPI sequence, FOV=26cm, matrix=128x128, slice=4mm, gap=1mm, TE=8ms, TR=350ms. A new set of up to 12 thermometry slices were acquired every 5.9s allowing real-time assessment of a 3D temperature volume. The MR-thermometry spatial temperature distribution was calculated using the PRF-shift method and a multi-point phase drift correction, achieving a temperature uncertainty of ± 1 °C. With every new set of MR-thermometry images, the rotation rate of the transurethral device as well as the ultrasound power and frequency of each individual transducer element were adjusted automatically (10 transducers, each 4.5x5.0mm², 4 or 14MHz, acoustic intensity ≤ 20 W/cm²), in order to shape the thermal pattern and heat the acute ablation boundary to 55°C. Post-treatment, contrast-enhanced (CE)-MR images were acquired (3D FGRE, TE=min, flip=13°, slice=5mm, matrix=256x256, FOV=23.4cm) after weight-adjusted intravenous injection of a gadolinium-based contrast agent (0.1mmol/kg). Treatment feasibility was evaluated by spatially comparing the resulting 55°C isotherm (MR-thermometry) to the planned acute ablation boundary (T2 planning), using linear and volumetric metrics of targeting accuracy and the Dice Similarity Coefficient (DSC). Thermal coagulation was confirmed by comparing the heating pattern (MR-thermometry) to the non-perfused volume (NPV) determined from CE-MRI.

RESULTS: MRI-guided TULSA was well-tolerated by all 16 patients treated to-date. There were no cases of urinary incontinence, fistula or rectal injury reported, and normal urinary function returned after catheter removal. Median treatment time and prostate volume were 29min (24–61min) and 45ml (34–95ml), respectively. The maximum temperature distribution measured during treatment depicted a continuous region of heating within the prostate and accurate heating of the acute ablation boundary to the 55°C target temperature (Fig. 2a). Spatial control of the thermal ablation was accurate and precise to within -0.1 ± 1.4 mm, with average over- and under-targeted volumes of 0.5ml (0.0–1.4ml) and 1.2ml (0.1–2.7ml), respectively, and DSC of 0.94 (0.90–0.96). Immediate post-treatment cell kill, as visualized by the peripheral region of enhancement surrounding the NPV⁴, correlated well with the thermal pattern measured by MR-thermometry (Fig. 2b). Successful treatment was further indicated by a median PSA decrease at 1-month of 87% (60–99%) to 0.7ng/ml (0.1–3.3ng/ml), with the nadir expected by 6 months.

CONCLUSION: Preliminary results of this phase I clinical trial indicate that MRI-guided TULSA for whole-gland ablation of the prostate is feasible, safe, accurate and precise. MRI-guidance enables accurate planning, real-time dosimetry and control, and post-treatment assessment of the thermal ablation volume. This technology could be an attractive approach for minimally-invasive treatment of localised prostate cancer.

REFERENCES: 1) Ahmed *et al.*, Lancet Oncol 2012, 13:622-632. 2) Chopra *et al.*, Radiology 2012, 265:303-313. 3) Chopra *et al.*, Phys Med Biol 2009, 54:2615-2633. 4) Boyes *et al.*, J Urol 2007, 178:1080-1085.

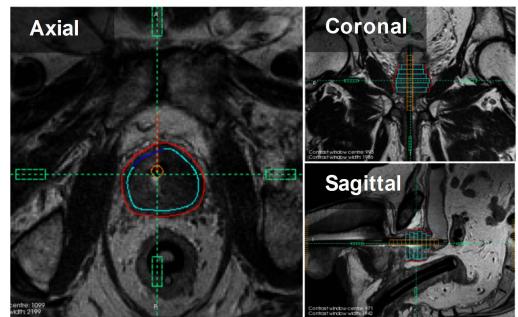


Figure 1: Treatment planning. The prostate was traced (red) and acute ablation boundary (cyan) defined 3mm inside the prostate.

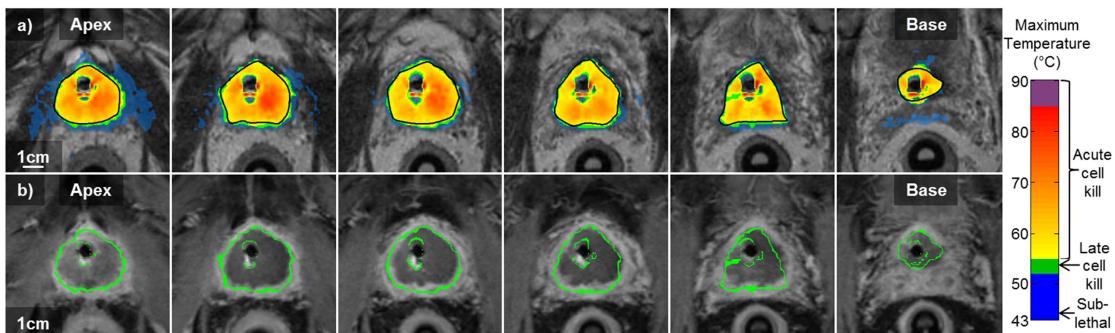


Figure 2: Example clinical treatment shown on 5mm oblique-axial images acquired transverse to the ultrasound device, aligned with the transducer elements, and spanning the apex to the prostate base. (a) Maximum temperature measured during treatment by MR-thermometry overlaid on the T2w planning images, illustrating the accuracy and precision of MRI-guided TULSA. The acute cell kill pattern (≥ 55 °C, yellow-red) is shaped to the planned acute ablation boundary (black line), surrounded by expected late cell kill (52–55°C, green) and sub-lethal heating (< 52 °C, blue). (b) Expected late cell kill (52–55°C, green) overlaid on the CE-MRI acquired immediately after treatment, showing good correlation between the thermal pattern and the peripheral region of enhancement surrounding the NPV.