Transurethral ultrasound applicators with dynamic multi-sector control for prostate thermal therapy: *In vivo* evaluation under MR guidance

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The purpose of this study was to explore the feasibility and performance of a multi-sectored tubular array transurethral ultrasound applicator for prostate thermal therapy, with potential to provide dynamic angular and length control of heating under MR guidance without mechanical movement of the applicator. Test configurations were fabricated, incorporating a linear array of two multi-sectored tubular transducers (7.8–8.4 MHz, 3 mm OD, 6 mm length), with three 120° independent active sectors per tube. A flexible delivery catheter facilitated water cooling (100 ml min^{-1}) within an expandable urethral balloon (35 mm long $\times$ 10 mm diameter). An integrated positioning hub allows for rotating and translating the transducer assembly within the urethral balloon for final targeting prior to therapy delivery. Rotational beam plots indicate $\sim 90^\circ$ – 100° acoustic output patterns from each 120° transducer sector, negligible coupling between sectors, and acoustic efficiencies between 41% and 53%. Experiments were performed within *in vivo* canine prostate ($n = 3$), with real-time MR temperature monitoring in either the axial or coronal planes to facilitate control of the heating profiles and provide thermal dosimetry for performance assessment. Gross inspection of serial sections of treated prostate, exposed to TTC (triphenyl tetrazolium chloride) tissue viability stain, allowed for direct assessment of the extent of thermal coagulation. These devices created large contiguous thermal lesions (defined by 52 °C maximum temperature, $t_{43} = 240 \text{ min}$ thermal dose contours, and TTC tissue sections) that extended radially from the applicator toward the border of the prostate ($\sim 15 \text{ mm}$) during a short power application (~ 8 – 16 W per active sector, 8–15 min), with $\sim 200^\circ$ or 360° sector coagulation demonstrated depending upon the activation scheme. Analysis of transient temperature profiles indicated progression of lethal temperature and thermal dose contours initially centered on each sector that coalesced within $\sim 5 \text{ min}$ to produce uniform and contiguous zones of thermal destruction between sectors, with smooth outer boundaries and continued radial propagation in time. The dimension of the coagulation zone along the applicator was well-defined by positioning and active array length. Although not as precise as rotating planar and curvilinear devices currently under development for MR-guided procedures, advantages of these multi-sectored transurethral applicators include a flexible delivery catheter and that mechanical manipulation of the device using rotational motors is not required during therapy. This multi-sectored tubular array transurethral ultrasound technology has demonstrated potential for relatively fast and reasonably conformal targeting of prostate volumes suitable for the minimally invasive treatment of BPH and cancer under MR guidance, with further development warranted. © 2008 American Association of Physicists in Medicine.

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I. INTRODUCTION

High-temperature thermal therapy devices have been developed and utilized for treatment of benign and malignant prostate disease. Many modalities of heating have been used for prostate thermal therapy, including radio-frequency (RF),¹ microwaves,^{2–4} and ultrasound.^{5,6} In most cases, prostate heat treatments are being used and studied as an alternative to surgical procedures and are often delivered with transurethral or transrectal devices. For benign prostate hyperplasia (BPH) therapy, recent reviews and studies have suggested similar results with transurethral microwave therapy (TUMT) devices compared to transurethral resection of the prostate (TURP) surgeries, but with less major complications when using TUMT.^{2,7} In addition, studies have been conducted that indicate higher temperatures produced from high-energy TUMT devices may improve postprocedure symptom scores.^{8,9} Transurethral thermal therapy appears to be an effective option for treating BPH, but the evidence suggests that increased spatial control of the temperatures and more accurate targeting of the anterior/lateral lobes of the prostate may further improve treatment.^{10,11} For treating prostate cancer, thermal therapy is typically used as an alternative to radical prostatectomy in high risk patients who are not surgical candidates and for treatment of local recurrence after external beam radiotherapy.^{6,12} Cancer treatments require accurate targeted thermal dose delivery to assure destruction of the cancerous tissue, while avoiding damage to surrounding tissues (rectum, prostatic sphincters, neurovascular bundles). Transrectal high-intensity focused ultrasound (HIFU) devices offer a high degree of control over the creation of a thermal lesion in the prostate,^{5,13,14} and recent advancements in ultrasound imaging-based treatment monitoring may further improve treatment results.¹⁵ However, transrectal HIFU devices require significant treatment times to ablate large volumes and face difficulties targeting the anterior portion of the gland.⁵

Magnetic resonance (MR) imaging techniques are being investigated for noninvasive monitoring of thermal therapy.¹⁶ MR temperature monitoring offers the potential to guide the delivery of thermal treatments and improve the accuracy of delivering target thermal doses. Recently, MR-guided thermal therapy with HIFU devices has become commercially available for the treatment of uterine fibroids.^{17,18} Noninvasive MR monitoring of thermal treatment of prostate tissue has been applied in canine models^{19,20} and humans.²¹ Prostate thermal therapy devices with a greater degree of spatial control during treatment can take advantage of real-time MR temperature measurement feedback and offer a more accurate way to target and verify thermal treatment.

Transurethral ultrasound devices are currently under pre-clinical evaluation as an alternative technique for thermal treatment of BPH and cancer.²² Directional planar,^{23–25} curvilinear,²⁶ and single-sectored tubular^{27,28} ultrasound transducers have been incorporated into transurethral heating applicators. The applicators can be rotated and positioned

manually or with computer controlled MR compatible motors during treatment to accurately conform heating to a predetermined target region of prostate.^{24–26} Planar and curvilinear ultrasound applicators appear to provide good penetration and control of thermal lesions; however, due to an inherent narrow acoustic beam width (~ 4 mm), they require scanning and treatment times from ~ 10 to >30 min to ablate large regions of the prostate as demonstrated within canine prostate *in vivo*, in phantom, and in simulations.^{24–26,29,30} Treatment durations could be increased if pelvic bone is in close proximity to the gland, due to selection of higher frequencies and lower powers in order to reduce bone heating.³⁰ Mechanical manipulation of the applicators during treatment can create problems and inaccuracies with proton resonance frequency (PRF) based MR temperature imaging because phase subtraction methods are very sensitive to movement in a series of images. As the numbers of sequential rotation steps and heat treatment durations increase, the more likely it is that applicator movement, tissue movement, image phase drift, or a change in prostate dimensions will create significant inaccuracies in temperature measurement. A device that does not require mechanical manipulation during heating and can accurately treat a target volume in a relatively short period of time should further decrease temperature monitoring errors. Recent developments of transesophageal ultrasound applicators for tumor ablation under MR guidance have demonstrated advantages of stationary cylindrical phased arrays³¹ compared to rotating planar devices.^{24,25} Similar advantages have recently been demonstrated with interstitial ultrasound applicators, consisting of small multisectored tubular ultrasound transducers [<1.8 mm outer diameter (OD)], which are able to conform heat treatment in the angular dimension without requiring applicator movement during treatment.³² A stationary, larger multisectored transducer configuration incorporated into a transurethral catheter could offer a practical solution for prostate thermal therapy with MR guidance.

The objectives of this study were to design, develop, and evaluate the feasibility of multisectored transurethral ultrasound applicators for dynamic control of prostate thermal therapy under MR guidance. In concept, a 4–5 cm long linear array of multisectored transducers, with independent power control to each sector, could be adjusted to control both the angular and longitudinal heating pattern without requiring mechanical movement of the device during treatment. The basic performance of this design was evaluated in this study by fabricating a prototype applicator array with two multisectored tubular transducers, which was characterized using bench top acoustic measurements and *in vivo* canine prostate heating experiments under MR guidance. In the experiments, real-time MR temperature maps, thermal dose calculations, and visual inspection of thermal lesions demonstrated the feasibility of angular and longitudinal control of thermal treatment with these devices.

II. MATERIALS AND METHODS

II.A. Design and characterization of multisectorized applicators

The transurethral heating applicators designed in this study for test purposes incorporated two high-frequency tubular ultrasound transducers (PZT-4 Piezoceramic, 7.8–8.4 MHz, 3 mm OD, 6 mm length) sectorized into three independent 120° partitions with a silicon wafer dicing saw (Automatic Dicing Saw DAD-2H/6, Disco Abrasive Systems, Tokyo, Japan). Each sector was individually powered through small diameter (0.1 mm) silver wire (California Fine Wire, Grover Beach, CA) leads soldered to the outer transducer electrode, with a common ground soldered to the inner electrode. The wires were then connected to miniature coaxial cables (0.69 mm OD, Temp-Flex Cable, South Grafton, MA) that were fed to a six-pin quick connect (REDEL, Alpine Electronics, San Jose, CA) on the back end of the applicator. To construct an applicator, the two transducers were aligned with the same orientation and mounted onto an inner polyimide tubing with a silicone adhesive (NuSil, Carpinteria, CA). The lumen of this inner tubing would also provide input of water flow cooling to the delivery catheter and urethral cooling balloon described later. The outer surface of the transducer assembly was coated with a thin layer of mineral oil and covered with thin-walled (0.025 mm) PET (polyester) tubing (Advanced Polymers, Salem, NH). Another polyimide tube was placed over the inner polyimide lumen to protect the lead wires from damage and applicator cooling flow. A plastic Y-connector (Qosina, Edgewood, NY) at the proximal end of the applicator isolated the input water cooling flow from the miniature coaxial cables.

The catheter was designed in this study to contain the applicator and provide return water cooling flow through a urethral cooling balloon. The main portion of the catheter consisted of TPX tubing (4.3 mm OD) secured to a large bore, Touhy-Borst hub at the proximal end. The distal portion of the catheter consisted of a PET urethral cooling balloon (10 mm OD, 40 mm length, Advanced Polymers) secured to a PEBAX tip (4 mm OD, Danforth Biomedical, Santa Clara, CA). A polyimide tubing lumen ran the down the center of the catheter to provide a filling system for a C-Flex urinary bladder balloon (Extrusionengineering, Placentia, CA) that was secured to the PEBAX tip. An MR-compatible titanium rod (0.71 mm OD) was inserted within the center polyimide tubing lumen to provide structural support within the catheter body and across the urethral balloon to the distal catheter, but is flexible enough for insertion within the urethra and bladder. The multisectorized applicator was placed within the transurethral catheter, allowing for concentric water cooling flow through the inner lumen of the applicator assembly and out through the catheter and positioning hub. The water flow through the urethral balloon provided acoustic coupling of the ultrasound energy to the tissue and cooled both the applicator and adjacent tissue. The hub at the proximal end of the catheter enabled both rotation and translation of the applicator within the catheter for accurate positioning before heating. Manganin wire (0.025 mm OD, California

FIG. 1. (a) Schematic diagram of the interior of the transurethral catheter and incorporated multisectorized transducer. (b) Diagram of the tip of the multisectorized transurethral ultrasound applicator with concentric water flow cooling, urethral cooling balloon, and urinary bladder placement balloon. (c) Photograph of the applicators used in this study with a translating and rotating hub for accurate positioning of the transducer assembly.

Fine Wire) was wrapped around the catheter near the proximal end of the urethral cooling balloon to act as a fiducial marker in MR images. A generalized design scheme of the applicator design is shown in Fig. 1, along with a photograph of one of the constructed devices.

The force balance technique for cylindrical ultrasound sources³³ measured the acoustic output power and acoustic efficiency, the percentage of RF power converted to ultrasound, of the multisectorized transducers. For each sector on each transducer, the optimal operating frequency, as defined by maximum efficiency, was determined by conducting measurements at net applied powers of 3 and 7 W for every 0.1 MHz step between 7.6 and 8.5 MHz. The acoustic output pattern was determined by obtaining rotational beam plots²⁷ of the acoustic pressure-squared as measured from a computer-controlled scanning needle hydrophone (0.6 mm diameter, NTR Systems, Seattle, WA). The applicators were scanned within the catheter with the urethral balloon (10 mm OD) inflated by active water cooling flow (100 ml min⁻¹). The hydrophone was scanned 10 mm axially in 0.2 mm steps at a fixed radial distance, 4 mm from the outer surface of the urethral balloon (7.5 mm from the transducer surface), while the applicator was rotated 360° in 2.5° steps. These rotational acoustic beam plots, normalized to the peak maximum value of pressure-squared measured for each transducer segment or sector under test, were used to characterize the angular acoustic output pattern, the acoustic dead zone between individual sectors, and whether the sectors were electrically and mechanically isolated from another.

TABLE I. MR imaging parameters used for the *in vivo* canine prostate experiments.

MR parameters	Canine 1	Canine 2	Canine 3
Echo time (TE)	14.3/21.5/28.6	14.3/21.5/28.6	14.3/21.5/28.6
TE1/TE2/TE3 (ms)			
Acquisitions	2	1	2
Relaxation time (TR) (ms)	170	160	190
Flip angle (FA) (deg)	60	60	60
Field of view (FOV) (cm)	18 × 12.5	16 × 16	18 × 12.5
Acquired resolution (pixels)	256 × 72	96 × 96	192 × 72
Reconstructed temperature map resolution (pixels)	96 × 72	96 × 96	96 × 72
Bandwidth (kHz)	15.6	12.5	12.5
Slice thickness (mm)	5	5	5

II.B. MR temperature monitoring

MR temperature imaging was used to monitor and evaluate the heating performance of the multisectoral applicators during *in vivo* experiments. The temperature images were based on the proton resonance frequency (PRF) phase subtraction method¹⁶ and acquired with a receive-only prototype endorectal coil 0.5 T interventional scanner (Signa SP, GE Healthcare, Milwaukee, WI). The endorectal coil was fitted with a water cooling flow jacket to protect the rectum during heat treatments. The specific imaging parameters for each *in vivo* canine experiment are listed in Table I. Three echo times were acquired in one or two acquisitions and averaged to increase the signal-to-noise ratio (SNR) and improve the accuracy of the temperature measurements in postprocessing. During the real-time monitoring, one of these echo times was used to display the temperature maps. The reconstructed temperature resolution was used for postprocessing.^{34,39} The temporal resolution of the temperature monitoring was 12–15 s in the experiments. Three imaging slices (5 mm thick with 1 mm spacing), centered in the middle of the transducer assembly, were used for real-time monitoring. The baseline temperatures used for the MR thermal imaging were determined immediately prior to heating using invasive measurements of core body temperature as described later. Custom software displayed the temperature maps in all three image slices during treatment and allowed the user to set three different temperature thresholds (e.g., 48, 52, and 60 °C) for monitoring the temperature in real-time. The software also had the capability of monitoring maximum temperature at each pixel and thermal dose.

The thermal dose (t_{43}), measured in equivalent minutes at 43 °C, was calculated from the postprocessed MR temperature data, where the SNR was improved by averaging all the echo times. The calculation was performed using the Sapareto-Dewey isoeffect thermal dose equation as a function of temperature and time:³⁶

$$t_{43} = \sum_{t=0}^{t_{\text{final}}} \Delta t R^{(T-43)},$$

where $R=2$ for $T \geq 43$ °C, $R=4$ for $T < 43$ °C, T is measured temperature (°C), Δt is the time between temperature

measurements, and t_{final} is the total heating time. R is a constant that is empirically derived from Arrhenius analysis of thermal cell killing and protein denaturation.³⁵ A thermal dose of $t_{43}=240$ min was used to define the thermal lesion boundary, based on previous studies of the temperatures and thermal dose that caused thermal necrosis in soft tissue,^{35,37} including prostate tissue.^{19,20,29,38} The 52 °C contour is used in our study for benchmark comparisons of effective thermal penetration and as an approximate delineation of lethal thermal dose exposure, and clearly defines a definite region of coagulation and acute thermal destruction (>15 – 30 s exposure, $t_{43}>256$ – 512 min). Note that as treatment duration increases, tracking the 52 °C contour could underestimate the extent of thermal damage, whereas a lower temperature contour (e.g., 48 or 50 °C) could be selected to more closely track with the lethal thermal dose contours.

II.C. *In vivo* canine prostate experiments

The heating performance of the multisectoral transurethral applicators was tested in three separate *in vivo* canine prostate glands following procedures approved by the Institutional Animal Use and Care Committee at Stanford University. The animals were anaesthetized and intubated for the duration of the procedure, and their vital signs were continuously monitored. Due to differences between human and canine anatomy, an urethrostomy was performed to access the urethra, and a 20 French introducer sheath was inserted into the urethra. The animals were positioned supine, headfirst into the 0.5 T interventional scanner, and the bottom part of the abdomen was secured to minimize movement due to breathing. The multisectoral transurethral applicator being tested was inserted into the introducer sheath, which was subsequently removed. The bladder placement balloon was then filled with 8–10 ml of a 4% gadolinium solution and the applicator was gently retracted until firmly seated within the bladder neck. The endorectal imaging coil with a water cooling jacket was inserted within the rectum and positioned adjacent to the prostate. Based upon pretreatment MR images and integrated fiducial markers that marked the position of the applicator, the transducer assembly was rotated and translated within the catheter for positioning in relation to the

FIG. 2. Screen captured sagittal MR image to demonstrate the typical applicator setup within the prostatic urethra. The applicator, endorectal coil with cooling, and prostate are labeled on the image.

predetermined target region. Once positioned, the applicator was locked into place and the urethral cooling balloon was expanded with degassed water. A sagittal MR image (resolution 256×128 pixels, FOV 20×20 cm², TE/TR 13/150 ms, flip angle 60° , bandwidth 6.94 kHz) of the transurethral applicator in the prostatic urethra is labeled and displayed to represent an illustration of the typical experimental setup in Fig. 2.

Immediately prior to applying power to the applicator, ambient temperature water flow cooling was provided by peristaltic pumps outside the MR suite to the endorectal jacket (60 ml min^{-1}) and applicator (100 ml min^{-1}). RF power was applied to the applicator by two custom, four-channel RF amplifiers (Advanced Surgical Systems, Tucson, AZ) located outside the suite. Coaxial cables from the amplifier were connected to the applicator through a shielded access panel. RF noise at the Larmor frequency of the 0.5 T scanner was reduced by in-line, high power, 0–11 MHz low-pass filters with 60 dB attenuation at 20 MHz (Werlatone, Brewster, NY) to prevent degradation of the MR images. The core body temperature of the animal was measured by a deep nasal thermocouple probe before each heating trial to establish the baseline temperature for MR temperature imaging.

After treatment, the animals were removed from the scanner and sacrificed ~ 60 – 90 min later. The prostate was removed and cut into ~ 5 mm serial slices, which were immediately placed into a 2% triphenyl tetrazolium chloride (TTC) stain for 15–20 min. TTC is a redox indicator that is reduced by enzymes in viable tissues, and stains those tissues red. It can be used to distinguish viable and nonviable cells and clearly mark the border of thermal coagulative necrosis.^{40,41} Care was taken to align the serial slices of prostate as close as possible to the central MR imaging plane used within the *in vivo* experimental setup to allow for visual inspection and quantification of the thermal necrosed tissue produced during the experiments. However, for purposes of this study an exact registration of the prostate histology, gross examination, and correlation of each to the MR temperature image planes was not required nor performed.

Each of the canine prostate experiments was performed under MR guidance to evaluate the heating performance of multisectoral transurethral applicators and establish compatibility within the MR suite. In Canine 1, the transducer assembly was positioned mid-gland in the region of greatest cross-section toward the base of the prostate and rotated to direct two active sectors (S1, S2) toward the ventral portion of the gland and the remaining inactive sector toward the rectum. Different power levels were applied to the active sectors on each transducer (T1, T2) [Fig. 3(a)] and adjusted during treatment to contour the lethal thermal exposure toward the outer boundary of the prostate, according to the MR temperature measurements. Higher maximum temperatures were targeted across S1 compared to S2 to provide heterogeneous but necrosing temperature profiles for related histological investigations.⁴¹ Temperature was continuously monitored in three MR axial imaging slices. The central slice was positioned through the center of the transducer assembly, serving as the primary images for monitoring treatment progression and controlling the applicator power levels. Temperature thresholds and thermal dose calculations from

FIG. 3. Power delivered to two active sectors (S1, S2) on both transducers on an applicator (T1, T2) in (a) Canine 1 and (b) Canine 3, as adjusted by hand using visual MR temperature feedback.

FIG. 4. Example rotational beam plot measured for a single tubular transducer segment (3 mm OD, 6 mm length, $3 \times 120^\circ$ sectors) of the transurethral ultrasound applicator, with normalized output from all three sectors. The radial distance of the scan was set at 4 mm from urethral balloon surface as the applicator was rotated 360° .

the MR temperature measurements determined the extent of thermal damage and were correlated with the acute TTC stained tissue.

In Canine 2, the transducer assembly was positioned mid-gland with all three sectors active to target the whole angular cross-section area of the prostate. The transducers were rotated to position sector 1 (S1) on both transducers (T1, T2) ventrally and sectors 2 and 3 (S2, S3) dorsally, with the acoustic dead zone between S2 and S3 directed toward the rectum. The applied RF power levels delivered to all elements (~ 11 W/sector) remained constant for the duration of the treatment (15 min). The MR temperature images were obtained in three axial slices as described for Canine 1.

In Canine 3, the transducer assembly was translated and positioned toward the proximal end of the urethral cooling balloon to demonstrate the ability to reposition within the balloon and target the apex region of the prostate. The applicator was rotated and positioned to target the ventral portion of the gland, as described for Canine 1. Three coronal MR imaging slices were used to monitor temperature during treatment, with the central slice in plane with the applicator. The applied RF power to each sector (S1, S2) on each transducer (T1, T2) was adjusted [Fig. 3(b)] to fit the 52°C temperature contour to the border of the prostate, according to visual feedback from the MR temperature measurements in the center imaging slice (slice 1).

III. RESULTS

Prior to the animal experiments, the multisector transurethral applicators were characterized by measurements of acoustic power output efficiency and beam distributions. The peak acoustic efficiencies, at the optimal drive frequencies of each sector, ranged from 41% to 53%, within a frequency range of 7.8–8.4 MHz. Rotational beam plots with one, two, and three sectors simultaneously active demonstrated 90° – 100° active acoustic patterns (defined by 10% contour) associated with each 120° partition with no apparent cross-coupling between sectors. Figure 4 displays a typical rotational beam plot for three sectors of a tubular transducer, with normalized distributions for each sector. In consideration of experiments performed in an MR suite, separate RF electrical power measurements indicated $\sim 30\%$ of the RF

power delivered by the amplifier to the applicator was lost in the ~ 15 m coaxial cable and low-pass RF filters. The initial driving power of each sector in three *in vivo* canine experiments was adjusted according to the measurements of acoustic efficiency and transmission loss in the coaxial cable sets, and visual observation of the composite acoustic waveform.

The ability of the multisector applicators to control the angular shape and radial depth of clinically relevant heating patterns was examined in three *in vivo* canine prostate glands. These experiments were carried out under MR temperature imaging guidance to assess the controllability of the devices using either axial or coronal imaging planes. In Canine 1, two sectors were active and the third sector was inactive, to ablate a large ventral portion of the gland, while directing heat away from the rectum. Figure 3(a) displays the power levels applied to sectors S1 and S2 on each transducer (T1, T2) over the course of the treatment. Higher power levels were delivered to S1 on T1 and T2 than to S2 in order to evaluate the heating patterns attainable with different maximum temperatures from each sector and demonstrate the effectiveness of independent power control. The 52°C contours were displayed continuously during treatment with MR temperature monitoring and were used to control power levels applied during the treatment. The 52°C contour is used in our study for benchmark comparisons of effective thermal penetration and as an approximate delineation of lethal thermal dose exposure. The radial progression of the 52°C contour during the procedure is displayed in Fig. 5(a) for the following time points (80, 180, 355, 505 s) to illustrate the therapeutic temperature elevations and dose as a function of time and applied power. The radial temperature profiles extending from the center of S1 and S2 [corresponding to the linear track denoted by arrow in Fig. 5(a)] are shown in Figs. 5(b) and 5(c) for the four time points. The temperature profiles increased quickly as a function of radial distance within 1–2 mm of the urethral cooling balloon and gradually decreased after reaching a peak temperature 3–4 mm from the applicator, as expected due to the urethral cooling. After 505 s of power application the 52°C contour penetrated to the prostate boundary along S1. The lower power delivered to S2 translated into a lower peak temperature in the tissue adjacent to this sector and slightly less radial penetration of the 52°C contour. Thermal redistribution due to blood flow and thermal conductivity filled in any gaps in ultrasound energy that were seen in the acoustic pressure profiles and created a contiguous 52°C and $t_{43}=240$ min boundary, predictive of the thermal destruction. The 52°C contour is slightly smaller than the $t_{43}=240$ min contour at the outer boundary for the longer time points, most likely due to increased accumulation of lethal thermal dose at lower temperatures. These results demonstrate the potential of multisector transurethral ultrasound applicators to produce conformal, contiguous heating patterns in the angular dimension through differential power level control to each sector.

Figure 5(d) shows the contours of lethal thermal dose threshold ($t_{43}=240$ min) as calculated from the MR temperature measurements at the same time points during treat-

FIG. 5. MR temperature and thermal dose measurements of a 2 active sector (S1, S2) heat from a multisector transurethral ultrasound applicator at 80 s (●●●), 180 s (●—●), 355 s (— —), and 505 s (solid). The 52 °C contour throughout time (a) and the radial profile of the heating along the white arrows (S1, S2) (b,c) are shown. The thermal dose ($t_{43}=240$ min) at the different times (d) was calculated from the MR temperature measurements and corresponded with acute gross examination of the thermal lesion (e).

ment (80, 180, 355, and 505 s). An aberration in the thermal dose contour at 505 s was noted outside the ventral portion of the prostate gland and was most likely caused by temperature measurement artifact in one of the MR images. The MR image SNR, which determines the accuracy of the temperature measurement, decreases rapidly with increasing distance from the endorectal coil. Therefore, temperature measurement artifacts are more likely to occur where image SNR is low. Furthermore, the cumulative thermal dose distribution, based upon calculations that are nonlinear with respect to temperature rise, was calculated without temporal filtering and was very susceptible to artifacts and small transient errors in MR temperature measurement. Figure 5(e) displays the TTC-stained prostate section obtained after thermal treatment and demonstrates a clear contiguous thermal lesion in the targeted portion of the gland, while the red-stained viable tissue indicates the dorsal portion of the prostate toward the rectum was protected from thermal damage. The lethal thermal dose contour and final 52 °C contour [Fig. 5(a)] appeared to correspond very closely to the outer boundary of thermal destruction identified from the gross tissue analysis of the TTC stained tissue section.

In Canine 2, fast, complete thermal bulk ablation of the prostate was performed. The experiment was conducted with all sectors active on each transducer at constant applied

power levels. The progression of the 52 °C contour, as monitored in the central MR imaging slice during treatment, is shown in Fig. 6(a). Time points (150, 240, 360, and 450 s) were selected for this case to best illustrate the radial progression of the temperature and thermal dose contours extending toward the border of the prostate during treatment. The corresponding cumulative lethal thermal dose contours ($t_{43}=240$ min) at the different treatment time points are shown in Fig. 6(b). Within 4 min, thermal redistribution filled any gaps in the heating pattern and created a contiguous lesion shape. The radial temperature profiles as a function of time in front of each sector are shown in Figs. 6(d)–6(f) corresponding to the arrows (S1, S2, S3) in Fig. 6(a), respectively. The peak temperature was 4–5 mm from the urethra and the 52 °C and $t_{43}=240$ min contour reached the edge of the prostate centered on S1 and S2 (~15 mm radial) and closed off S3 (~12 mm) in less than 8 min. The MR temperature monitoring prematurely ended after this time point due to complications in this particular experiment, but treatment delivery was continued without monitoring for a total of 15 min of power application. The TTC cross-section is shown in Fig. 6(c), which demonstrates ~360° contiguous zone of thermal coagulation extending completely to the boundary of the prostate after the 15 min treat-

FIG. 6. MR temperature and thermal dose measurements of a three active sector (S1, S2, S3) bulk ablation of a canine prostate with a multisector transurethral ultrasound applicator at 150 s (●●●), 240 s (●—●), 360 s (— — —), and 450 s (solid). The 52 °C temperature contours (a) expanded throughout the treatment and thermal conduction filled in the heating pattern at 240 s. The thermal dose contours ($t_{43}=240$ min) (b) fit closely to the 52 °C contour at the different time points and showed bulk ablation of the prostate in less than 7 min. Gross examination of the TTC stained prostate (c) verified thermal destruction of the tissue extending to the prostate boundary. The peak temperatures of the heating distribution from S1 (d), S2 (e), and S3 (f) were about 5 mm from the urethral cooling balloon.

ment. A small ~ 1 mm wide viable region of prostate boundary off S3 is noted, most likely due to the preferential placement of endorectal cooling in that sector as well as an inability to make compensating power adjustments after loss of MR imaging. It should be noted that this gross tissue analysis does not correspond directly to the thermal dose and temperature contours at the 8 min time point above, but provides ample evidence of power output capabilities and continued radial progression of thermal lesion boundary with time and without areas of under-treatment between sectors.

Experiments in Canine 3 evaluated the ability to use multiple coronal MR imaging planes to monitor and adjust the heating pattern. The transducer assembly was translated to the proximal portion of the urethral cooling and rotated for positioning to selectively direct heating to the ventral portion of the apical region of the prostate. The power levels applied during treatment were manually adjusted [Fig. 3(b)] using visual feedback from the MR temperature monitoring to extend the 52 °C contour to the outer edge of the prostate. In this experiment, the temperature was monitored in three imaging slices, but the power levels were based upon the measurements in the center slice (slice 1). Figure 7(a) displays the MR temperature map in slice 1 at the end of the thermal treatment where the 52 °C contour has reached targeted

boundary of the prostate. The cumulative lethal thermal dose contour ($t_{43}=240$ min) calculated from the MR temperature images is overlaid as a solid line on the temperature map and reaches the target boundary. In addition, the approximate position of the applicator and transducer assembly is displayed on the temperature image. The ventral prostate tissue experienced higher temperatures (slice 2) [Fig. 7(b)] due to the planned angular activation pattern of the applicator. There is a small region of temperature artifact located within the cooling balloon [Figs. 7(a) and 7(b)], possibly due to dynamic changes of water flow and the transducer assembly from the initial baseline measurement. Artifacts localized in close proximity or within the applicator balloon are typically disregarded, whereas the critical temperatures outside the balloon and extending toward the prostate boundary are artifact free. Slice 3 in Fig. 7(c) demonstrates that the prostate tissue dorsal to the applicator was not exposed to high temperatures, and that heating can be directed away from the rectum. Along the length of the applicator, two transducers (6 mm length, 2 mm spaced) created a thermal lesion 15–18 mm in length and 13–16 mm in radius from the urethra during a short 10 min treatment. The 52 °C contours were contiguous and displayed the ability of multiple transducer arrays to

FIG. 7. Three coronal MR temperature images at the end of a 10 min heat treatment and gross examination of the resulting thermal lesion from a multisector transurethral applicator with two active transducer elements. (a) The 52 °C contour was manually fitted to the border of the prostate according to visual MR temperature feedback. The thermal dose contour ($t_{43} = 240$ min) (solid line) was calculated from the MR temperature measurements. A schematic of the approximate applicator and transducer position is overlaid on the image. The imaging slices directly above (b) and below (c) the applicator displayed the large thermal dose delivered to the ventral portion of the gland and the protection of the tissue in the dorsal gland, respectively. (d) TTC stain of the thermal lesion and the approximate location of the monitored coronal imaging slices.

control heat delivery along the length of the applicator. The TTC-stained prostate, sliced axially, reinforced the temperature and thermal dose data acquired in the MR [Fig. 7(d)] and corresponded to the 52 °C and thermal dose contours in slices 1 and 2 [Figs. 7(a) and 7(b)]. The setup of MR imaging slices used to monitor the treatment is shown on Fig. 7(d), but the true locations of the imaging may be slightly different from those displayed due to differences with the slicing of the prostate for gross tissue examination.

IV. DISCUSSION

Multisector transurethral ultrasound applicators were developed and evaluated to determine their potential for delivering conformal thermal ablation to targeted regions of prostate tissue in conjunction with MR guidance and temperature monitoring. Furthering a design strategy first discussed for interstitial ultrasound technology,^{32,42} the transurethral applicator developed in this study was constructed with a linear array of larger diameter tubular radiators, each with three independently powered 120° sectors, for dynamically tailoring heat treatments in angle and length without requiring mechanical manipulation during treatment. The transducer assembly incorporated into the devices was capable of rotation and translation within the catheter for accurate positioning and selective targeting of thermal treatment. In a series of three *in vivo* experiments within canine prostate

glands, these devices proved to be capable of providing adaptable heat treatments to large target volumes in a relatively short treatment times. Treatment times were shortened by the ability to simultaneously apply and control power to all required sectors over the entire treatment volume without the need for rotational scanning. The treatment times and radial heating penetration were consistent throughout the three canine prostate experiments. By adjusting applied power levels to each sector on multiple transducers, the heating pattern could be effectively directed and controlled in the radial, angular, and longitudinal dimensions under MR temperature guidance.

The experiments performed in Canines 1 and 3 used two active sectors on each transducer, directed ventrally, to produce a well-defined thermal lesion that extended toward the outer boundary of the prostate, with no energy or heating directed toward the rectum (Figs. 5 and 7). The active cooling within the urethral cooling balloon provided a protective effect extending 1–2 mm from the urethra [Figs. 5(e) and 7(d)]. Angular control over the heating penetration was possible by applying different powers to each set of independent sectors (S1, S2) and controlling treatment duration (Fig. 3), according to MR temperature monitoring of the 52 °C contour. In the Canine 2 experiments, the transducer assembly was rotated and positioned with a sector notch and inherent acoustic dead zone directed toward the rectum. All three sectors on each transducer segment were activated to produce fast thermal ablation conforming to or near the boundary of the whole prostate gland axial imaging cross-section, with reduced maximum temperatures directly toward the rectum. Together these three *in vivo* experiments consistently demonstrated these applicators are capable of fast thermal ablation (7.5–10 min) extending 12–15 mm from the applicator to the prostate boundary, with the ability to shape the angular heating pattern by appropriate sector activation and positioning. The power handling capabilities and penetration depths of these multisector transurethral applicators are similar to previously reported values for fixed, single-sector directional tubular transurethral devices,^{24,28} but with the significant advantage of dynamic angular control.

An additional objective of this study was to determine the effect, if any, the acoustic dead zone that exists between sectors has on the angular heating distribution in prostate with multisector transurethral ultrasound applicators. The loss of acoustic output at the edge of the transducer sector of a tubular source is documented and can be attributed to physical loss of material during cutting, de-poling of material adjacent to the notch, and near-field diffraction patterns.²⁷ Recent investigations have demonstrated that the presence of acoustic dead zones on small diameter multisector tubular transducers (<1.8 mm OD) for interstitial applications did not significantly impact angular control of heating.³² The larger diameter transurethral transducers (3 mm OD) used in this study displayed a 90°–100° active acoustic zone (defined by 10% contour) from each 120° sector as measured 4 mm outside the urethral cooling balloon (Fig. 4). It was important to investigate the possible effects of the sectoring of the tubular transducer in an *in vivo* model, where the blood

perfusion and other thermal effects may reduce homogeneity. In this study during power application with two or three sectors active, discontinuity in the 52 °C contour and $t_{43}=240$ min contour due to the acoustic dead zones was noted during the initial phase of power application, but by ~5 min the effects were negligible as higher temperatures were achieved and contours coalesced to produce uniform and contiguous zones of thermal destruction between sectors, with smooth outer boundaries and continued radial propagation in time. Additionally, as demonstrated in Fig. 5, the 52 °C contour and resulting thermal lesion remained contiguous despite driving sectors at different power levels and creating different maximum temperatures adjacent to each sector.

Heating control along the length of the applicator was accomplished using a linear array of two short transducers (6 mm). A linear array of ultrasound transducers has been shown to provide adaptable lesion control along the length of a heating applicator,^{24,25,28} however, as more transducers are added to the array, the power control and driving systems become significantly more complicated. The transducer assembly designed in this study could be translated into a designated heating position without moving the catheter, allowing for heating one area in the prostate and then moving to a different area. Heating in multiple steps with two transducer arrays may be practical with multisectoral transurethral ultrasound applicators because of the short treatment time to ablate a large tissue area. In addition, heating the entire prostate in multiple steps may simplify the applicator power delivery system and setup and provide an alternative to large transducer arrays. However, it should be noted that more complex but longer segmented arrays could also be employed to treat larger volumes and completely avoid translation during therapy.

These *in vivo* evaluations demonstrated regions of thermal coagulation out to 15 mm radial from the applicator, which extended to the boundaries of 3–4 cm wide prostates during treatment, and directly indicate potential to treat large focal regions of prostate or to the periphery of glands that are ~4 cm in cross-section (Fig. 7). Furthermore, as demonstrated in experiments and theory of previous studies of tubular applicators, it is possible to extend penetration to 15–20 mm radial with increased power and longer treatment times,^{20,24,27,30} indicating that future optimization of design and treatment delivery strategies can be performed to potentially treat larger glands up to ~5 cm width if necessary. However, the radial divergence of the acoustic energy from tubular radiators may limit effective penetration for glands greater than ~5 cm. In contrast, recent studies show that clinically relevant but small prostate glands of ~3 cm cross-section can be heated quickly and with less concern of pelvic bone heating using tubular applicators compared to rotating planar and curvilinear devices.³⁰

In these *in vivo* studies we used real-time MR temperature monitoring and thermal dose calculations to evaluate these multisectoral devices by measuring the time progression or thermal dosimetry of thermal therapy delivered. As a second means of performance evaluation, visual observation of the

TTC stained serial sections of the prostate, approximately aligned with the central treatment zone and monitored plane, were used to quantify and verify zones of thermal coagulation. Due to our experimental design and intent, we did not attempt to correlate or establish the accuracy of the MR temperature monitoring and thermal dose calculations to post-treatment gross tissue analysis or histology. However, the approach of using MR temperature and thermal dose monitoring to accurately predict thermal damage during transurethral ultrasound ablation has been validated and critically assessed in recent studies which have provided detailed comparisons to histology, TTC gross tissue inspection, and MR contrast enhanced images posttreatment.^{20,29,39,41}

Currently, the methods available for heat treatment of prostate cancer with ultrasound are external and transrectal HIFU devices that typically involve rapid thermal damage (<10 s) to multiple small volumes of tissue.^{5,43} MR verification of the delivered temperatures from HIFU devices has been recently approved for the treatment of uterine fibroids.¹⁸ For prostate cancer, ultrasound imaging has recently been suggested and used as a noninvasive temperature monitoring system for improving treatment heating patterns with HIFU devices by adjusting the treatment parameters between pulses.¹⁵ Regardless of the method used to monitor and control HIFU prostate thermal therapy, the heating requires significantly long treatment times for prostate cancer (169 min average⁵). When monitoring the temperature with MR, the cost and resources involved can become significant with this long treatment. In comparison, an important benefit of multisectoral transurethral ultrasound applicators for treating prostate cancer and BPH is their ability to ablate a large volume in a short period of time, while controlling the shape of a thermal lesion in the angular dimension. In this study, bulk ablation of the prostate area was accomplished in a short treatment duration (<10 min) (Fig. 6) under MR temperature monitoring.

Transurethral ultrasound applicators are currently under preclinical evaluation as an alternative to HIFU for high-temperature ultrasound thermal therapy. Transurethral devices heat larger volumes in a single treatment and offer less severe thermal gradients at the boundaries of heating than HIFU devices. The slower growth of the thermal lesion boundary and shorter overall treatment times possibly make the transurethral devices more practical for use with MR temperature feedback.^{20,24,44} The multisectoral transurethral ultrasound applicators developed in this study were evaluated in a 0.5 T interventional magnet because of the ease of access to the canine during experimental setup. A recent study explored the optimal spatial and temporal resolutions in the 0.5 T scanner to balance image and temperature map resolution with higher SNR.³⁴

Rotating transurethral applicators with planar or curvilinear transducers can thermally ablate narrow zones of prostate tissue extending 15–20 mm toward the boundary of the gland in around 60 s.^{24–26} In order to treat larger target volumes, mechanical scanning is required to sweep out and contour a composite ablative region while using MR temperature im-

aging as feedback with these devices, which may significantly increase overall treatment duration or complexity. Previous studies with directional tubular transurethral ultrasound applicators (180° sector) were able to ablate a large tissue volume in a short treatment, but these devices lacked the flexibility to more carefully control the angular dimension of the thermal lesion during treatment.^{22,27} With a very directional sectored transducer (90°), angular control was accomplished by rotating the transducer during treatment;²⁴ however, this extended the overall treatment time and introduced mechanical movement during treatment. Although these rotating transurethral devices are very controllable, the requirement to rotate or sweep during therapy delivery can induce movement artifact or errors in PRF-based MR temperature monitoring, due to the sensitivity of the measurements to any motion with respect to the initial baseline image, and an increase in treatment complexity by requiring an MR-compatible rotation motor system.^{25,26} One applicator configuration under investigation incorporates a planar transducer rotated within a rigid plastic and brass construct (6.5 mm diameter), which can be positioned in the dog prostate^{25,29} and fixed directly to the rotation motor assembly and translation stage mounted on the MR table. This rigid configuration has been shown to substantially reduce the movement artifact associated with rotation when compared to flexible delivery catheter systems (4 mm diameter), which may be more susceptible to torque and movement during rotation.^{22,24,26} In addition, longer treatment duration with some applications of the scanning transurethral heating devices could also introduce temperature measurement errors associated with image phase drift or a change in prostate dimensions due to heating.

When controlling rotating scanning transurethral applicators with MR temperature feedback, the treatments would typically be monitored in the axial imaging plane. As seen in Fig. 5, multisectored transurethral applicators can be monitored in the other imaging planes (coronal, sagittal) because the device power control does not have to depend on the temperature maps in the axial imaging plane. This may prove to be advantageous in clinical situations where alternate imaging planes can be used to more precisely monitor contouring of the thermal distribution along the axis of the applicator, for example a series of coronal or sagittal planes when treating BPH in the anterior/lateral prostate to clearly define the bladder neck and verumontanum in relation to the heating field. When compared to rotating transurethral ultrasound applicators, multisectored devices offer less angular control of heating patterns, however, the multisectored devices allow much simpler heating control with MR temperature feedback, do not require any device manipulation during treatment or rotational motors, and can be employed within flexible delivery catheters. These factors and the short treatment times to ablate a large volume of tissue, as found in this study, contribute to multisectored transurethral ultrasound applicators being suitable and practical for prostate heat treatments with MR temperature monitoring.

This study has demonstrated the feasibility and clinical potential of this design concept for prostate thermal therapy. The multisectored tubular ultrasound device configuration could be useful for thermal ablative treatment of BPH, which typically targets the anterior/lateral lobes of the human prostate to reduce obstructive hyperplastic tissue.^{8,9,45} Compared to TUMT devices, these multisectored transurethral ultrasound applicators offer increased spatial heating control both in positioning toward the bladder neck and in directing the energy into the anterior/lateral portion of the gland. This improved control, coupled with faster treatment times and greater heating penetration, may improve overall clinical efficacy and durability. Other multisectored transducer configurations (e.g., number of sector and angles, intentional dead zones) may be applicable or tailored to BPH treatment. Although not required for treating BPH, using MR temperature guidance with these ultrasound devices would allow more precise and thorough targeting of the obstructive tissue and patient specific therapy. In contrast, cancer treatment would require MR temperature monitoring to ensure that the targeted cancer region receives a prescribed thermal dose, while avoiding damaging the rectum, sphincters, or neurovascular bundles. Additional studies are warranted to optimize applicator design, including the number of sectors and transducers, and develop disease specific treatment strategies to ensure adequate target destruction and protection of non-targeted tissues.

In summary, multisectored transurethral ultrasound devices offer dynamic angular and longitudinal control over the creation of contiguous thermal lesions and the potential to conform a heat treatment to specified target regions within the prostate. Fast treatment times (8–15 min), radial heating penetration (~15 mm, to boundaries of 4 cm wide prostates), and formation of contiguous thermal lesions (200°–360° sectors) were achieved within *in vivo* canine prostate. The multisectored transurethral ultrasound applicator configuration is practical for dynamic spatial control of large regions of coagulation in conjunction with MR temperature guidance without requiring any device motion during treatment. This multisectored tubular array transurethral ultrasound technology has demonstrated potential for relatively fast and reasonably conformal targeting of prostate volumes suitable for the minimally invasive treatment of BPH and cancer under MR guidance. Further investigation of applicator design and validation of MR-guided monitoring and control schemes specific to this approach for treatment of prostate are warranted.

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