Endocervical ultrasound applicator for integrated hyperthermia and HDR brachytherapy in the treatment of locally advanced cervical carcinoma

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Purpose: The clinical success of hyperthermia adjunct to radiotherapy depends on adequate temperature elevation in the tumor with minimal temperature rise in organs at risk. Existing technologies for thermal treatment of the cervix have limited spatial control or rapid energy falloff. The objective of this work is to develop an endocervical applicator using a linear array of multisectorized tubular ultrasound transducers to provide 3-D conformal, locally targeted hyperthermia concomitant to radiotherapy in the uterine cervix. The catheter-based device is integrated within a HDR brachytherapy applicator to facilitate sequential and potentially simultaneous heat and radiation delivery.

Methods: Treatment planning images from 35 patients who underwent HDR brachytherapy for locally advanced cervical cancer were inspected to assess the dimensions of radiation clinical target volumes (CTVs) and gross tumor volumes (GTVs) surrounding the cervix and the proximity of organs at risk. Biothermal simulation was used to identify applicator and catheter material parameters to adequately heat the cervix with minimal thermal dose accumulation in nontargeted structures. A family of ultrasound applicators was fabricated with two to three tubular transducers operating at 6.6–7.4 MHz that are unsectored (360°), bisected ($2 \times 180^\circ$), or trisected ($3 \times 120^\circ$) for control of energy deposition in angle and along the device length in order to satisfy anatomical constraints. The device is housed in a 6 mm diameter PET catheter with cooling water flow for endocervical implantation. Devices were characterized by measuring acoustic efficiencies, rotational acoustic intensity distributions, and rotational temperature distributions in phantom.

Results: The CTV in HDR brachytherapy plans extends 20.5 ± 5.0 mm from the endocervical tandem with the rectum and bladder typically < 8 mm from the target boundary. The GTV extends 19.4 ± 7.3 mm from the tandem. Simulations indicate that for 60 min treatments the applicator can heat to 41°C and deliver $> 5\text{EM}_{43^\circ\text{C}}$ over 4–5 cm diameter with $T_{\text{max}} < 45^\circ\text{C}$ and $1\text{ kg m}^{-3}\text{ s}^{-1}$ blood perfusion. The 41°C contour diameter is reduced to 3–4 cm at $3\text{ kg m}^{-3}\text{ s}^{-1}$ perfusion. Differential power control to transducer elements and sectors demonstrates tailoring of heating along the device length and in angle. Sector cuts are associated with a $14\text{--}47^\circ$ acoustic dead zone, depending on cut width, resulting in a $\sim 2\text{--}4^\circ\text{C}$ temperature reduction within the dead zone below T_{max} . Dead zones can be oriented for thermal protection of the rectum and bladder. Fabricated devices have acoustic efficiencies of 33.4%–51.8% with acoustic output that is well collimated in length, reflects the sectoring strategy, and is strongly correlated with temperature distributions.

Conclusions: A catheter-based ultrasound applicator was developed for endocervical implantation with locally targeted, 3-D conformal thermal delivery to the uterine cervix. Feasibility of heating clinically relevant target volumes was demonstrated with power control along the device length and in angle to treat the cervix with minimal thermal dose delivery to the rectum and bladder. © 2011 American Association of Physicists in Medicine. [DOI: [10.1118/1.3512803](https://doi.org/10.1118/1.3512803)]

Key words: hyperthermia, thermal therapy, HDR brachytherapy, cervix, cancer, ultrasound, catheter-based, endocavity

I. INTRODUCTION

Cervical cancer causes more than 250 000 deaths per year worldwide.¹ Although stage I (FIGO) disease can generally be well managed, treatment of more advanced tumors is often unsuccessful; 5 year survival for stage II disease is 70%, dropping to 40% for stage III and 15% for stage IV.² The current standard of care calls for cisplatin-based chemotherapy combined with radiotherapy consisting of external

beam radiotherapy and high-dose-rate (HDR) brachytherapy. However, extensive hypoxia present in cervical cancers can preclude their successful management with targeted radiotherapy and has been linked with poor prognosis.^{3–5} Hyperthermia (HT), or temperature elevation to $41\text{--}43^\circ\text{C}$, improves tumor control when delivered adjunct to radiotherapy or chemotherapy by increasing tumor blood flow, decreasing hypoxia, enhancing cellular damage, and inhibiting damage

repair by denaturation of repair enzymes.^{6,7} Randomized trials comparing the combined treatment of HT and radiotherapy to radiotherapy alone for locally advanced cervical cancer have shown dramatic improvements in tumor control and overall survival with the dual modality therapy.^{8–11} A phase II study employing trimodality treatment regimens of radiotherapy, chemotherapy, and HT has demonstrated promising initial results,¹² and a multicenter phase III trial is underway.¹³

The efficacy of thermal therapy depends on the delivery of targeted heating in close spatial and temporal sequences with conformal radiotherapy, while toxicity depends on the extent of heating in nontargeted tissue. Thermal dose delivery has been positively correlated with tumor response, with cumulative thermal dose thresholds of 6–10 equivalent minutes at 43 °C ($EM_{43\text{ }^{\circ}\text{C}}$) required for HT to exhibit significant therapeutic enhancement.^{14–17} Inadequate heating techniques resulting in low thermal dose delivery to tumors have been a primary reason for studies failing to demonstrate a clinical benefit of adjunct HT.^{18–20} Although deep regional HT devices have yielded positive results in cervical cancer,^{10,17} low temperature and thermal dose is typically obtained in the cervix ($T_{90} < 40\text{ }^{\circ}\text{C}$, $< 1.5EM_{43\text{ }^{\circ}\text{C}}$), with temperatures in the rectum and bladder at or above tumor temperature.^{12,21} In addition, hot spots created by microwave arrays due to the differing electrical properties of muscle, fat, and bone can occur outside the cervix and result in thermal toxicity.^{22,23} The production of these hot spots and the ability to treat deep-seated tumors are dependent on patient weight and position.^{24,25} Endocavity devices for localized HT in the cervix have been developed based on radiofrequency or microwave sources, but these devices have limited thermal penetration or limited control over temperature distributions.^{26–28}

The objective of this work was to develop and characterize an endocervical ultrasound applicator for 3-D conformable HT delivery to the cervix adjunct to HDR brachytherapy. This device, shown in concept in Fig. 1, consists of a linear array of tubular transducers to provide power control along the device length, with each transducer divided into acoustically isolated sectors to control energy output in angle. The device is integrated within the endocervical catheter of a HDR brachytherapy delivery applicator for minimally invasive, locally delivered heating targeted to the region surrounding the cervix. The endocervical ultrasound device was developed through a consideration of clinical target volumes, extensive theoretical analysis, and experimental characterization. Details of the device development are presented along with expected performance based on thermal simulation and measurements of acoustic output and heating patterns.

II. METHODS

II.A. Anatomical inspection

Treatment planning data based on CT and MRI scans were evaluated for 35 patients implanted for HDR brachytherapy delivery to the cervix. The HDR source (Ir^{192}) is

FIG. 1. (a) Endocervical ultrasound applicator integrated within HDR brachytherapy tandem and ring catheter. 3-D conformal hyperthermia is delivered locally to the uterine cervix by a linear array of multisectoral transducers with differential power control to sectors and transducers. (b) Sagittal MR image of brachytherapy implant showing the position of the endocervical tandem with respect to cervical target, rectum, and bladder.

introduced through an applicator (Nucletron, Inc.) consisting of an endocavity catheter, or tandem, along with (1) a ring surrounding the cervical os, (2) two ovoid-shaped structures placed in the vaginal fornices, or (3) a vaginal cylinder. The dimensions of gross tumor volumes (GTVs) and target clinical treatment volumes (CTV) identified by the physician for radiation dose delivery were measured to assess the dimensions of potential clinical targets for HT. The distances of the rectum and bladder from the tandem, CTV, and GTV were measured. The relative positions of GTV, CTV, tandem, and organs at risk are shown in Fig. 2.

II.B. Theoretical evaluation

II.B.1. Biothermal model

The influence of applicator design parameters on heating profiles was investigated using an acoustic and biothermal model of ultrasound HT in homogeneous uterine tissue. Tem-

FIG. 2. Axial MR section with clinical target volume (CTV), gross tumor volume (GTV), rectum, bladder, endocervical tandem, and interstitial catheters. The rectum and bladder closely approach the CTV and GTV on the posterior and anterior aspect, respectively, requiring angular control of heating distributions to treat the tumor without inducing thermal damage in these organs. Interstitial catheters can be used for thermal monitoring and feedback control of power levels.

perature distributions in cross-section and along the applicator length were derived from a finite difference solution to the classic Pennes bioheat equation,²⁹

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot k \nabla T + \dot{\omega} c_b (T_b - T) + \dot{q}, \quad (1)$$

where ρ is density (kg m^{-3}), c is heat capacity ($\text{J kg}^{-1} \text{ } ^\circ\text{C}^{-1}$), T_b the blood temperature ($^\circ\text{C}$), k the thermal conductivity ($\text{W m}^{-1} \text{ } ^\circ\text{C}^{-1}$), $\dot{\omega}$ the mass flow rate of blood ($\text{kg m}^{-3} \text{ s}^{-1}$), and $\dot{q}$ the ultrasound power deposition (W m^{-3}). The finite difference solution for tissue temperature T was computed using the Crank–Nicholson method with mixed implicit and explicit integration to improve numerical stability with fine grid spacing.³⁰ The correlation of the finite difference acoustic and biothermal model to *ex vivo* and *in vivo* temperatures and thermal lesion data has been demonstrated in past work.^{30–32} Thermal dose was computed by the Sapareto and

Dewey³³ formulation for equivalent minutes at $43 \text{ } ^\circ\text{C}$ ($\text{EM}_{43 \text{ } ^\circ\text{C}}$). The ultrasound power deposition is related to the acoustic intensity by³⁴

$$\dot{q} = 2\alpha \frac{1}{r} I_0 e^{-2\mu(r-r_0)}, \quad (2)$$

where α is acoustic absorption ($\text{Np m}^{-1} \text{ MHz}^{-1}$), I_0 the surface intensity of the transducer, μ the acoustic attenuation ($\text{Np m}^{-1} \text{ MHz}^{-1}$), r the radial distance from the center of the applicator (m), and r_0 the outer radius of the transducer (m). Ultrasound intensity was modeled as uniform across sectors, along the applicator length at a given radius, and set to zero between transducer sectors over a defined dead zone angle. The electrical power applied to the transducers was converted to acoustic power by assuming a 50% acoustic efficiency. The model was solved in cylindrical coordinates in cross-section (r – θ) or along the device length (r – z). The applicator was a 3.5 mm diameter tubular transducer operated at 6.5–8 MHz and housed within a 6 mm outer diameter (OD) catheter with 0.25–0.50 mm wall, embedded in homogeneous uterine tissue. In order to accurately resolve temperature elevation in the catheter wall with overall reduced computation time, variable radial node spacing was employed following a sigmoidal function that increased from 0.005 mm near the transducer surface to 0.5 mm at 4 cm radial depth in tissue. Acoustic and thermal tissue properties used in the biothermal model are given in Table I.^{35–38} Blood temperature T_b was $37 \text{ } ^\circ\text{C}$ and blood specific heat capacity c_b was $3825 \text{ W m}^{-2} \text{ } ^\circ\text{C}^{-1}$.³⁷ Attenuation and absorption were set equal under the assumption that scattered energy is locally absorbed and contributes to heating. A range in blood perfusion from 0.5 – $3 \text{ kg m}^{-3} \text{ s}^{-1}$ was considered to bracket physiological variation in cervical cancers.³⁹ A convective boundary was applied at the inner catheter wall to model heat removal as $h(T_{\text{cool}} - T_i)$ by cooling water flow with h the convective cooling coefficient ($\text{W m}^{-2} \text{ } ^\circ\text{C}^{-1}$) and T_{cool} the cooling flow temperature ($^\circ\text{C}$). An adaptive power control scheme using PID control was implemented following Lin *et al.*,⁴⁰

$$P = \begin{cases} P_{\text{max}}, & T < T_{\text{max}} - 2 \\ K \left[(T_{\text{max}} - T_n) + (\pi/80) \sum_n (T_{\text{max}} - T_n) - (3/\pi)(T_{\text{max}} - T_n) \right], & T_{\text{max}} - 2 < T < T_{\text{max}} + 1 \\ 0, & T > T_{\text{max}} + 1, \end{cases} \quad (3)$$

with the maximum power P_{max} , gain K , and time constant τ as adjustable parameters with the goal of ramping temperature from baseline to a set T_{max} in 5 min with minimal overshoot and oscillation. The power value was updated every 5 s.

II.B.2. Catheter material

The effects of ultrasound absorption by the catheter on temperature profiles were examined by parametrically varying catheter material properties along with cooling water flow rate in the catheter. Catheter absorption was set to 20,

TABLE I. Thermal and acoustic properties of cervix and catheter materials employed in the finite-difference model.

Property	Uterus	Catheter
ρ (kg m ⁻³)	1060 ^{a,b}	1100 ^f
c (J kg ⁻¹ °C ⁻¹)	3600 ^{a,b}	1600 ^f
k (W m ⁻¹ °C ⁻¹)	0.56 ^{a-c}	0.23 ^f
ω (kg m ⁻³ s ⁻¹)	0.5–3 ^d	0
μ (Np m ⁻¹ MHz ⁻¹)	6.9 ^e	
α (Np m ⁻¹ MHz ⁻¹)		20–80 ^g
T_{cool} (°C)		20–25
h (W m ⁻² °C ⁻¹)		500–1000

^aDuck, 1990.

^bBaldwin, 2001.

^cOlsrud, 1998.

^dLyng, 2001.

^eSiddiqi, 1999.

^fNominal values for plastic, Kaye, 1995.

^gBloomfield, 2000, Guess, 1995, Hung, 1983, Kaye, 1995.

40, 60, or 80 Np m⁻¹ MHz⁻¹ to reflect the range of values in the materials considered for use in the catheter design: Nylon 6/6, Pebax (Arkema Inc.), TPX (Matsui Plastics, Inc.), polyethylene terephthalate (PET) (Advanced Polymers, Inc.), and Celcon (Ticona Polymers Inc.).^{41–44} These materials differ in stiffness and may require different wall thickness to avoid kinking and to be compatible with 2–3 day HDR brachytherapy implantation. Catheter thickness was therefore varied from 0.125 to 0.500 mm in 0.125 mm intervals. Ranges in thermal conductivity from 0.15–0.30 W m⁻² °C⁻¹ and ρc product from 1.5×10^6 – 2.1×10^6 J m⁻³ °C⁻¹ for the catheter were tested but effects on penetration of the 41 °C contour were negligible and so these variations were not considered in further analysis. Nominal values used for the plastic catheter were 0.23 W m⁻² °C⁻¹ for thermal conductivity, 1100 kg m⁻³ for density, and 1600 J kg⁻¹ °C⁻¹ for heat capacity.⁴⁴ Cooling water temperature T_{cool} was set to 20 or 25 °C and convective cooling coefficient h to 500 or 1000 W m⁻² °C⁻¹ based on other catheter-cooled endocavity devices.^{45–47} Catheter material and cooling flow effects were assessed at 1 and 3 kg m⁻³ s⁻¹ tissue blood perfusion. Catheter material comparison tests were conducted using bisected transducers (2 × 180°) operating at 7 MHz with 30° acoustic dead zones. T_{max} was set to 43, 45, or 47 °C in the power controller. Temperature profiles were evaluated at 15 min, after steady-state had been reached.

II.B.3. Transducer sectoring

The impact of acoustic dead zones on temperature distributions in angle was assessed in a series of simulations. Temperature elevation induced by trisected (3 × 120°) and bisected (2 × 120°) transducers with inactive dead zones (zero acoustic output) of 20°, 30°, 40°, or 50° between transducer sectors were compared to an unsectored (360°) transducer at blood perfusion levels of 0.5, 1, 2, or 3 kg m⁻³ s⁻¹. T_{cool} was set to 25 °C and h to 500 W m⁻² °C⁻¹ for cooling flow. Maximum acoustic power levels in the adaptive controller were set from 0.75–3.75 W (1.8–4.1 W cm⁻² surface

acoustic intensity) to achieve a T_{max} of 43, 45, or 47 °C and 15 min was again used as a time point for comparison of steady-state temperature profiles. The catheter was given a nominal absorption of 40 Np m⁻¹ MHz⁻¹ and wall thickness of 0.250 mm.

II.B.4. Patient treatment simulations

A series of simulations were performed in which transducer length, number, frequency, and sectoring were varied to shape the heating profile in axial and sagittal planes to illustrate how the endocervical ultrasound device might be used to treat tumor targets from clinical data while avoiding overheating of rectum and bladder. Applicators with one to three transducers that were 10–15 mm in length and operated at 6.5–8 MHz were modeled. Transducers were unsectored or multisected with 2 × 180° or 3 × 120° sectoring. Acoustic dead zones between sectors were set to 30°. Cooling flow parameters were set at $h=500$ W m⁻² °C⁻¹ and $T_{\text{cool}}=25$ °C. 60 min HT treatment simulations were conducted, with T_{max} of 43, 45, or 47 °C. As HT would likely be administered in multiple fractions, single fraction thresholds of 41 °C and 5EM_{43 °C} were used as indicators of therapeutic heating profiles, in accordance with suggested guidelines for cumulative thermal dose delivery of 6–10EM_{43 °C} obtained over multiple treatment sessions.^{14–17} Power control was implemented based on T_{max} or pilot points in tissue representing the location of interstitial catheters or intraluminal temperature sensors within organs at risk. The rectum temperature was limited to 41.5 °C, while bladder temperature was limited to 42.5 °C, as the bladder has a higher thermal damage threshold of >80EM_{43 °C} (43.5 °C for 1 h) compared to rectal damage thresholds of 20–40EM_{43 °C} (42.2–42.8 °C for 1 h).^{48–50}

II.C. Endocervical applicator fabrication

A family of ultrasound applicators was constructed based on input from biothermal simulations. These devices have two to three tubular transducers (PZT-4, Boston Piezo Optics) that are 3.5 mm in diameter, 10 mm in length, and operate within a 6.5–8 MHz range. Uncut tubes are employed along with tubes that have been cut through one-half wall thickness into two sectors of 180° (2 × 180°) or three sectors of 120° (3 × 120°) using an automatic dicing saw (Disco Corporation). In order to control the size of the dead zone in acoustic output between sectors, tubes are sectored using either a single cut or two adjacent cuts with 0.1–0.2 mm separation. A polyimide tube (1.47 mm OD, Small Parts) at the center of the applicator conducts cooling water flow and acts as a base for mounting the tubular elements. Transducers are mounted on this polyimide tube over smaller polyimide tubes (0.7 mm OD, Cole-Parmer) and secured in place with silicone (NuSil Technology) at the transducer edges to maintain air-backing. Transducer sectors are individually wired with coaxial cable (0.5 mm OD, Temp-Flex Cable) that runs to Redel RF power connectors (Lemo S.A.) at the back end. The transducer assembly is covered with a thin layer of epoxy (310M, Epoxy Technology) and polyester

FIG. 3. Endocervical ultrasound device integrated within HDR brachytherapy delivery applicators (Nucletron, Inc.). The device is housed in a tipped PET catheter bent at 30° that replaces the intrauterine tandem of the brachytherapy applicator. (a) A three-element tandem and ovoid device with power connector and integrated cooling flow. [(b) and (c)] Two-element tandem and ring and three-element vaginal cylinder devices.

heat shrink (4.8 mm OD, Advanced Polymers). An outer polyimide tubing layer (3.4 mm OD, Professional Plastics) protects the cables and provides structure.

The ultrasound applicators are housed within a custom catheter modeled after an endocervical brachytherapy tandem. The PET catheters (Advanced Polymers) have a 6 mm OD with 0.25–0.50 mm wall and are formed with a 30° angle at the distal portion to accommodate the inflection from the vagina to the uterine cavity. Annular water flow couples acoustic energy between the transducers and catheter and cools the catheter surface. The back end of the catheter has a hemostasis valve (Qosina Corporation) for applicator insertion, positioning in length and angle, and sealing cooling flow. The PET catheter can replace the endocervical tandem portion of the same diameter in the HDR brachytherapy applicator (Nucletron, Inc.) and can be used for brachytherapy delivery. The fabricated endocervical ultrasound device is shown in Fig. 3.

II.D. Acoustic characterization

Acoustic characterization of endocervical ultrasound applicators consisted of measuring (1) the frequency of peak electrical impedance magnitude for bare tubes, (2) acoustic efficiencies of transducers and transducer sectors on completed applicators, and (3) rotational acoustic intensity profiles.

Electrical impedance was determined for unmodified tubes over a 5–10 MHz frequency range using a Network Analyzer (HP 3577A, Hewlett-Packard) and the frequency corresponding to peak electrical impedance was measured. Acoustic efficiencies for all tubes and sectors mounted on fabricated applicators were determined using a radiation force balance method adapted for cylindrical transducers,⁵¹ in which the device is centered within a brass acoustic reflector with a conical inner surface to direct acoustic waves toward an absorptive rubber target suspended from an electronic balance (Mettler AE200-S, Mettler Instrument Corp.). A function generator (Wavetek 273, Wavetek Corp.) with RF amplifier (ENI 2100L, Electronic Navigation Industries) was used to apply 3 W electrical power to all transducer sectors. Input electrical power to the device was measured with a power meter (HP 438A, Hewlett-Packard). Acoustic efficiency measurements were first acquired over a 0.6 MHz

frequency range with 0.1 MHz step, centered on the peak frequency determined from the network analyzer, and then over 0.3 MHz within this range in 0.05 MHz intervals. Three measurements were acquired at each frequency, with 0.1%–0.3% standard error.

Rotational acoustic intensity profiles of endocervical applicators were measured in deionized, degassed water with a hydrophone scanned under motor control.⁵² A needle-type hydrophone (Onda HNP-0400, Onda Corp.) was positioned at 8 mm from the device surface with a stepping motor system (XSlide, Velmex Inc.) that moved the hydrophone along the length of the transducers while the applicator was successively rotated by a rotational motor (B5990TS Rotary Table, Velmex Inc.). All motors were under computer control. Plots were obtained over 360° in rotation with 2° angular step size and 0.25 mm step size along the applicator length. The hydrophone signal was read on an oscilloscope (HP 54600A, Hewlett-Packard). A function generator (Wavetek 273, Wavetek Corp.) was used to trigger the amplifiers powering the transducer elements (500–009 RF Generators, Advanced Surgical Systems, Inc.) with a 50% duty cycle at 200 Hz. The oscilloscope window was adjusted to display only the acoustic signal at the end of the 200 cycle pulse. Applicators were scanned with all sectors powered to 2 W cm^{-2} surface acoustic intensity at peak acoustic efficiency.

II.E. Thermal characterization

Short duration heating patterns produced by the devices were investigated in tissue-mimicking phantom. This phantom has thermal and acoustic properties similar to soft tissue ($k=0.58 \text{ W m}^{-1} \text{ }^\circ\text{C}^{-1}$, $\mu=0.53 \text{ dB/cm/MHz}$).⁵³ The applicator was implanted in an 8 cm diameter cylindrical phantom in a water bath held at 22°C . Cooling flow was run at 22°C and 60 ml min^{-1} ($h \approx 1000 \text{ W m}^{-2} \text{ }^\circ\text{C}^{-1}$). Multi-junction constantan-manganin thermocouple probes ($4 \times 2.5 \text{ mm}$ spacing, Ella-CZ) encased in polyimide (0.58 mm OD, Small Parts) and housed in 20-gauge stainless steel needles (Becton-Dickerson S.A.) were implanted 10 mm from the transducer surface, vertically centered on the elements, and spaced every 45° around the device. Probe position was verified by CT. Thermometry data were acquired with a 48-channel HP data acquisition system (HP 34970A).

TABLE II. Summary of clinical target volume (CTV) and gross tumor volume (GTV) dimensions and distances of organs at risk from CTV and applicator based on 35 HDR brachytherapy treatment plans (GTV is available for 5 patients).

Parameter	Average $\pm$ SD (mm)	Range (mm)
Max CTV radius (anterior)	17.7 $\pm$ 4.7	0–42
Max CTV radius (posterior)	20.0 $\pm$ 5.1	5–44
Max CTV radius (overall)	20.5 $\pm$ 5.0	10–44
Max GTV radius (overall)	19.4 $\pm$ 7.3	6–32
GTV length	15.6 $\pm$ 3.6	12–20
Rectum distance from applicator	23.5 $\pm$ 4.5	12–44
Rectum distance from CTV	7.4 $\pm$ 3.6	1–33
Bladder distance from applicator	17.7 $\pm$ 5.5	10–66
Bladder distance from CTV	4.7 $\pm$ 3.6	0–47

Transducer sectors were driven at 1–2 W cm⁻² surface acoustic intensity for 5 min at peak acoustic efficiency. The phantom was then allowed to equilibrate for 3 h in order to reach baseline temperature. After equilibration, the applicator was rotated 15° and the sectors were again powered at 1–2 W cm⁻² surface acoustic intensity for 5 min. This procedure was repeated once more in order to obtain rotational temperature distributions with 15° angular resolution.

III. RESULTS

III.A. Anatomical inspection

A summary of the anatomical data describing target volume dimensions and location of organs at risk is given in Table II. The CTV averages 20.5 $\pm$ 5.0 (standard deviation) per patient in maximum distance in any direction from the tandem. The CTV is often eccentric with respect to the uterine cavity, with the posterior aspect typically extending farther than the anterior aspect (20.0 $\pm$ 5.1 vs. 17.7 $\pm$ 4.7, $p=2 \times 10^{-5}$, Student's paired t-test). The GTV, representative of the hypoxic tumor core that is the true thermal therapy target, is contained within the CTV and contoured in only the five patients who had MRI in addition to CT. The GTV averages 19.4 $\pm$ 7.3 mm per patient in maximum radial distance from the tandem with a range of 5–28 mm. The GTV is 12–20 mm in length. The minimum distance of the rectum and bladder to the tandem is 12.1 and 10.4 mm with average distances of 23.5 $\pm$ 4.5 and 17.7 $\pm$ 5.5 per patient, respectively. Both rectum and bladder are <1 mm from the CTV boundary in some patients and average <8 mm from the CTV boundary (rectum: 7.4 $\pm$ 3.6 mm; bladder: 4.7 $\pm$ 3.6 mm).

III.B. Theoretical evaluation

III.B.1. Catheter material

The maximum radial extent of the steady-state 41 °C contour ranges from 13.7 to 23.8 mm (with $T_{\max}=45$ °C) depending on catheter, cooling flow, and tissue parameters. The effects of the catheter on thermal penetration are minimal for a 0.125–0.250 mm wall but become more apparent with a 0.375–0.500 mm wall and absorption of

80 Np m⁻¹ MHz⁻¹ [Fig. 4(a)]. Increased catheter thickness and attenuation cause increased heating within the catheter wall, which decreases the effectiveness of cooling flow, bringing the $T_{\max}$ closer to the catheter and reducing the thermal penetration for a given $T_{\max}$ (Table III). The effects of changes in cooling flow parameters for a given catheter configuration are slight, with a 1.1–2.3 mm range in the radial extent of the 41 °C contour across all cooling levels. Tissue perfusion has a marked and consistent effect on thermal penetration; high tissue perfusion of 3 kg m⁻³ s⁻¹ reduces the radial extent of the 41 °C contour by 3.7 $\pm$ 0.2 mm with respect to a lower perfusion case of 1 kg m⁻³ s⁻¹. The perfusion effect will likely be less consistent *in vivo* as perfusion may increase or decrease during the course of heat delivery.^{54–57} The 45 °C $T_{\max}$ point is located 2.8–9.0 mm from the transducer and 10.8 $\pm$ 1.1 mm closer to the transducer than the 41 °C contour. Thermal penetration can be increased if $T_{\max}$ is allowed to increase; for an intermediate case of catheter properties ($\alpha=40$ Np m⁻¹ MHz⁻¹, 0.25 mm wall), cooling flow ($h=500$ W m⁻² °C⁻¹, $T_{\text{cool}}=20$ °C), and tissue perfusion (1 kg m⁻³ s⁻¹), the radial extent of the 41 °C contour increases from 21.7 to 23.8 mm if $T_{\max}$ is increased from 45 to 47 °C.

Temperature within the catheter wall ranges from 27.8–44.0 °C over the parameters tested and is predominately dependent on catheter thickness. The peak temperature in the catheter wall always occur at the outer edge of the catheter. The catheter wall is effectively cooled with $T < 37$ °C for wall thickness <0.375 mm. At 0.375 mm wall thickness, cooling becomes less effective, resulting in peak catheter wall temperatures from 32.6–42.4 °C. Catheter wall temperature is >41 °C at high attenuation values (60–80 Np m⁻¹ MHz⁻¹) with $h=500$ W m⁻² °C⁻¹, $T_{\text{cool}}=25$ °C, and 3 kg m⁻³ s⁻¹ perfusion. At 0.500 mm catheter wall thickness, peak catheter wall temperatures of 34.5–44.0 °C occur, equivalent to 0–120 EM₄₃ °C over 60 min.

III.B.2. Transducer sectoring

Thermal coverage in angle depends on sectoring and acoustic dead zone size [Fig. 4(b)]. Trisected (3 $\times$ 120°) transducers maintain better thermal penetration within dead zones than bisected (2 $\times$ 180°) transducers; the minimum extent of the 41 °C contour with 40° dead zones between sectors is 16.0 mm vs. 14.0 mm for a 3 $\times$ 120° vs. 2 $\times$ 180° device at 1 kg m⁻³ s⁻¹ perfusion and 11.2 mm vs. 8.5 mm at 3 kg m⁻³ s⁻¹ perfusion ($\alpha_{\text{cath}}=40$ Np m⁻¹ MHz⁻¹, 0.25 mm wall, $h=500$ W m⁻² °C⁻¹, $T_{\text{cool}}=20$ °C). Within sectors, the maximum radial extent of the 41 °C contour between these devices differs by <0.5 mm from each other and from the 360° device. Sufficient power to sectors is necessary to provide therapeutic heating throughout dead zones; if $T_{\max}$ is 43 °C or $T_{\max}=45$ °C with 50° dead zones, tissue temperature does not reach 41 °C within the dead zones at a perfusion of 3 kg m⁻³ s⁻¹.

FIG. 4. Therapeutic thermal penetration assessed at steady-state with parametric changes in ultrasound transducer, catheter, and tissue properties. (a) Radial extent of 41 °C contour for a higher ($3 \text{ kg m}^{-3} \text{ s}^{-1}$, indicated by bars) or lower ($1 \text{ kg m}^{-3} \text{ s}^{-1}$, indicated by symbols) perfusion with 0.125–0.500 mm catheter wall thickness and 20–80 $\text{Np m}^{-1} \text{ MHz}^{-1}$ catheter attenuation. Empty symbols correspond to $T_{\text{max}}=47 \text{ }^{\circ}\text{C}$ in the lower perfusion case ($T_{\text{max}}=45 \text{ }^{\circ}\text{C}$ for all other data points). (b) Minimal and maximum radial extent of 41 °C contour for $2 \times 180^{\circ}$ and $3 \times 120^{\circ}$ transducers with an acoustic dead zone of 20° – 50° between sectors at blood perfusion levels of 1 or $3 \text{ kg m}^{-3} \text{ s}^{-1}$ and $T_{\text{max}}=45 \text{ }^{\circ}\text{C}$.

III.B.3. Patient treatment simulations

The $41 \text{ }^{\circ}\text{C}$ and $5\text{EM}_{43 \text{ }^{\circ}\text{C}}$ contours extend $>2 \text{ cm}$ radially with $T_{\text{max}}=45 \text{ }^{\circ}\text{C}$ at 7 MHz operating frequency and moderate perfusion ($1 \text{ kg m}^{-3} \text{ s}^{-1}$) in simulated 60 min HT treatments (Fig. 5). Multisectorized applicators have similar penetration within sectors as 360° applicators with a radial reduction $<5 \text{ mm}$ in the $41 \text{ }^{\circ}\text{C}$ and $5\text{EM}_{43 \text{ }^{\circ}\text{C}}$ contours within the 30° dead zone at the sector cut [Figs. 5(a)–5(c)]. The $5\text{EM}_{43 \text{ }^{\circ}\text{C}}$ contour within dead zones can be pushed out 3–5 mm radially by applicator rotation 30–45 min into a 60 min treatment. The PID-based power controller can be used to control angular temperature distributions based on a pilot point set to $41.5 \text{ }^{\circ}\text{C}$ in the rectum and $T_{\text{max}}=45 \text{ }^{\circ}\text{C}$ within sectors [Fig. 5(c)]. Power can be controlled to individual transducers along the device length to tailor penetration, such as in Fig. 5(d), where the thermal profile follows the typical radiation dose profile with more extensive coverage in the cervix that tapers toward the fundus of the uterus. Temperature and thermal dose overlays from patient-specific simulations demonstrate coverage of target volumes with an unsectorized applicator with organs at risk far from the target [Fig. 5(e)] or with the use of transducer sectoring and power control guided by thermal feedback based on a pilot point in the rectum limited to $41.5 \text{ }^{\circ}\text{C}$ and interstitial pilot points within the target limited to $T_{\text{max}}=47 \text{ }^{\circ}\text{C}$ [Fig. 5(f)].

III.C. Acoustic output

A summary of peak frequencies, acoustic efficiencies, and dead zone sizes measured for fabricated applicators is given in Table IV. Overall acoustic efficiencies of ultrasound transducers and sectors range from 33.4%–51.8% and depend on peak electrical impedance magnitude, transducer mounting on the applicator, and transducer sectoring. Transducer sectors have significantly increased efficiency over unsectorized transducers; 120° and 180° sectors have acoustic efficiencies of $44.1 \pm 3.6\%$ vs. $39.7 \pm 2.6\%$ for unsectorized transducers ($p=0.005$, Student's t -test). The frequency corresponding to peak acoustic efficiency ranges from 6.60 to 7.45 MHz. Fall-off of efficiency away from peak frequency is moderate and varied, with a $4.7 \pm 2.3\%$ (1.0%–10.2%) reduction in efficiency at 0.1 MHz off peak and a $17.3 \pm 7.1\%$ (7.9%–27.1%) reduction in efficiency at 0.2 MHz off peak.

Rotational acoustic intensity plots demonstrate collimated energy output from the transducers along the device length and directional acoustic output from device sectors (Fig. 6). Angular dead zones in acoustic energy between transducer sectors range from 13.8 to 51.0° as defined by the region with relative acoustic intensity $<10\%$ of the maximum within each sector. Acoustic output within sectors is inhomogeneous with higher intensities generally present near the edges of elements and sectors and dips in acoustic intensity in the center of sectors. Acoustic intensity peaks are relatively sharp, with only 0.25%–1.8% of measurement points $>80\%$ maximum intensity and 1.6%–11% of points $>60\%$ maximum intensity within transducer sectors. 360° applicators have uniformly higher intensities over the transducer compared to within sectors of $2 \times 180^{\circ}$ or $3 \times 120^{\circ}$ applica-

TABLE III. The effects of catheter parameters on thermal penetration and thermal dead zone with $2 \times 180^\circ$ applicator. A range of values for catheter attenuation, thickness, convective cooling coefficient (h), and cooling flow temperature T_{cool} with $3 \text{ kg m}^{-3} \text{ s}^{-1}$ or $1 \text{ kg m}^{-3} \text{ s}^{-1}$ uterine blood perfusion are considered in their influence on steady-state electrical power level P_{electric} (50% acoustic efficiency), location of T_{max} (45°C), minimum radial extent of the 41°C contour in the dead zone and maximum radial extent of the 41°C contour within the transducer sector.

Attenuation ($\text{Np m}^{-1} \text{ MHz}^{-1}$)	Thickness (mm)	Perfusion ($\text{kg m}^{-3} \text{ s}^{-1}$)	h ($\text{W m}^{-2} \text{ }^\circ\text{C}^{-1}$)	T_{cool} ($^\circ\text{C}$)	P_{electric} (W)	T_{max} radius (mm)	41 $^\circ\text{C}$ radius	
							Min (mm)	Max (mm)
20	0.25	1	500	25	1.4	9	15.3	20.9
20	0.25	1	1000	20	1.7	10.3	16	22.5
20	0.5	1	1000	20	1.6	9.4	15.7	21.3
20	0.25	3	1000	20	2.3	8.9	11.5	18.9
80	0.25	1	500	25	1.5	8.3	15	20.1
80	0.25	1	1000	20	1.9	9.8	15.7	21.7
80	0.5	1	1000	20	1.9	8	14.7	19.7
80	0.25	3	1000	20	2.6	8.2	11.5	18.2

tors; 80%–92% of measurement points are $>20\%$ maximum acoustic intensity and 20%–50% of measurement points are $>40\%$ maximum intensity for unsectored transducers while for multisectored applicators, 56%–76% of points within sectors are $>20\%$ maximum acoustic intensity and 14%–38% of points are $>40\%$ maximum intensity.

III.D. Thermal characterization

Rotational temperature distributions in phantom reflect the patterns observed in the relative acoustic intensity plots, averaged over transducer length. Zones of reduced temperature elevation correspond to dead zones in acoustic output (Fig. 7). Within transducer sectors, greater uniformity is observed in temperature than acoustic intensity profiles, as variations in acoustic intensity are smoothed by thermal conduction. The 360° applicator tested had normalized temperature elevation ranging from 0.87 to 1.0 in rotation around the applicator [Fig. 7(a)] corresponding to a normalized acoustic intensity range of 0.62–1.0. Control of angular temperature elevation for multisectored transducers is achieved by power modulation to individual transducer sectors; Fig. 7(b) demonstrates a normalized temperature elevation of 1.0 with 2 W cm^{-2} surface acoustic intensity applied to the sector spanning 0 – 180° and 0.7 with 1.0 W cm^{-2} surface intensity applied to the sector spanning 180 – 360° . Figure 7(c) shows a trisector applicator with all sectors powered to 2.0 W cm^{-2} surface acoustic intensity or with the sector spanning 0 – 120° receiving zero power, resulting in a 120° zone with normalized temperature elevation <0.5 of the maximum. Temperature rise was verified to be highly reproducible ($<0.2^\circ \text{C}$ variation) at the same time point and applicator position after 3 h equilibration for various orientations in the phantom.

IV. DISCUSSION

The clinical efficacy and adoption of hyperthermia technology rely on its being straightforward to use, adapted to the tumor site, capable of conformal heat delivery, and amenable to combination with radiotherapy. The anatomical lo-

cation of the cervix allows for access through a natural body cavity for minimally invasive, localized delivery of heat and radiation. Endocavity applicators in existence for locally targeted heating to the cervix do not provide sufficient penetration or control of heating to be practical. Deep heating devices, although completely noninvasive, also offer limited control over thermal distributions with creation of hot spots outside the cervix. The objective of this work was to develop a device that uses arrays of multisectored tubular transducers to deliver localized heating that is more controllable than existing heating technology so that a more favorable efficacy-toxicity profile can be achieved by creating a higher differential between tumor temperatures and temperatures in organs at risk. Control over thermal delivery, demonstrated in thermal simulation and experiment, is afforded by power selection to transducer elements and sectors and orientation of intersector dead zones. Integration of the endocervical applicator with a HDR brachytherapy catheter facilitates the alignment of conformal hyperthermia with radiation dose profiles. The feasibility for clinical use of the device was explored by comparing the extent of therapeutic temperature achieved in thermal simulation, influenced by transducer, catheter wall, and tissue parameters, to tumor volumes and radiation target volumes from a set of patients who underwent radiotherapy for locally advanced cervical cancer.

Analysis of patient database, theoretical studies, device fabrication and testing, and experiments in phantoms has demonstrated that the endocervical ultrasound applicator can apply therapeutic levels of HT to 4–5 cm diameter regions localized around the cervix. HDR brachytherapy treatment planning data present CTV that average 4 cm in diameter, and the GTV, which is the site of hypoxic regions that can lead to radioresistance and recurrence,^{3–5} is a smaller region still within this target (Table II). HT simulations indicate that a GTV <4 cm in diameter can be covered by therapeutic heating ($T > 41^\circ \text{C}$) with the endocervical ultrasound applicator at moderate perfusion levels (0.5 – $2 \text{ kg m}^{-3} \text{ s}^{-1}$) and with low maximum temperature ($T_{\text{max}} = 45^\circ \text{C}$). Catheter

FIG. 5. Temperature and thermal dose distributions after 60 min HT in uterine tissue (thick lines indicate thermal dose of 5EM_{43°C}) with 1 kg m⁻³ s⁻¹ blood perfusion in the biothermal model. (a) The 41 °C contour extends >4 cm in diameter for an unsectored transducer with T_{max}=45 °C. (b) A 2 × 180° with both sectors under PID control to T_{max}=45 °C demonstrates a temperature reduction at sector cuts (30° dead zone) which can be mitigated by rotating the applicator 90° at 45 min (5EM_{43°C} contour for treatment with rotation indicated by dashed line). (c) A 3 × 120° applicator demonstrating power control to sectors based on the use of a pilot control point limited to 41.5 °C. The dashed 5EM_{43°C} contour is shown for rotation at 30 min. (d) Power control along the device length shapes the longitudinal heating profile. (e) Thermal dose overlay for a 360° device encompassing the CTV. (f) Demonstration of laterally directed energy output with a 2 × 180° device using reduced heating at sector cuts to limit temperature rise in rectum and bladder.

TABLE IV. Acoustic characterization of fabricated devices. Frequency ranges corresponding to peak acoustic efficiencies (mean $\pm$ SD) are given for each transducer along with intersector dead zone sizes (angle between 10% acoustic intensity contours).

Applicator	Sectoring	Transducers	Peak frequency (MHz)	Efficiency (%)	Dead zone ($^{\circ}$)
1	$3 \times 120^{\circ}$	2	6.95–7.10	43.8 ± 2.2	45.7 ± 3.3
2	$3 \times 120^{\circ}$	2	7.35–7.45	45.1 ± 4.0	17.8 ± 2.2
3	$2 \times 180^{\circ}$	2	6.60–6.75	40.5 ± 7.3	19.4 ± 1.3
4	$2 \times 180^{\circ}$	3	7.05–7.15	43.5 ± 5.3	34.9 ± 3.0
5	360°	2	7.35	41.1 ± 1.3	None
6	360°	3	7.20–7.30	40.3 ± 3.1	None

material properties have a moderate impact on temperature distributions, with catheter thickness < 0.5 mm and attenuation < 60 Np m $^{-1}$ MHz $^{-1}$ preferable to maximize thermal penetration and reduce temperature elevation in the catheter wall (Fig. 4).

At higher perfusion levels, higher power with increased maximum temperature ($T_{\max} = 47^{\circ}\text{C}$) may be required to extend therapeutic thermal coverage ($> 41^{\circ}\text{C}$) in the target volume. Maximum temperatures reported for clinical hyperthermia in the pelvis range from 41 – 42°C for deep heating systems to 43 – $> 45^{\circ}\text{C}$ for endocavity or interstitial, respectively.^{21,27,57,58} Past clinical studies using RF heating technology with little control over spatial heating distributions note increased toxicity and complication rates (rectal or bladder fistula) associated with temperatures $> 43^{\circ}\text{C}$.^{59–61} In contrast to RF sources, tandem ultrasound technology can direct heating energy and maximum temperatures to tumor target sites while maintaining temperatures much less than 43°C in the bladder and rectum so that higher maximum

temperatures may be achieved with possibly reduced complications. Furthermore, the volumes of tissue at 45 – 47°C would be small, confined within the tumor and in close proximity to the ultrasound source.

For tumors or target volumes > 4 – 5 cm in diameter, the endocervical ultrasound applicator could be used in conjunction with interstitial ultrasound applicators, which are smaller than the endocervical device (2.4 vs. 6 mm diameter) and placed within brachytherapy catheters implanted directly in the tumor⁶² in order to extend heating to the outer margin of the implant. Larger tumors may alternatively be treated by a combined HT approach involving deep regional heating and endocervical conformal heating as a thermal dose boost to the hypoxic tumor core, as regional heating devices may only achieve tumor temperatures of 39 – 39.5°C .^{12,24}

The intent of this study was to develop an endocervical ultrasound applicator to deliver conformal hyperthermia concurrent with the HDR boost portion of radiotherapy. In this setting the tandem catheter is placed during surgery, CT/MR

FIG. 6. Rotational acoustic pressure-squared distributions in water at 8 mm from the device surface. (a) A two-element, 360° device with collimated beam output. (b) A three-element, $2 \times 180^{\circ}$ device with discrete zones of higher acoustic intensity separated by large low acoustic intensity zones between sectors. (c) A two-element, $3 \times 120^{\circ}$ device with smaller dead zones between transducer sectors.

Fig. 7. Comparison of normalized temperature elevation in phantom at 10 mm radius after 5 min of heating to rotational acoustic intensity in water at 8 mm for the applicators used to produce the acoustic intensity distributions in Fig. 6 (intensity is averaged over the device length every 2° in angle and normalized to the maximum average intensity). (a) A 360° applicator, (b) a $2 \times 180^\circ$ applicator with one sector at 2 W cm^{-2} surface acoustic intensity and the other at 1 W cm^{-2} surface acoustic intensity, and (c) a trisected applicator ($3 \times 120^\circ$) with two or three sectors active.

is performed for position verification and planning purposes to tailor treatment to the target, and thermometry can be placed in ancillary catheters for treatment monitoring and control. This intrauterine technology can be complementary with deep heating techniques in the sense that hyperthermia can be delivered in the HDR brachytherapy session, in addition to deep regional heating concurrent with the external beam radiotherapy phase of treatment,^{10,63} thereby allowing greater cumulative thermal dose delivery. Although not investigated in this study, it may be possible to integrate the intrauterine ultrasound tandem with a Smit Sleeve to allow simple, reproducible insertion and placement within the cervix for local hyperthermia delivery sequential to specific fractions of external beam radiotherapy.

Concomitant with a consideration of adequate thermal coverage of the tumor volume to the successful administration of HT is minimization of thermal exposure to the rectum and bladder. The selection of unsectored or sectored devices in clinical HT delivery will depend on the location of organs at risk with respect to the target volume. These organs can lie <10 – 12 mm from the delivery catheter and <1 mm from the CTV boundary (Table II); thermal delivery must be well controlled in these situations to treat the target while minimizing thermal dose deposition in organs at risk. As shown in Fig. 5, in cases where the rectum and bladder are >2 – 3 cm from the applicator, unsectored transducers can be safely employed. If the bladder and rectum are <2 – 3 cm from the applicator, sectored applicators can be positioned so that the sector sites are aimed toward the bladder and rectum in order to limit heating of these organs and direct thermal penetration laterally into the parametrium.

The implications of dead zones in the acoustic field between transducer sectors are complex. It is possible to use regions of reduced heating advantageously by aligning them with nontargeted tissues that will cause undesirable side effects if overtreated. When zones of low acoustic intensity are present within the target volume, however, care must be taken to maintain adequate thermal dose delivery, particu-

larly in the presence of high perfusion. A range in demands on angular heating profile can be accommodated by modifying the size of acoustic dead zones. By adjusting the width of sector cuts, dead zones in acoustic output between sectors ranged from 18 to 46° (Table IV). In the face of higher perfusion, an applicator with smaller dead zones could be used to avoid undertreatment. When organs at risk are in close proximity to the applicator, larger dead zones can be used and aligned with these organs to minimize thermal toxicity. Transducers can also be sectored to any angular dimension to create dead zones in acoustic output of any size. With a given sectoring configuration, the effects of reduced heating at the sector site can be mitigated by applicator rotation during treatment, as illustrated in Figs. 5(b) and 5(c). This allows the overall heating pattern to be retained but higher thermal dose to be achieved closer to the applicator and farther in depth at the original orientation of the sector cuts. This comes at the expense of a reduced maximum radial extent of therapeutic thermal dose within the sectors.

The effects of uniformity of acoustic output within sectors, variations in the intersector dead zones, and acoustic power modulation observable in beam plots correlate to differences in the resulting temperature elevation in tissue-mimicking phantom. Temperature profiles are smoothed out with respect to acoustic intensity by thermal conduction mechanisms, the extent to which depends on the homogeneity of transducer sectors (Fig. 7). Unsectored transducers have more uniform acoustic output than multisector elements and thus induce more uniform temperature elevation. The impact of relatively large dips (50% – 75% reduction from maximum) in acoustic intensity within sectors are reflected in temperature profiles as much more moderate dips in temperature (10% – 25% reduction from normalized maximum). Acoustic dead zones $<20^\circ$, even with minimum intensity $<5\%$ of the maximum, cause minimal perturbations in the temperature profile that are comparable to dips in temperature associated with low intensity zones within sectors. Acoustic dead zones $>30^\circ$ cause more prominent drops in

temperature ($>40\%$ reduction from normalized maximum) that can be oriented for thermal protection of organs at risk.

Treatment control aided by thermal monitoring will ensure adequate thermal dose delivery to the treatment target and thermal protection of nontargeted organs. Interstitial catheters routinely implanted within the cervix lateral to the treatment catheter for HDR brachytherapy can be adapted for thermometry within the treatment zone and intraluminal catheters with temperature sensors may be placed in the bladder and rectum similar to deep HT for additional feedback. Catheter-based ultrasound technology is also amenable to noninvasive MR thermal imaging for feedback power control of multiple transducer elements and sectors.^{64–66}

In vitro and *in vivo* data suggest that the thermal enhancement of cell kill by HT when combined with radiotherapy is greatest when the modalities are delivered simultaneously^{67–69} and has led to device development and clinical investigations for sites such as deep pelvis⁷⁰ and recurrent chest wall.^{71–73} The endocervical ultrasound applicator can potentially accommodate simultaneous thermoradiotherapy by the insertion of the HDR brachytherapy source in the central lumen of the device. Initial measurements have indicated a 4%–6% attenuation of radiation emittance by a HDR brachytherapy source,⁶⁶ which could be accounted for in brachytherapy treatment planning. In implementing simultaneous thermoradiotherapy, the benefit of increased cell kill in the tumor must be weighed against possibly increased toxicity in surrounding tissues and remains an important topic of discussion. In this intracavitary setting, the multisector ultrasound applicator is immediately adjacent to the target tissue and can direct heating to the tumor while limiting heating of normal tissue at risk, and thus may provide for an improved technique to deliver simultaneous heat and radiation while minimizing increased toxicity to nontargeted tissue.

Treatment planning can aid the clinical delivery of HT by the endocervical ultrasound device. Geometric information obtained from brachytherapy planning can be used to determine applicator positioning. Temperature-based HT treatment planning⁷⁴ could be used to determine *a priori* power levels that are likely to provide adequate thermal coverage of the target with minimal temperature elevation in the rectum and bladder.

V. SUMMARY

An endocervical ultrasound applicator has been developed for locally targeted, 3-D conformal HT delivery to the uterine cervix in conjunction with HDR brachytherapy. The device consists of a linear array of multisector tubular transducers, allowing control of heating in length and angle. Conformal heating from simulated HT treatments was compared to clinical target volumes for HDR brachytherapy, demonstrating that targets <4 – 5 cm could be adequately covered with therapeutic temperature (>41 °C) by a single endocervical applicator. Thermal exposure to the rectum and bladder can be reduced when using a multisector applicator configuration by the strategic orientation of acoustic dead

zones between sectors toward these structures. Conformal heating can be directed by feedback thermometry using interstitial catheters routinely placed within the target. Acoustic and thermal characterization confirms conformal energy delivery capabilities. The endocervical ultrasound device is now under clinical investigation with institutional IRB approval and FDA Investigational Device Exemption (IDE G040168) to assess the safety and feasibility of endocervical ultrasound HT in the cervix adjunct to HDR brachytherapy. HT delivery can be guided by the use of treatment planning for *a priori* selection of proper device and power levels.

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