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Catheter-based ultrasound hyperthermia with HDR brachytherapy for treatment of locally advanced cancer of the prostate and cervix

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Abstract

A clinical treatment delivery platform has been developed and is being evaluated in a clinical pilot study for providing 3D controlled hyperthermia with catheter-based ultrasound applicators in conjunction with high dose rate (HDR) brachytherapy. Catheter-based ultrasound applicators are capable of 3D spatial control of heating in both angle and length of the devices, with enhanced radial penetration of heating compared to other hyperthermia technologies. Interstitial and endocavity ultrasound devices have been developed specifically for applying hyperthermia within HDR brachytherapy implants during radiation therapy in the treatment of cervix and prostate. A pilot study of the combination of catheter based ultrasound with HDR brachytherapy for locally advanced prostate and cervical cancer has been initiated, and preliminary results of the performance and heating distributions are reported herein. The treatment delivery platform consists of a 32 channel RF amplifier and a 48 channel thermocouple monitoring system. Controlling software can monitor and regulate frequency and power to each transducer section as required during the procedure. Interstitial applicators consist of multiple transducer sections of 2–4 cm length $\times$ 180 deg and 3–4 cm $\times$ 360 deg. heating patterns to be inserted in specific placed 13g implant catheters. The endocavity device, designed to be inserted within a 6 mm OD plastic tandem catheter within the cervix, consists of 2–3 transducers $\times$ dual 180 or 360 deg sectors. 3D temperature based treatment planning and optimization is dovetailed to the HDR optimization based planning to best configure and position the applicators within the catheters, and to determine optimal base power levels to each transducer section. To date we have treated eight cervix implants and six prostate implants. 100 % of treatments achieved a goal of >60 min duration, with therapeutic temperatures achieved in all cases. Thermal dosimetry within the hyperthermia target volume (HTV) and clinical target volume (CTV) are reported. Catheter-based ultrasound hyperthermia with HDR appears feasible with therapeutic temperature coverage of the target volume within the prostate or cervix while sparing surrounding more sensitive regions. (NIHR01CA122276).

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Keywords

Ultrasound; Hyperthermia; Thermal Therapy; Interstitial; Endocavity

1. INTRODUCTION

Phase II and III randomized studies have demonstrated that the addition of hyperthermia to radiation therapy and/or chemotherapy can dramatically improve local control and overall response rates for cancer treatment[1, 2]. Large external electromagnetic arrays, RF devices, and interstitial (RF and MW) implants are often considered for delivering heating energy to deep sites such as cervix and prostate. Some examples of improved response rates with the addition of hyperthermia to the standard radiation therapy include: complete response rates increased from 43% to 77% for breast cancer and 39% to 55% for deep pelvic tumors; locally advanced cervical cancer 3 yr survival increased from 27 to 51% and local control 41 to 61%; and 2 yr local control increased from 28% to 46% for melanoma. In the typical setting, tumor temperatures are elevated to 40–45 °C for approximately 60 min within a short interval before or after radiation. The best response rates are obtained with $T_{90} > 40.5$ °C and minimum thermal dose > 6 –10 equivalent minutes @43°C conforming to the tumor or target volume, which is difficult with most existing equipment.

We have been developing catheter-based ultrasound heating applicators, support systems, and treatment delivery strategies, with the goal of applying hyperthermia, typically in conjunction with radiation therapy and/or chemotherapy, for the treatment of pelvic cancer[3–10]. These heating applicators can be introduced via interstitial or endocavity approaches and are compatible with standard brachytherapy procedures. Numerous bench-top experiments and animal studies have demonstrated the equivalence and superiority of this ultrasound technology in ability for spatial control of therapeutic heating compared to predicated microwave, RF current fields, thermal conduction, and laser devices already approved for use in the clinic.

The objective of this study is to report on the current progress of a clinical pilot study of catheter-based ultrasound integrated with HDR brachytherapy for the treatment of locally advanced cervical and prostate cancer, using interstitial and endocervical ultrasound applicators.

2. CATHETER-BASED ULTRASOUND APPLICATORS & SYSTEM

2.1 Interstitial applicators

The interstitial ultrasound applicators utilize arrays of small tubular ultrasound radiators, designed to be inserted within plastic implant catheters used for interstitial HDR brachytherapy[3, 8] (Fig. 1). Water-flow is used during power application to couple the ultrasound energy and improve thermal penetration. Multi-transducer devices (1–4 segments) have been fabricated with transducer diameters of 1.5 mm and outer catheter diameter of 2.4 mm (13 gauge). The applicators are fabricated with multiple tubular segments, with separate power control, so that the power deposition or heating pattern can be adjusted in real time along the applicator axis. The frequency of operation is determined

by the maximum efficiency and the thickness of the transducer wall, and typically range between 6.5 and 9 MHz. The ultrasound energy emanating from each transducer section is highly collimated within the borders of each segment so that the axial length of the therapeutic temperature zone remains well defined by the number of active elements over a large range of treatment duration and applied power levels. Furthermore, the angular or rotational heating pattern can be modified by sectoring the transducer surface. In this fashion, active zones can be selected (i.e., 90°, 180°, 270° or 360°) to produce angularly selective heating patterns. The orientation of these directional applicators within a catheter can be used to protect critical normal tissue or dynamically rotated and power adjusted to more carefully tailor the regions of heating. Multi-applicator implants of interstitial ultrasound applicators have been demonstrated to produce contiguous zones of therapeutic temperatures between applicators with separation distances of 2–3 cm, while maintaining protection in non-targeted areas. Thus, considering an implant pattern typical of HDR brachytherapy, the length of heating within each catheter can be tailored to fit the clinical target volume. The insertion depth of the applicator within the plastic catheter can also be adjusted by sliding the device within the sealing hemostasis valve (Fig. 1). Furthermore, enhanced radial penetration allows larger applicator separation, and if necessary directional applicators can be selected to either protect non-targeted tissues (e.g., bladder, rectum) or preferentially target eccentric tumor volumes.

2.2 Endocavity applicators

An endocavity catheter-based ultrasound applicator has been designed to integrate with an HDR brachytherapy applicator and heat from within the uterine cervix for cases for treating locally advanced cervical cancer[9]. An endocavity ring applicator (Nucletron) for delivering HDR brachytherapy is shown in Fig. 2. The applicator is positioned in the vagina with the ring compressed against the cervix, and the central intrauterine tube (tandem) placed within the cervical os extending into the uterus. The length/angle bend of this tandem and the ring diameter can be pre-adjusted or selected prior to implantation. Both the tandem and the ring have hollow lumens to allow for tracking of the radiation source. The multielement ultrasound heating applicator will apply hyperthermia directly from the intrauterine (IU) component to the clinical target volume surrounding the uterine cervix. The design schema is similar to the interstitial devices, except that the multiple sectors can be activated per tube.

2.3 32-channel RF amplifier system

A computer controlled 32-channel amplifier system (RF Generator 500-020, Advanced Surgical Systems) with independent RF power (0 – 25.0 W) and frequency control (5.0 – 10.0 MHz) supplies power to the applicators (Fig. 3). This amplifier continuously monitors forward and reflected power levels on each channel, and has automatic shutoff capabilities if power levels deviate beyond preset thresholds. The amplifier system is controlled and monitored in realtime through software using an RS-232 interface connection to a stand-alone laptop computer devoted to ultrasound power control. The amplifier control software, written with the LabVIEW 8.2 Professional Development System, uses a graphical user interface (GUI) to allow the operator to implement changes to the applied power and operating frequency of each channel during treatment and to display the frequency and the

set, forward, and reflected power values for each channel (Fig. 5). From previous experience, it was determined that manual control of applied power levels based upon measured temperatures will be sufficient. The GUI also includes an additional feature of a visual alarm to alert the operator if the reflected power for any channel exceeds 15% of the forward power. High levels of reflected power does not compromise patient safety but indicates a damaged transducer segment, failed wiring, or a damaged amplifier channel. A data log of the applied frequencies and power levels during treatment is automatically recorded and saved to the hard disk for each session.

2.4 48-channel temperature monitoring system

An HP data acquisition system (HP 34970A) with 48 channels of thermocouple monitoring modules (34902A multiplexer/switch unit with temperature sensing) and a custom isothermal connector block are used to monitor temperatures (Fig. 4). The temperature sensors used in this study are commercially available Teflon-coated, multi-junction constantan-manganin thermocouple probes (Ella-CZ) with either 4 junctions at 5 mm or 10 mm spacing or 7 junctions at 5 mm or 10 mm spacing. Constantan-manganin thermocouples have been shown to minimize thermal conduction artifact when used in a multi-sensor configuration, and are as accurate as the standard type-T (copper-constantan) thermocouples with a single point calibration.

The temperature measurement system is calibrated with the constantan-manganin multi-junction thermocouple sensors prior to sterilization of the multi-sensor probes and treatment. During calibration, the temperature probes are connected to the thermometry system and placed within an isothermal block immersed within a temperature regulated waterbath. The calibration temperature (waterbath temperature) is measured to within 0.05°C using a certified mercury in-glass thermometer. This calibration data is stored on the computer hard disk and re-applied at the time of treatment. This thermometry configuration has $\pm 0.25^{\circ}\text{C}$ accuracy after this software and hardware calibration. The calibration data specific to a family of temperature probes is stored in a data file that is loaded prior to treatment.

The thermometry system is monitored in real-time through software using an RS-232 interface connection to a standalone laptop computer devoted to thermometry measurement. The thermometry software module, written with the LabVIEW 8.2 Professional Development System, can monitor up to 48 thermocouple channels with each scan completing within 3 seconds, and features a GUI that displays temperature and cumulative thermal dose ($t_{43^{\circ}\text{C}}$) in tabular format for each channel in real-time (Fig. 4). Color-coded objective limit indicators for both temperatures and thermal dose are used for feedback for the physicist to adjust the applied power levels or applicator position during treatment. A software key toggles the display between a transient temperature data plot or tabular display of temperature and thermal dose points in updated real-time. The elapsed time and data scan number are continuously updated and displayed while the software is running. A data log of the temperature values during treatment are automatically recorded and saved to the hard disk during treatment.

The thermometry GUI also incorporates an optional visual display that allows the user to register thermocouple positions relative to anatomy and applicator transducers based on

HDR planning tools (CT/MRI/US overlays) for improved treatment control and documentation. During treatment, the user can freely scroll through up to 20 image slices displaying the locations of the thermocouples. The colors of the identifying thermocouple channel numbers in this display reflect their respective temperature ranges in real-time according to color-coded temperature objective limits.

Post-treatment analysis includes calculation of temperature and thermal dose descriptors (T_{90} , T_{50} , $T_{\min}$, and $T_{\max}$), CEM 43 T_{90} , and t_{43} for each temperature point will be calculated and displayed in tabular format after each treatment.

3. CLINICAL PILOT STUDY

3.1 Design of Clinical Study

The purpose of this clinical pilot study is to evaluate the feasibility & safety of catheter-based ultrasound hyperthermia integrated with HDR brachytherapy. Two disease sites or cohorts are targeted (n=12 each site): primary and recurrent cervical cancer (Stage IB2-IVA) and locally advanced prostate cancer. Each patient will receive standard chemotherapy, radiation, and HDR brachytherapy – with one hyperthermia session per implant. In this setting, typically two implants are given, approximately 1–3 weeks apart. Hyperthermia of 40–45°C for 60 min is targeted. This protocol is approved under NIH R01CA122276, FDA Investigational Device Exemption G040168, and UCSF Institutional Review Board approval H10778-32056-012. To date four patients with cervical cancer and three with prostate cancer have enrolled, with eight and six implants treated, respectively.

3.2 Preliminary Results

To date a total of six prostate implants in three patients and eight cervix implants in four patients have been treated with the catheter-based ultrasound system. For prostate, between 3–5 directional 180° applicators were placed in the posterior prostate, with energy aiming away from rectum toward the anterior gland. Initial applied power levels to each transducer section were determined using 3D optimization-based treatment planning [10], and used as a starting point and adjusted during treatment as required. Examples of the 3D reconstructed anatomy and implant geometry from HDR, treatment setup, and temperature profiles within the prostate midgland are shown for two typical cases in Fig. 5–6.

For treatments of uterine cervix, directional and 360° interstitial ultrasound applicators were used, as well as dual-directional endocervical applicator placed in the tandem. The directional applicators were applied to direct energy to areas of necrotic gross disease, as well as avoid overheating bladder and rectum. Typical treatment setup and temperature profiles are shown in Fig. 7 for interstitial alone, and Fig. 8 demonstrating effective heating of the tandem alone to 2 cm radius and extension by the addition of interstitial heating in the periphery to heat larger regions.

4. SUMMARY

Catheter-based ultrasound devices for hyperthermia in conjunction with HDR brachytherapy can provide very conformal and 3D controllable heating patterns. In order to deliver and

control hyperthermia treatments in this setting a treatment delivery platform and associated software interfaces have been developed. The 32 channel amplifier system and 48 channel thermometry system, with controlling software interfaces, have been tested and approved for use in clinical pilot study. A clinical study has been initiated to evaluate the catheter-based ultrasound technology for delivering hyperthermia with HDR for locally advanced cervical and prostate cancer, and approved for a total of 24 patients. Preliminary analysis of the clinical study has so far demonstrated that catheter-based ultrasound system can produce 3D conformable heating patterns within an HDR implant within uterine cervix or prostate. Intrauterine or endocervical devices and interstitial devices provide conformal & selective therapy of cervix GTV or prostate, and can reduce bladder and rectum exposure while delivering efficacious temperatures and thermal dose. In the 14 treatments delivered in seven patients, therapeutic temperatures were achieved in all cases, > 60 min duration achieved, and no adverse events or toxicity associated with hyperthermia. Revision of implant strategies and tandem design for cervix are ongoing. Analysis of thermal dose and volume coverage, and accuracy of planning will be analyzed in future efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Interstitial ultrasound applicators designed for heating from within brachytherapy catheters. Separate control of multiple transducer sections, ability to sector or direct energy, and favorable energy penetration make these the most controllable interstitial heating technology.

Fig. 2. Endocavity ultrasound applicator designed for heating uterine cervix from within an HDR ring applicator.

Fig. 3.
Advanced Surgical Systems 32-Channel RF amplifier system and computer software interface for controlling frequency and applied power levels.

Fig. 4. Thermometry interface module for the 48-channel thermocouple system and computer software interface for monitoring temperatures and thermal dose.

Fig. 5.

Prostate Case example #1: (a) 3D reconstruction of implant catheters within prostate from HDR treatment planning, showing adjacent rectum and bladder; (b) patient setup for hyperthermia treatment with thermometry probes and applicators placed within plastic brachytherapy catheters; (c) positions of 180 deg. directional applicators are designated as triangles, aiming energy away from rectum, and steady-state temperatures measured midgland during the treatment.

Fig. 6.

Prostate Case example #2: (a) 2D sagittal reconstruction of implant catheters within prostate from HDR treatment planning, showing adjacent rectum and bladder; (b) patient setup for hyperthermia treatment with thermometry probes and applicators placed within plastic brachytherapy catheters; (c) positions of three 180 deg. directional applicators are designated as triangles, aiming energy away from rectum, and steady-state temperatures measured midgland during the treatment.

Fig. 7.

Cervix Case example #1: (a) 2D sagittal reconstruction of implant catheters within cervix from HDR treatment planning, showing adjacent rectum and bladder; (b) positions of two 180 deg. directional applicators aiming towards necrotic GTV and steady-state temperatures measured during the treatment.

Fig. 8. Cervix Case example #2: Resulting temperature profile within the cervix and hyperthermia target volume. Temperatures are shown for (a) dual-directional tandem applicator alone and (b) in combination with a 360° interstitial applicator.