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Thermal Dosimetry Characteristics of Deep Regional Heating of Non-Muscle Invasive Bladder Cancer

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Abstract

Purpose—To report thermal dosimetry characteristics of external deep regional pelvic hyperthermia combined with intravesical mitomycin C (MMC) for treating bladder cancer following transurethral resection of bladder tumor, and to use thermal data to evaluate reliability of delivering the prescribed dose of heat to bladder.

Materials and Methods—14 patients were treated with MMC and deep regional hyperthermia (BSD 2000 RF phased array hyperthermia system, Sigma Ellipse or Sigma 60). The hyperthermia objective was 42±2°C to the interior surface of the bladder wall for a minimum of 40 minutes per treatment. Temperatures were monitored with thermistor probes in rectum, bladder, and oral cavity, and on the skin surface of upper inner thigh, buttocks, abdomen, and spine to help focus heat within the bladder. Recorded temperatures were used to calculate thermal dose and evaluate treatment. AP separation, bladder depth, and anterior fat layer thickness were examined for possible correlations between anatomy and heating.

Results—The hyperthermia thermal prescription was achieved in all treatments except for the first three treatments of Patient 1. Mean treatment time with bladder >40°C was 61.9±11.4 minutes and mean thermal dose was 21.3±16.5 CEM43. Average thermal doses obtained in normal tissues were 1.6±1.2 CEM43 for the rectum and 0.8±1.3 CEM43 in superficial normal tissues. Combined with BSD2000 standard treatment planning and patient feedback, real-time temperature monitoring allowed thermal steering of heat sufficient to attain the prescribed thermal dose to bladder within patient tolerance in 88.6% of treatments. No significant correlation was seen between patient anatomical characteristics and thermal dose achieved in bladder.

Conclusions—This study demonstrates that a hyperthermia prescription of 42±2°C for 40-60 minutes can be delivered safely to the bladder with external radiofrequency phased array applicators for a typical range of patient sizes. Using the available thermometry and treatment

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planning, the BSD 2000 hyperthermia system was shown to be an effective method of focusing heat regionally around the bladder with good patient tolerance.

Keywords

Thermal dosimetry; hyperthermia; thermochemotherapy; deep heating; bladder cancer

1. Introduction

Bladder cancer is the fourth most common cancer in men and the ninth most common in women in the United States.(1) The lifetime probability of developing bladder cancer has been estimated to be 2.7-3.6%. The most common type, occurring in almost 90% of cases, is urothelial carcinoma, which originates from the urothelium that lines the inside of the bladder. There are two broad clinical phenotypes of bladder cancer: (i) non-muscle invasive bladder cancer (NMIBC), which is limited to the bladder mucosa, and (ii) muscle invasive bladder cancer (MIBC), where invasion of tumor occurs into the muscularis propria or beyond. NMIBC has high risk of local recurrence but low risk of metastasis, whereas MIBC is prone to progression and metastasis. Consequently, these two phenotypes of bladder cancer are managed differently.(2)

A major goal in the treatment of NMIBC is reducing the risk of bladder cancer recurrences, which often occur repeatedly over many years, with multiple surgeries significantly reducing quality of life for patients as well as escalating health care costs. Immunotherapeutic agents such as bacillus Calmette-Guérin (BCG) are given intravesically and are generally considered first line adjuvant therapy after transurethral resection of bladder tumor (TURBT) for patients at intermediate or high risk of recurrence.(3, 4) Intravesical chemotherapy is an alternative to BCG and likewise is effective in reducing tumor recurrences.(3, 5) However, for patients that do not respond to first line BCG therapy, there is considerable room for improvement as recurrence occurs in 40-80% of such cases and progression to muscle invasive disease in 30-50%.(6, 7)

Hyperthermia has been investigated for decades, and it has been demonstrated that the effects of mild temperature elevation on cell physiology and tumor microenvironment significantly enhance the efficacy of chemotherapy and radiotherapy.(8-10) In recent years, bladder hyperthermia has been investigated as a means to enhance the delivery and effectiveness of chemotherapeutic agents to tumor cells inside the bladder. Over the past decade, three European trials have shown that moderate temperature (42-44°C) local bladder hyperthermia improves efficacy of intravesical chemotherapy, most commonly mitomycin C (MMC).(11-13)Combined hyperthermia and MMC has not, to our knowledge, been studied clinically in North America.

Several methods have been proposed to achieve bladder hyperthermia(14), including: circulating externally heated chemotherapy fluid within the bladder, microwave heating from a miniature antenna inserted via an intravesical catheter (12), intravesical magnetic nanoparticle solution excited by an external magnetic field (15, 16), and deep regional pelvic heating with an external radiofrequency phased array applicator.(17, 18) When used in combination with radiation therapy, deep regional hyperthermia has been shown effective in

heating pelvic disease.(19) Located centrally in the pelvis and filled with lossy non-perfused urine (and drug), the bladder may be expected to heat preferentially using an appropriately phased array of radiofrequency antennas located around the torso to provide a broad focus of power deposition in and around the bladder. A 15-patient Phase I clinical trial was conducted at Duke University Medical Center from 2008 to 2011 to study the feasibility of treating BCG refractory NMIBC with intravesical MMC combined with external deep pelvic hyperthermia. We hypothesized that this combined treatment would produce effective bladder heating with minimal toxicity, and be well-tolerated by the patients. The objectives of this paper are to: 1) report the thermal dosimetry characteristics of this heating approach and 2) use the thermal data to evaluate the reliability of delivering the prescribed dose of heat to the bladder.

Materials and Methods

1.1 Treatment procedures

15 patients met the eligibility criteria and consented to the Duke IRB approved clinical trial, as registered at www.clinicaltrials.gov (NCT00734994) under IDE G030263. One subject withdrew from the study after a single treatment attempt due to intolerance of the supine position as a result of severe chronic obstructive pulmonary disease. 14 patients were treated weekly with MMC and deep regional hyperthermia for a 6-week induction phase. This was followed by clinical evaluation and 4 additional monthly maintenance treatments in patients exhibiting complete response after the induction phase. Details of the trial design and clinical outcome are reported separately.(20)

Deep hyperthermia of the bladder was achieved with the BSD 2000 RF phased array hyperthermia system in conjunction with either the Sigma Ellipse or Sigma 60 applicator (BSD Medical Corporation, Salt Lake City, UT, USA). Applicator selection was based on patient size: 12 patients with an AP separation <25 cm were treated in the Sigma Ellipse while 2 patients with an AP separation >25 cm were treated in the larger Sigma 60. Planning CT scans (13 patients) or measured patient dimensions (1 patient) were used to establish patient anatomy and preplan patient-specific treatment settings of phase and amplitude using the BSD 2000 treatment planning software. Optimum phase and amplitude plans were generated for four different frequencies (generally between 85 and 100 MHz) for each patient and saved in the treatment planning and control console for recall during treatment. The plans were generated with a goal of producing a maximum SAR in bladder, which would yield a broad heat focus in the region of pelvis including this organ.

Treatment plans were selected during treatment from the available treatment plans and modified by the operator as appropriate to maximize differential heating in bladder and minimize patient complaints of hot spots. System power and frequency, and relative antenna power and phase, were adjusted frequently during treatment to optimize bladder heating and patient tolerance, based on measured temperatures, blood pressure, and patient verbal feedback. Following the first heat treatment in each patient, additional information available to the operator to assist treatment guidance included relative success of previously used frequency and corresponding phase and amplitude distributions. Power levels, antenna phase and frequency were varied continuously during treatment in response to measured

temperatures and patient feedback. The typical order of adjustment of treatment parameters to improve bladder temperature or patient comfort was:, i) relative phase, ii) relative amplitude, iii) system power, iv) system frequency, and in a small number of cases, v) applicator position over pelvis

1.2 Hyperthermia parameters

The hyperthermia objective for this study was 42±2°C to the interior surface of the bladder wall (heating target) for a minimum of 40 minutes per treatment without temperatures exceeding 45°C anywhere in the patient. The duration of active heating (i.e., time the applicator was powered on) was restricted to a maximum of 60 minutes per treatment. Temperatures were monitored for ≥10 min after power was turned off to record the often slow decay of intra-bladder temperature.

1.3 Thermometry

Temperatures were monitored throughout each treatment using 8 high-resistance lead thermistor probes and recorded by the BSD 2000 treatment control computer. A temperature plot displaying the monitored temperatures throughout a typical treatment is shown in Figure 1. An in-house MATLAB-based analysis program was used retrospectively to calculate the thermal dose (CEM43) (21, 22) to bladder, rectum, and superficial tissues from BSD 2000-recorded temperature data, and also to determine the duration of bladder temperatures greater than 40°C, 41°C, 42°C, 43°C, 44°C, and 45°C. Independently calculated CEM43 values were cross-checked with the BSD 2000 thermal dosimetry which was available during treatment. The more extensive dosimetry was used to evaluate the effectiveness of treatment plans to achieve the prescribed thermal dose in bladder while the BSD system dosimetry was used to provide real-time feedback for steering the focus of heating into bladder.

1.3.1 Stationary thermometry—Internal temperatures were monitored in the bladder and rectum using BSD 2000 thermistor probes inserted within sterile blind end catheters (15 gauge Flexineedle, Best Medical International, Springfield, VA). To monitor intrabladder temperature, a thermistor was inserted to the tip of a 40 cm long, 1.98 mm OD catheter that was positioned within the central lumen of a three port Foley. Exact location within the bladder was not determined but the sensor is expected to be floating in the 40ml of MMC drug and slowly increasing volume of urine within the bladder. To monitor rectal temperature, a thermistor sensor was inserted to the tip of a 20 cm long, 1.98 mm OD blunt tip catheter placed within the rectum and positioned with the sensor close to the posterior wall of bladder. Additional sensors were used to monitor temperatures on the skin surface of the upper inner thigh, buttocks, abdomen, and spine, and to record oral temperature at several times during the treatment. Because oral temperatures changed slowly during treatment, the oral probe was only placed in the mouth periodically to record oral temperature.

1.3.2 Temperature mapping—In addition to the stationary sensors, a thermistor probe was moved at 5 minute intervals in 1 cm increments along a second 1.98 mm OD blunt end catheter inside the rectum. Mapping of the temperature profile along the rectum provided

additional feedback for adjusting position of the applicator in the superior-inferior direction to focus heating within the bladder and away from the lower pelvis. Mapping was not possible inside the bladder as great care was required to manually advance the probe to the tip of Foley due to natural curvature of the urethra and passage through prostate in male patients.

1.4 Correlation between heating and patient anatomy

Three anatomical characteristics – AP separation, bladder depth, and anterior fat layer thickness – were determined from planning CTs for 13 of the 14 patients using an axial slice through the bladder mid-plane (largest bladder cross-section) as seen in Figure 2. As a method of examining possible correlations between anatomy and heating characteristics, these patient dimensions were considered as functions of the average treatment time in minutes that temperatures were greater than 40°C, 41°C, and 42°C in the target. Ease of heating would presumably be indicated by longer treatment durations at higher target temperatures.

2. Results

2.1 Applied Power

Power levels were varied continuously during treatment in response to measured temperatures and patient comfort, and changes in operating frequency. For the majority of patients, power varied from 600-1000W total applied power, during and between treatments. For all treatments, power ranged from 200-1300W. In general, higher power (600-800W) was used for the first 10-15 min of heating and reduced subsequently to maintain bladder temperature. The average power per treatment weighted by percentage time duration was 740±162 W. The average time power was applied per treatment was 53.1±8.8 minutes.

2.2 Temperatures and thermal doses

The average time durations that bladder temperature reached values >40-45°C per treatment for each patient are shown in Figure 3. Heating was successfully maintained below the upper limit of 45°C, with only 2 individual treatments briefly exceeding 45°C for 0.5 minutes and 0.2 minutes, respectively. On average, treatments exceeded the upper temperature prescription of 44°C for 0.4±1.2 minutes. Across all patients, the average time per treatment the bladder was heated >40°C was 61.9±11.4 minutes, well above the prescribed minimum threshold of 40 minutes >40°C.

The 40 minute minimum time >40°C was achieved on average for all patients with the exception of Patient 1, which fell just 3.8 minutes short of that goal. For the first patient of this trial, somewhat more conservative heating was used in initial treatments before scaling up to higher doses with experience and lack of toxicity. While the minimum of 40 minutes >40°C was achieved for 7 out of 10 treatments for that first patient, the average (36.2 minutes) was lowered by reduced temperatures in the patient's first 3 treatments.

The range and average of thermal doses delivered to bladder, rectum, and superficial normal tissues (thigh, buttocks, abdomen, and spine) across all treatments are displayed for each

patient in Figure 4. Average thermal doses to the bladder target per treatment per patient are shown in Figure 4A, expressed in CEM43 as defined previously(8, 21). While the protocol for this study did not specify a target thermal dose range, the minimum prescribed heating parameters (40-44°C for 40 minutes) correspond to a wide thermal dose range of 0.6-80.0 CEM43. Across all patients, the per-treatment average thermal dose to bladder was 21.3±16.5 CEM43, which falls within this prescribed thermal dose range.

The ranges of thermal dose to the rectum (Figure 4B) were low, ranging from 0-9.0 CEM43 with a median thermal dose across all treatments of 1.0 CEM43. While a large range of superficial thermal dose values (Figure 4C) was seen in some patients (whiskers indicate maximum and minimum values), it should be noted - as indicated by the boxes - that these were outliers; the median thermal dose across all treatments was only 0.1 CEM43. Furthermore, these outlier incidences of high temperature in superficial tissues were generally well-tolerated by patients and loosely correlated with patient feedback regarding hot spots. Across all patients, the average thermal dose per treatment to normal tissues was acceptably low with only 1.6±1.2 CEM43 to rectum and 0.8±1.3 CEM43 to superficial locations.

2.3 Temperature feedback

Real-time temperature monitoring provided feedback that was used during treatment to steer heating into the bladder and away from critical normal tissues. The temperature plots in Figures 5A and 5B show example cases of patients in the Sigma 60 and Sigma Ellipse applicators respectively. The data illustrate the desired separation of temperatures between bladder (target) and rectum (critical normal tissue), with rectal temperatures remaining below 42°C and a minimum of 1-2°C lower than the bladder. Figure 5C shows an example case where real-time temperature feedback allowed the focus of heating to be steered away from the rectum and into the bladder.

Temperature mapping in the rectum provided important feedback identifying the axial position of the heat focus within the patient. Figure 6 shows rectal maps taken during the time of essentially steady state target temperature for all 10 treatments for a single patient. The tip of the mapping catheter (distal position = 0 cm) was located adjacent to the bladder target. The rectal temperature maps in Figure 6A indicate that heating was focused low in the abdomen at various positions along the lower rectum. After a re-simulation of the patient, the applicator was shifted 4 cm superiorly for the following treatments. Rectal temperature maps for the next 6 treatments (Figure 6B) show a shift of the maximum temperatures to be adjacent to the bladder, indicating successful axial shift of the heat focus to the bladder target.

2.4 Correlations between patient anatomy and heating

Figure 7 shows average time per treatment above temperature indices of 40°C, 41°C, and 42°C in bladder plotted against the patient anatomical characteristics of AP separation (20.0-29.8 cm), bladder depth (5.4-10.4 cm), and anterior fat layer thickness (1.0-3.2 cm). As can be seen by the spread of time values across all distances and depths, there was no clear correlation between time at target temperature values and any of these anatomic

characteristics. While there is the suggestion of a trend toward lower heating times at higher anterior fat layer thicknesses (R^2 values are 0.163 for time >40°C, 0.308 for time >41°C, 0.374 for time >42°C), the number of patients in this particular study to draw definite conclusions.

2.5 Patient Discomfort

Patient discomfort, primarily due to heat, pain, or pressure, was noted at some time during 41.2% (54/131) of treatments. Out of the 79 patient complaints noted, 88.6% (70) were addressed sufficiently by the operator to allow treatment to continue. 82.9% (50) were resolved through heating parameter adjustments (e.g., power, frequency, amplitude, phase), 8.6% (6) were resolved through a short (5-10 min) break from treatment, 5.7% (4) were resolved through applicator repositioning, and 2.9% (2) were resolved through relieving pressure by releasing water from the bolus. Out of the 9 cases where treatment was ended due to patient discomfort, 8 were the result of hyperthermia-related intolerance and 1 case was discomfort from a full bladder; 55.6% (5) treatments still met the hyperthermia prescription of 40 minutes ≥40°C in bladder.

3. Discussion

The goals of this clinical pilot study were to assess the safety and tolerability of treating recurrent non-muscle invasive bladder cancer by administering MMC intravesical chemotherapy concurrent with local bladder hyperthermia. A summary of the clinical endpoints of this trial is reported separately.(20) This paper examines the feasibility of delivering the prescribed hyperthermia treatment of 40±2°C for 40-60 minutes to the bladder while preserving low CEM43 thermal dose in the rectum and superficial locations, and acceptable patient comfort.

The results of this clinical pilot study demonstrate that the prescribed heating parameters can be achieved (per treatment average of 61.9±11.4 minutes >40°C in bladder) while maintaining low thermal doses in non-targeted tissues such as rectum (1.6±1.2 CEM43) and superficial normal tissues (0.8±1.3 CEM43). Real-time temperature monitoring provided feedback that allowed both thermal steering during treatment (Figure 5C) and post-treatment plan evaluation and re-planning (Figure 6) to improve the focus of heating in the target and away from normal tissues.

An earlier study using the BSD 2000 deep regional heating system with the Sigma 60 and Sigma Eye applicators to treat cervical cancer reported greater rates of subcutaneous tissue toxicity in large patients with thicker dorsal subcutaneous fat.(23) In the current study, no significant increased heating trends were found for larger patient sizes or for different bladder depths. Although the plots for anterior fat thickness suggest a tendency for lower achievable heating times (particularly for temperatures >41°C and 42°C) with increasing fat thickness, this was not a significant trend for the small sample size of this study. The results, however, do indicate that adequate bladder heating was achievable for all patients in the study, which comprised a range of anterior fat thicknesses from 1.0 – 3.2 cm, bladder depths from 5.4 – 10.4 cm, and body sizes from 20.0 – 29.8 cm in AP separation.

4. Conclusion

A clinical pilot study of deep hyperthermia combined with MMC chemotherapy successfully demonstrated that a heating prescription of 42±2°C for 40-60 minutes can be delivered safely to the bladder for a typical range of patient sizes. Using the available thermometry and treatment planning, the BSD 2000 radiofrequency phased array hyperthermia system was shown to be an effective method of focusing heat regionally around the bladder with good patient tolerance.

Acknowledgments

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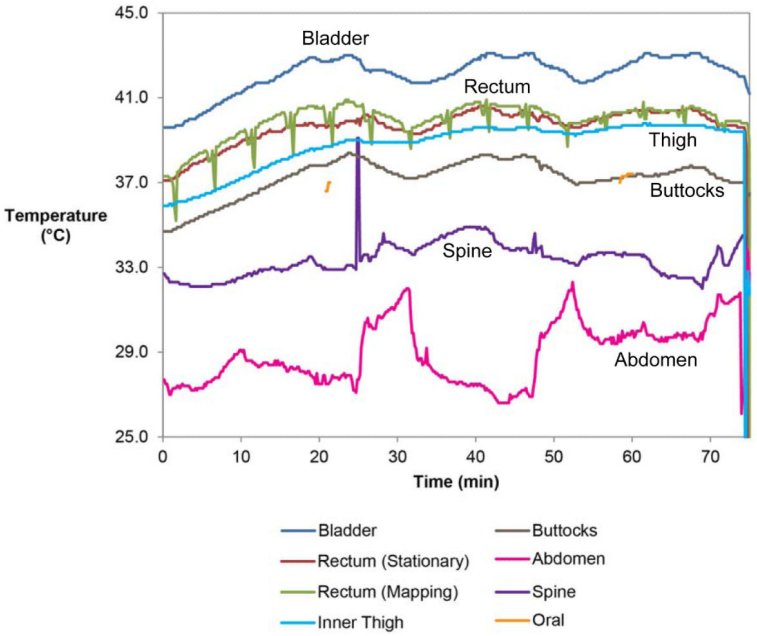

Figure 1.

Typical temperature plot for a single treatment session (Patient 13, Sigma Ellipse) showing temperature readings for all 8 monitored locations (bladder, rectum, rectum mapping, spine, abdomen, buttocks, inner thigh, mouth). Note the oral probe was inserted into the mouth to record core temperature only twice (at 21 and 58 minutes into treatment) and was floating in air (offscale) for the remainder of treatment. The lowest temperatures in the cycling rectal map were obtained at the most proximal portion of the rectum near the anus.

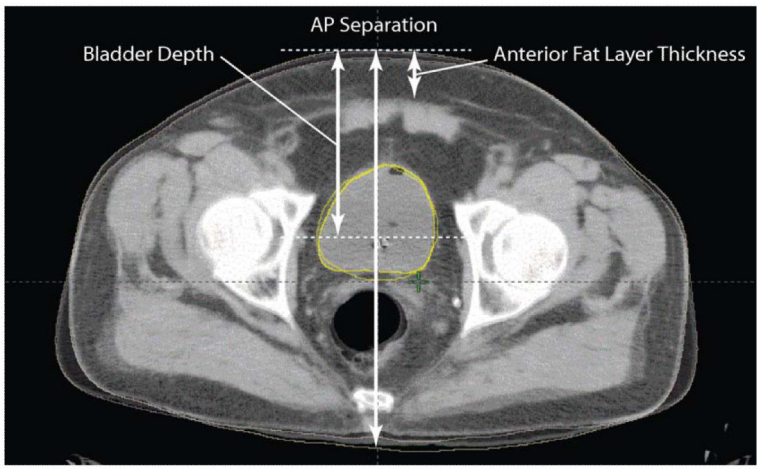

Figure 2.

Axial patient CT illustrating 3 patient anatomical characteristics – anterior-posterior (AP) separation, bladder depth (to largest cross sectional diameter), and anterior fat layer thickness – used to examine possible correlations between patient anatomy and heating.

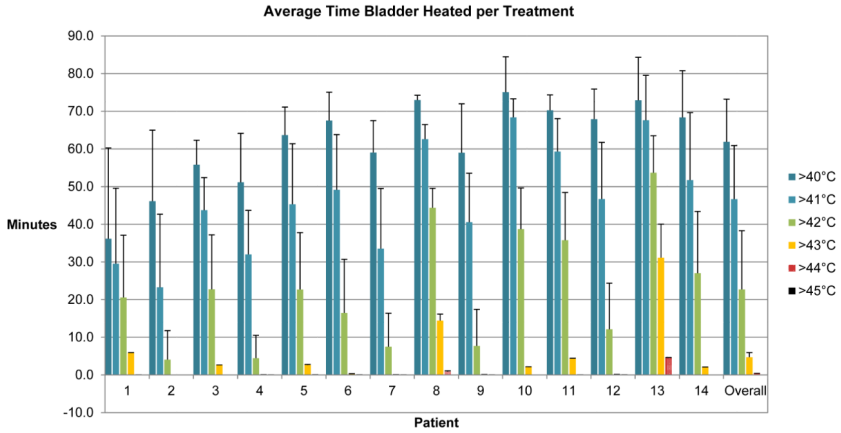

Figure 3.

Average treatment time with temperatures >40-45°C (bars displayed left to right) delivered to bladder per treatment for each patient. “Overall” indicates average across all patients. Temperatures within 40-44°C fall within the hyperthermia prescription for this study. Error bars indicate standard deviation.

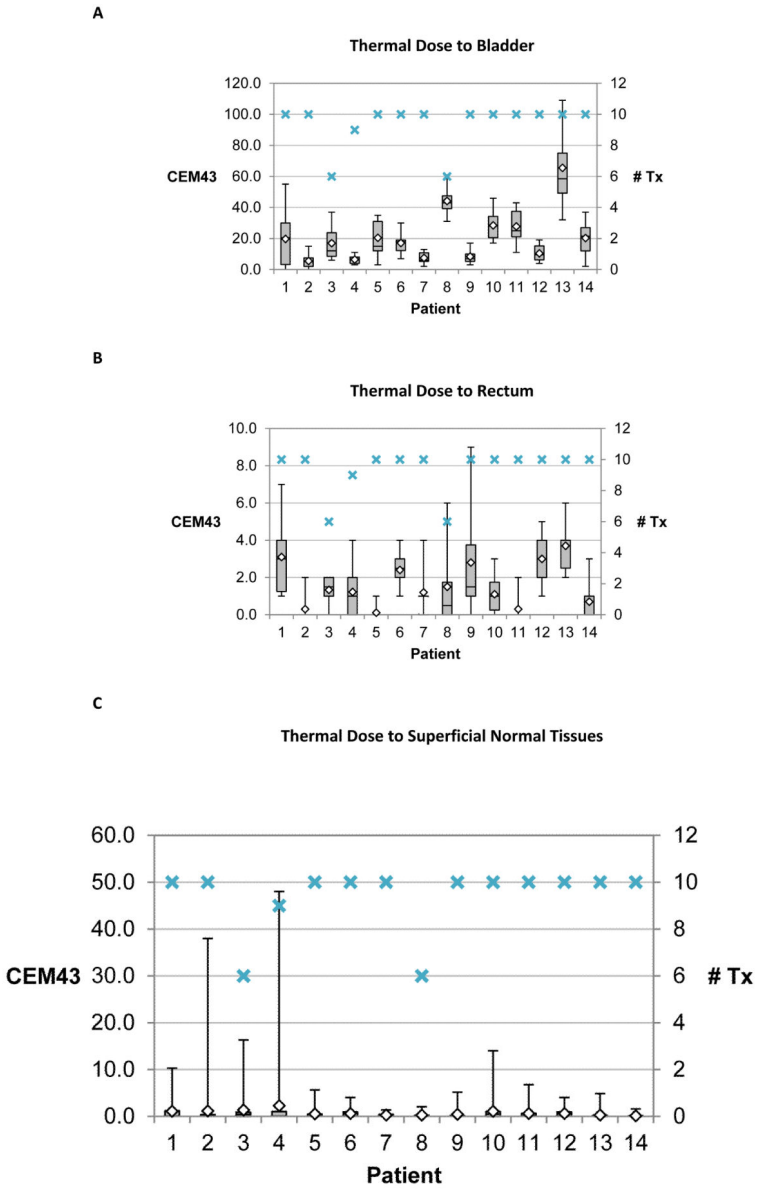

Figure 4.

Range of thermal dose (CEM43) per patient delivered to (A) bladder, (B) rectum, and (C) superficial normal tissues. Boxes indicate quartiles, diamonds indicate mean values, and whiskers indicate maximum and minimum values. In the case of plots without boxes (i.e., patients 2, 5, and 11 in B), the first, second, and third quartiles were all equal to 0 CEM43. X-markers indicate the number of treatments for each patient, using the scale at right.

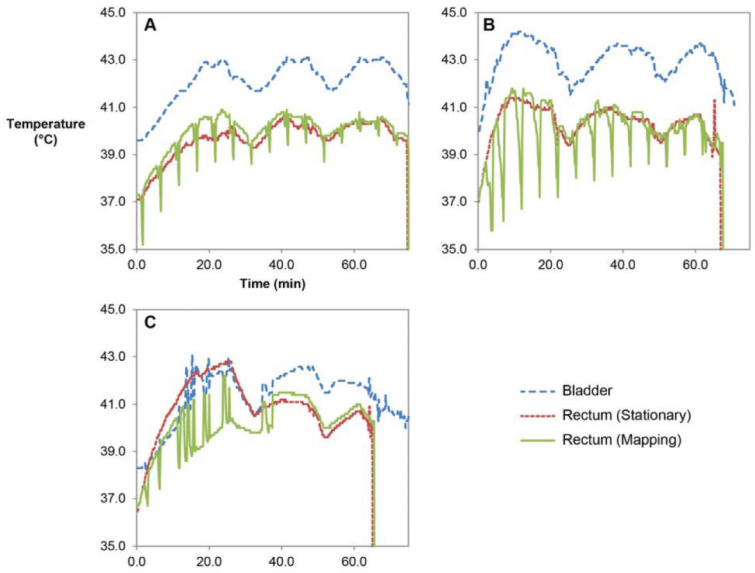

Figure 5.

Thermometry plots illustrating the effects of thermal steering. A (Patient 14, Sigma 60) and B (Patient 13, Sigma Ellipse) demonstrate effective separation of temperatures between bladder and rectum in both applicators due to effective treatment preplanning. C (Patient 9, Sigma Ellipse) provides an example case where real-time temperature monitoring and feedback was used in the first 20 minutes of treatment to steer the focus of heating for more effective differential heating of bladder in the remainder of treatment. Note that temperatures varied 2-4°C along the length of rectum recorded in each cyclic map.

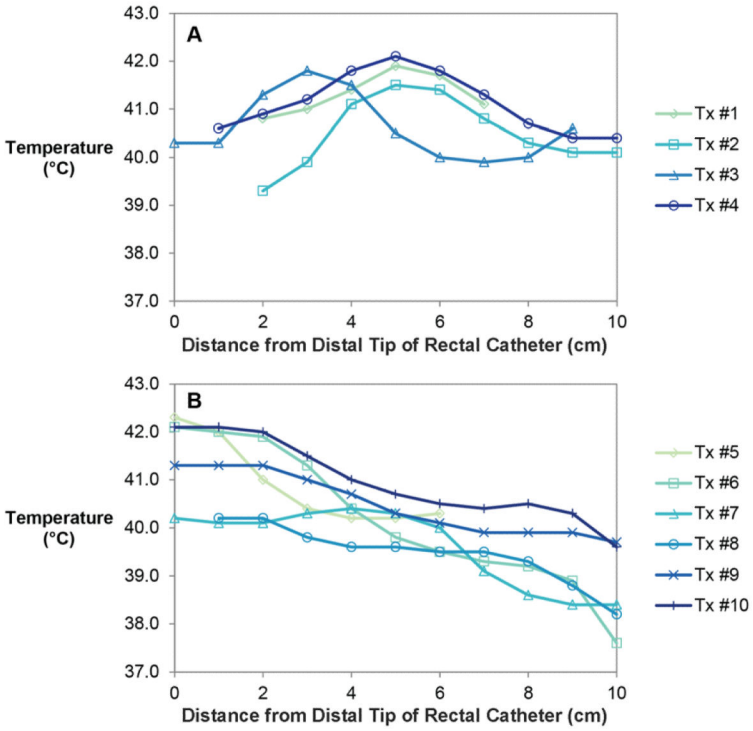

Figure 6.

Rectal maps at steady state target temperature showing temperatures relative to distal position in the rectum across 10 treatments for a single patient (Patient 9, Sigma Ellipse). The tip of the mapping catheter (distal position = 0 cm) was located adjacent to the bladder target. This particular case demonstrates use of the rectal temperature mapping data from the first four treatments (A) to evaluate the patient plan and adjust the Sigma applicator position for improved focus of heating on the bladder target in subsequent treatments (B).

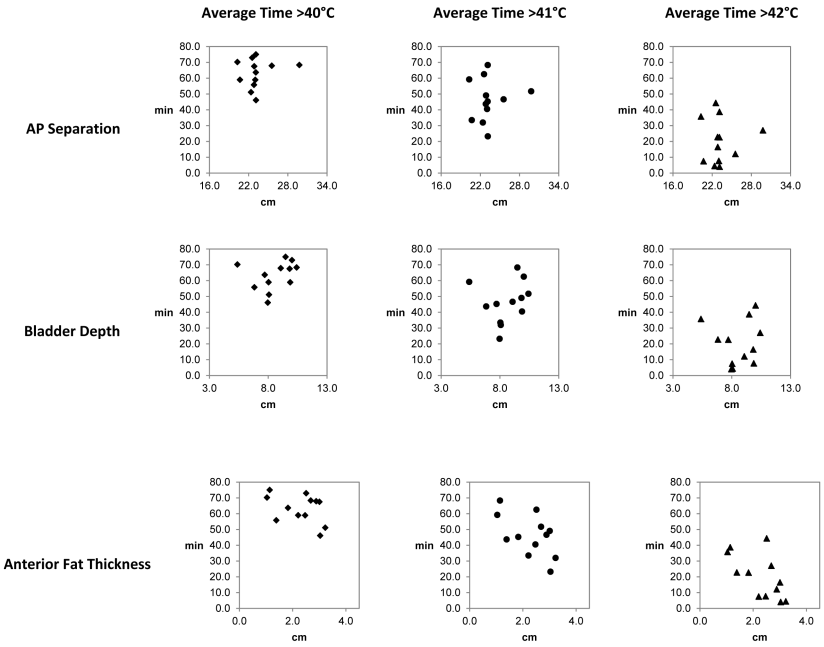

Figure 7.

Plots of the average time >40°C, 41°C, and 42°C (with higher values suggesting greater ease of heating) with respect to the anatomical characteristics of patient AP separation, bladder depth, and anterior fat layer thickness.