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RESEARCH PAPER

Development of a 70 MHz unit for hyperthermia treatment of deep-seated breast tumors

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A dedicated hyperthermia (HT) system was designed for tumors in intact breast extending beyond the heating depth of our superficial 434 MHz antennas, consisting of a treatment bed fitted with a 50 cm × 40 cm × 16 cm temperature controlled open water bolus. The patient lies in prone position with the breast immersed in the water positioned in front of a 34 cm × 20 cm 70 MHz waveguide operating in the TE_{10} mode. E-field patterns were measured in a tissue-mimicking phantom. HT was applied once a week with the 70 MHz applicator for six patients treated with thermoradiotherapy for deep lesions of recurrent breast cancer or melanoma. Two 14-sensor thermocouple thermometry probes were placed in catheters to monitor the invasive temperature. Results: Phantom measurements showed sufficient penetration depth up to 10 cm depth. The combination of 300–900 W antenna power and a water temperature of 42°C was well tolerated for the entire session of 1 h and resulted in good tumor temperatures with T90 = 39.8°C, T50 = 41.1°C, and T10 = 42.2°C. No toxicity or complaints were associated with the heating. A water mattress and other measures were needed to assure a comfortable position throughout the treatment. Conclusion: the 70 MHz breast applicator system performed well and tumor temperatures were good.

Keywords: Medical and biological effects, Antenna design, Modelling and measurements

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I. INTRODUCTION

Hyperthermia (HT) is the elevation of tumor temperatures to a clinically relevant temperature range of 40–43°C. HT is an adjuvant therapy, used to enhance the effects of radiotherapy (RT) and chemotherapy. The widely accepted thermal dose is 1 h at 43°C [1], though this temperature is often not achieved. The clinical outcome is strongly correlated with the thermal dose [2]; therefore, realizing a sufficiently high and homogeneous tumor temperature is important. The added value of HT has been demonstrated for many tumor types [3, 4]. HT is a standard treatment for breast cancer, the most common cancer in women. Local recurrences are a significant problem, occurring in ~10% of the patients. Treatment with RT combined with HT has proven effective, e.g. in the combined analysis of five randomized trials, which showed a complete response rate of 59% for RT + HT versus 41% for RT alone [5]. Other randomized and large cohort studies have confirmed the significant radiosensitizing effect of HT in the treatment of recurrent breast cancer [6–12]. Most local breast cancer recurrences are located a few centimeters below the skin and are routinely treated with many different systems. These include electromagnetic (EM) antennas operating at 434 and 915 MHz yielding tumor heating up to 4 cm depth, e.g. the 434 MHz Contact Flexible Microstrip Applicator (CFMA) and the 434 MHz ALBA ON4000 [13–17] and the 915 MHz BSD-500 [18]. Non-EM radiation-based systems used for heating recurrent breast cancer utilize absorption of ultrasound [19] and infrared radiation [20].

Tumors in intact breast require a different approach because of the shape of the breast and the different heating depth. Fenn *et al.* [21] developed a double antenna system, which required breast compression due to the limited penetration depth of the 915 MHz waveguides used. Decreasing the operating frequency and/or increasing the number of antennas are logical steps to achieving tumor heating in intact breast where tumors generally extend deeper than 4 cm. A similar approach is also used for heating deep-seated tumors (e.g. cervix or bladder) using phased array systems such as the BSD-2000 system [22, 23] and the four-antenna array developed at the Academic Medical Center (AMC) [24, 25]. Novel 70 MHz CFMAs suitable to treat breast tumors infiltrating more than 4 cm were designed, which can also be used in multi-antenna arrays [26, 27]. Wu *et al.* [28] developed a dedicated phased array of four end-loaded dipole antennas operating at 140 MHz for treatment of breast cancer where phase and amplitude steering is used to achieve preferential tumor heating.

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Stang *et al.* employed a large two-dimensional array of 915 MHz microstrip patch antennas [29]. Most of these EM-based breast HT systems did not make it into routine clinical use. Ultrasound-phased arrays for heating lesions in the breast were also developed [30, 31], which have the advantage that relatively small focal volumes can be achieved in comparison with EM systems. These systems are in clinical use, but mainly for rapid high-temperature ($T > 50°C$) ablation instead of moderate heating of the lesion at 43°C for 1 h to enhance the effectiveness of RT.

The purpose of this research is to design, construct, and clinically apply a dedicated HT system for treating tumors in intact breast with robust features to facilitate clinical use. This system is then evaluated in terms of:

(1) waveguide characteristics for a setup with a tissue equivalent phantom;
(2) ability to achieve an adequate and homogeneous thermal dose in the tumor >40°C;
(3) absence of treatment limiting normal tissue hot spots; and
(4) patient comfort and clinical feasibility.

II. METHODS

The treatment system consists of a treatment bed fitted with a 50 cm × 40 cm × 16 cm temperature-controlled open water bolus and antenna (Fig. 1). The water bolus serves a dual purpose; it is a matching layer between antenna and patient as well as providing a controlled thermal boundary condition to achieve the desired skin temperature. The concept of an open water bolus was chosen to provide optimal contact, similar to the coaxial transverse electric and magnetic (TEM) regional HT system [32]. The patient lies in prone position on a water-filled mattress with the breast immersed in the water positioned in front of a 70 MHz waveguide placed at the bottom of the bolus. The $\frac{1}{4}\lambda$ waveguide is 12 cm deep and has an aperture size of 20 cm × 34 cm, this waveguide is also used in the AMC-phased array system consisting of up to eight 70 MHz waveguides used for heating deep-seated tumors, including cervix, rectum, and bladder [25]. The water-filled waveguide operates in the TE_{10} mode with the dominant *E*-field direction parallel to the skin surface and perpendicular to the long side of the aperture with a cut-off frequency $f_c = 1/2a\sqrt{\mu\epsilon} \approx 50$ MHz for $a = 0.34\ \mathrm{m}^{-1}$. The EM field is absorbed in the tissue with a specific absorption rate (SAR):

$$\mathrm{SAR} = \frac{\sigma}{2\rho}|E|^2\ (\mathrm{W/kg}),$$

with σ the conductivity and ρ the density of tissue.

The waveguide is connected to an analogous amplifier (Henry Radio, Los Angeles, California, USA) providing 500 W output power. A double-slug tuner between the amplifier and antenna is used for tuning. The variable impedance of the applicator in combination with the patient has to be tuned with the fixed 50 Ω amplifier output.

A) Waveguide characteristics

The emitted *E*-field pattern was measured in the setup shown in Fig. 2 using an elliptical phantom filled with a muscle-equivalent 3 g/l saline solution. This solution has a relative dielectric permittivity of 77 and a conductivity of 0.51 S/m at 70 MHz and a water temperature of 22°C. The phantom has a cross-section of 24 cm × 36 cm and a length of 115 cm. The wall was made of polyvinyl chloride with a thickness of 2 mm. The waveguide is placed on top of the phantom; a water bolus containing de-ionized water is placed between waveguide and phantom.

The *E*-field was measured using an electric field vector probe, connected to a measurement system. The output was sent to a DAQ-unit (Labjack U12, labjack cooperation, Lakewood, USA) connected to a PC. An in-house developed MATLAB application interprets and stores the signals. The probe is mounted on an in-house developed computer-controlled x–y scanner. *E*-field measurements were performed in the transversal XY ($z = 0$) and sagittal YZ ($x = 0$) midplane (Fig. 2). Measurements were normalized in the center of the

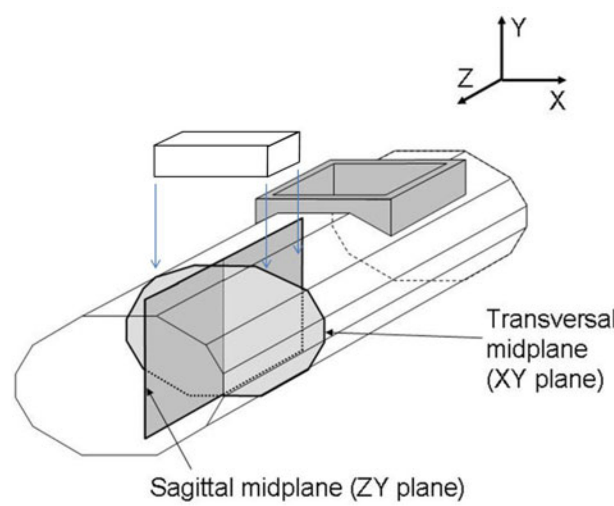

Fig. 2. Setup to determine *E*-field patterns of the 70 MHz waveguide in the transversal (*XY*) and sagittal (*ZY*) midplanes in the liquid saline phantom.

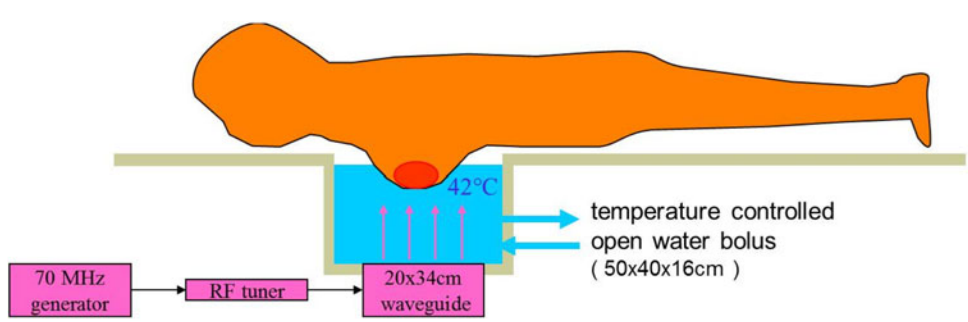

Fig. 1. Treatment setup: patient in prone position, breast immersed in open water bolus. 70 MHz waveguide placed at the bottom.

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phantom and center of the applicator. The amplitude of the *E*-field was defined to be 100% at this point.

Additionally, the reflection coefficient (*S*11), the Voltage Standing Wave Ratio and the relative reflected power were determined for this phantom setup.

B) Tumor temperatures

Patient selection for the clinical feasibility test of this system was based on tumor depth and whether the intact breast was sufficiently large to be immersed in the open water bolus. All treatment histologies were accepted. HT was applied using this system for a total of six patients. Patient characteristics are listed in Table 1. Four patients had adenocarcinoma, two had melanoma. Median age was 59 (42–75). RT dose was 32 Gy given in eight fractions of 4 Gy twice a week.

HT was given once a week for 4 weeks in combination with a RT session, commencing within 1 h after RT. The protocol allowed for a maximum of 30 min of preheating in order to achieve the desired temperature level of at least 40°C and this steady state then continued for 60 min. The maximum duration of treatment was thus 90 min.

Treatment was performed using the setup shown in Figs 1 and 3. The temperature of the water in the bolus starts at 39°C and is gradually increased to 42°C at steady state to permit the skin to gradually get accustomed to higher temperatures. Tap water is used and the water is not recirculated but continuously refreshed from the tap. Waveguide was positioned facing the breast containing a tumor. Both breasts are immersed in the water, but the healthy breast is enveloped in fabric creating 1 cm thick air layer isolating it from the EM field to prevent heating of this non-target breast (Fig. 3).

Tissue temperatures are recorded using 14-sensor copper-constantan thermocouple probes with a diameter of 0.9 mm (Ella CS, Hradec Kralove, Czech Republic). Temperatures are recorded every 30 s, switching off power for 5 s to prevent electronic disturbance during measurement [33]. Four probes are placed on the skin of the breast. In addition, two invasive probes are placed in lossless polyethylene catheters (diameter 1.3 mm), which are inserted in lateral and in cranial–caudal direction through the breast to obtain representative temperature profiles in the target region. The resulting tumor temperature distribution is characterized using T10, T50, and T90, the temperature achieved in 10, 50, and 90% of the treatment volume, respectively. The temperature parameters T10, T50, and T90 are averaged over the steady-state treatment period of 60 min per session and over all four sessions per patient.

C) Normal tissue hot spots

Incidence of normal tissue hot spots was determined from the recorded T10 values and by recording complaints about hot spots by the patients. Normal tissue temperatures exceeding 44°C were considered hot spots to be avoided associated with the risk of side effects.

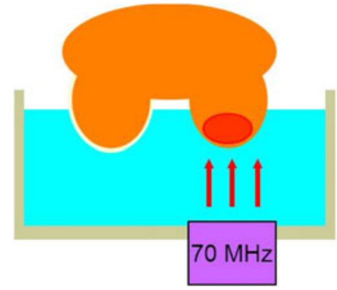

Fig. 3. Waveguide faces breast with tumor, healthy breast is isolated.

D) Patient comfort

Patient comfort and overall clinical feasibility were determined based on the aforementioned temperature parameters (tumor temperature and normal tissue hot spots) and the ability of patients to complete treatment as scheduled. The opinion of the patients on treatment comfort was also recorded after treatment.

III. RESULTS

A) Waveguide characteristics

The measured *E*-field patterns are shown in Fig. 4 and show that the effective field size is about 15 × 20 cm² and that the penetration depth is sufficient to heat intact breast up to 10 cm depth. The field patterns for this 70 MHz rectangular waveguide design match simulations using in house developed Finite Difference Time Domain software [34]. The waveguide properties in this phantom setup: reflection coefficient (S_{11}) is 6.84 dB, the Voltage Standing Wave Ratio is 2.668:1, and the relative reflected power is 20.7%. These waveguide properties are very acceptable for our clinical needs to heat an intact breast.

B) Tumor temperatures

In Figs 5 and 6, an example of an individual patient is shown, a 65-year-old patient treated with thermoradiotherapy for recurrent adenocarcinoma in the breast with both deep and superficial breast lesions. On this ground, the clinician decided to treat her complete breast with HT using the 70 MHz breast applicator. Prior to treatment, two 14-sensor thermocouple probes were placed in catheters inserted in lateral and in cranial–caudal direction through the breast at 5 and 3.5 cm depth, respectively (Figs 5 and 6).

Table 1. Patient characteristics and treatment parameters.

Patient	Age	Tumor type	Average power (W)	Average T90 (°C)	Average T50 (°C)	Average T10 (°C)
1	65	Adenocarcinoma	297	39.6	41.3	42.1
2	75	Adenocarcinoma	352	39.1	40.5	41.7
3	54	Melanoma	392	39.0	40.0	41.1
4	57	Adenocarcinoma	350	41.9	42.7	43.6
5	42	Adenocarcinoma	453	39.3	40.9	42.1
6	61	Melanoma	925	40.3	41.2	42.9

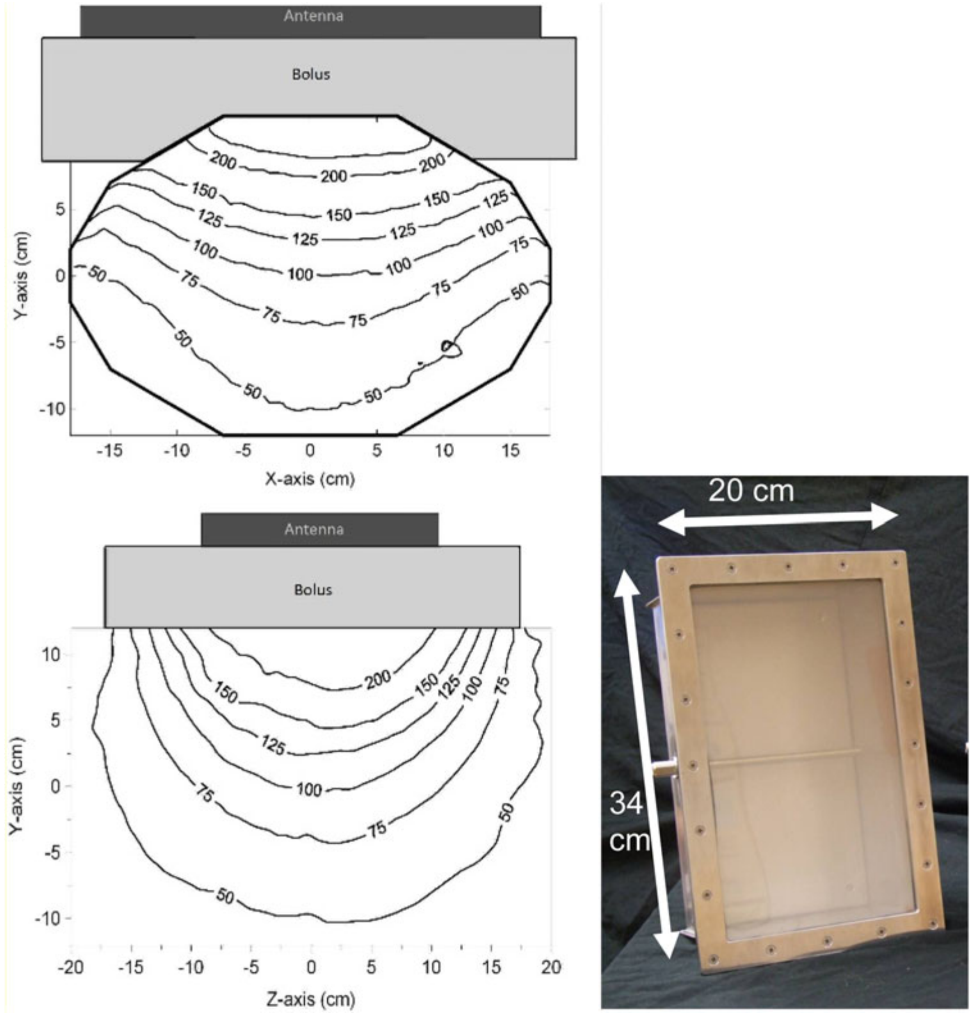

Fig. 4. *E*-field patterns measured in the *XY* midplane with the setup of Fig. 2.

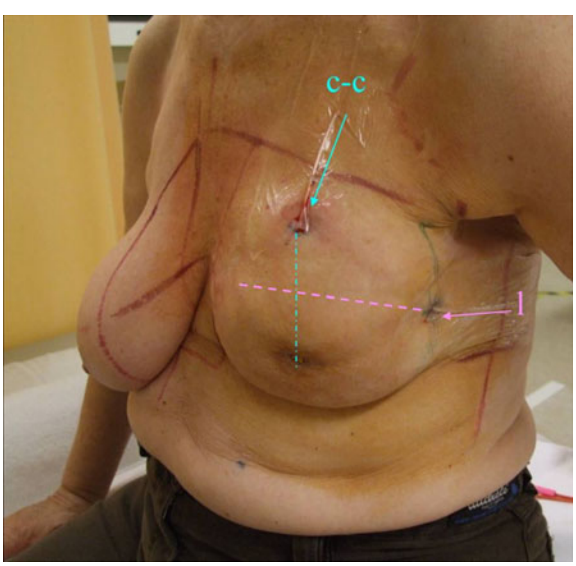

Fig. 5. Invasive lateral (*l*) and cranial–caudal (*c–c*) thermocouple probes placed in catheters in the breast of patient 1.

The combination of 300–400 W antenna power and a water temperature of 42°C was well tolerated for the entire session of 1 h and resulted in good tumor temperatures with T90 = 40.1°C, T50 = 41.6°C, and T10 = 42.1°C for the session of patient 1 shown in Figs 7 and 8.

Temperature profiles for the lateral and cranial–caudal catheters of patient 1 are shown in Figs 7 and 8. No toxicity or complaints were associated with the HT treatment. A water mattress and other measures were needed to assure a comfortable position throughout treatment.

Results for all six patients are shown in Table 1 and Figs 9 and 10. Tumor temperatures recorded during the steady-state period of 60 min averaged over all four sessions per patient and averaged over all six patients were T90 = 39.8°C, T50 = 41.1°C, and T10 = 42.2°C, which is quite acceptable both in terms of temperature uniformity and in terms of minimum temperature achieved. For all patients, the full 30 min preheating period was needed to achieve therapeutic temperature levels in the deepest measurement points in the breast. As the maximum temperature T10 was low in spite of consistently using maximum power for patients 1, 2, 3, and 5, we decided that even better temperatures should be possible by increasing the power level beyond 500 W. We therefore replaced after the fifth patient the 500 W 70 MHz Henry Radio generator with a more powerful generator, in this case the 2.5 kW 70 MHz generator formerly used for the coaxial TEM applicator [32]. The sixth patient was then treated with 900 W output power. This did result in higher

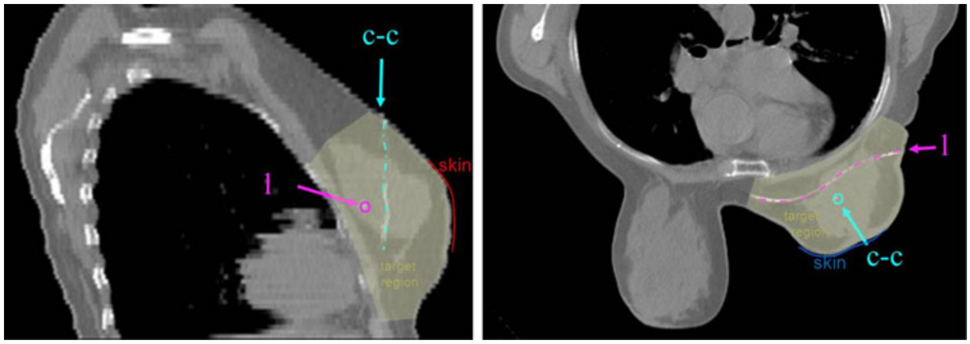

Fig. 6. CT showing the target region and the location of the invasive lateral (*l*) and cranial–caudal (*c–c*) thermocouple probes of Fig. 5, as well as the superficial thermocouple probes on the skin surface (skin).

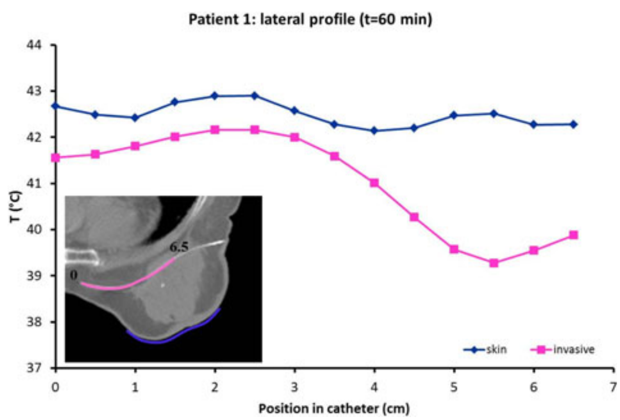

Fig. 7. Steady-state temperature profile in the lateral catheter of patient 1.

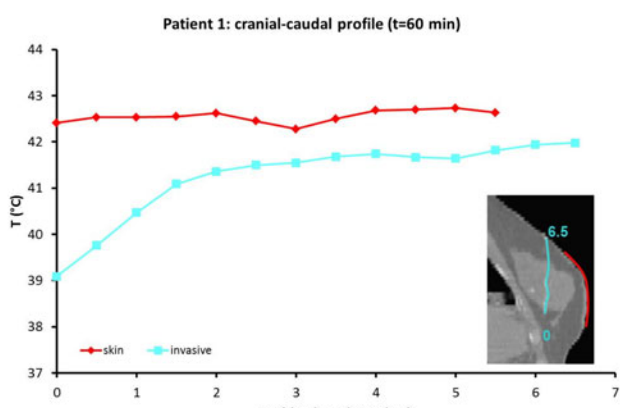

Fig. 8. Steady-state temperature profile in the cranial–caudal catheter of patient 1.

than average tumor temperatures for the sixth patient. Most of this need for a relatively high output power can be attributed to losses in the water bolus, which utilizes tap water, not deionized water. But also tissue perfusion was thought to be high for all patients except patient 4, the only patient where high temperatures were achieved at a relatively modest power level. Power absorption in the breast is definitely not uniform with a three times higher SAR in the muscle-like areas (the denser, lighter grey shade areas in the CT scans of Figs 6–8) compared WITH the more fat-like tissue (the darker areas in the CT scan). Nonetheless, the resulting steady-state temperature distribution is relatively uniform,

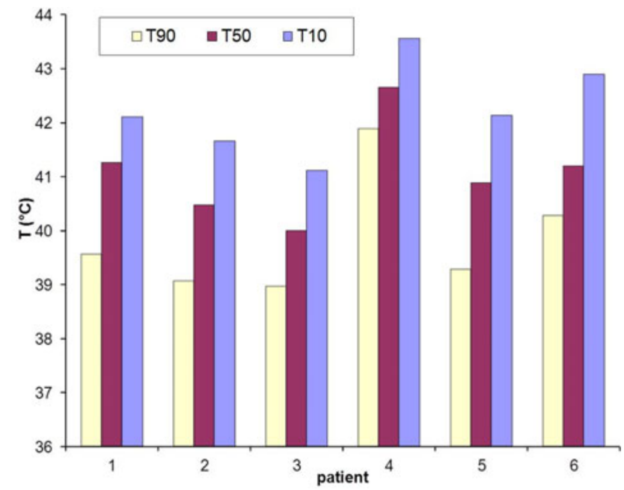

Fig. 9. Temperature achieved averaged over the four sessions per patient.

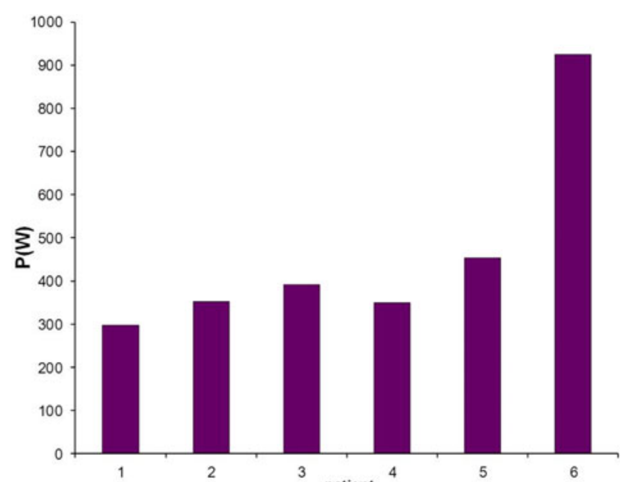

Fig. 10. Power during treatment averaged over the four sessions per patient.

due to thermal conduction and blood perfusion. This good clinical temperature distribution was achieved with only a single antenna, where other proposed breast applicators always use an array of antennas [28, 29], which gives good flexible steering to focus the energy but also adds complexity to the steering. We feel that our single-antenna system is a more robust approach for heating deep-seated breast tumors

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that is likely to provide adequate heating without the need for extensive pretreatment planning and online adaptive planning required for achieving optimal temperature distributions when using multi-antenna-phased array HT devices [35–37].

C) Normal tissue hot spots

The combination of up to 900 W antenna power and a water temperature of 42°C was well tolerated for the entire session of 1 h. None of our six patients complained about pain associated with the antenna power. Also none of our temperature measurements gave any indication of normal tissue temperatures exceeding 45°C. This is remarkable as during locoregional heating in the pelvic region with similar waveguides, much lower power per antenna (typically 200–300 W) is applied to avoid normal tissue hot spots. The use of an open water bolus is likely to be a major reason for this remarkable finding. During locoregional heating, a water-filled plastic bag is placed between waveguide and the skin of the patient, and many normal tissue hot spots occur due to fringing fields at the edge of the water bolus [38]. This fringing field effect no longer occurs when an open water bolus is used, but distinct anatomical features can still be associated with a high risk of hot spots [39]. Apparently, these anatomical features are not present in the intact breasts we treated with our applicator.

D) Patient comfort

Patients tolerated the treatment extremely well, and all sessions were completed as scheduled. No complaints were reported about either the water temperature or the antenna power. The only issue that caused patient complaints was the need to undergo treatment in prone position for up to 90 min. In spite of the water mattress used, most of the patients had difficulty with that position, in particular when patients were more obese. This part of the treatment system will need to be redesigned to increase patient tolerance. However, the EM part of the system seems to function properly without affecting patient comfort.

IV. CONCLUSIONS

The 70 MHz breast applicator system performed well and tumor temperatures were good. Some modifications in the system setup are desired to make the prone position more comfortable for the patient. When this modification has been achieved, this system will be used in a phase I/II study for deep-seated tumors in intact breast treated with RT and HT.

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