

Dedicated 70 MHz RF systems for hyperthermia of challenging tumor locations

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Research Paper

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Abstract

Hyperthermia (i.e. heating of tumor tissue to 40–43°C) is used in clinical oncology to enhance the therapeutic effect of chemotherapy and radiotherapy. Many tumor sites are heated either by a single RF or MW antenna positioned on the tumor location, or by a phased array positioned around the patient. Superficial tumors are generally heated with MW antennas (434–2450 MHz) and deep-seated tumors with RF antennas (70–150 MHz). These devices cover the major, more common tumor sites, but more rare locations require more dedicated applicators. We discuss dedicated RF systems aiming for heating semi-deep-seated tumors in the leg, breast, and upper thorax. Clinical results show that adequate heating is possible with these systems, with achieved temperatures in the therapeutic range.

Introduction

Clinical hyperthermia, heating a tumor to 40–45°C for 1 h, is a cancer treatment applied in combination with chemotherapy and/or radiotherapy, with the aim to enhance the effectiveness of the latter two therapies [1, 2]. Clinical results are very good, and adding hyperthermia typically yields an increase in tumor response on the order of 15–20% [3, 4]. Realizing a sufficiently high tumor temperature is important as treatment outcome is correlated with the achieved tumor temperature [5–8]. Hyperthermia is tumor-selective if given sequentially, shortly before or after radiotherapy. In that case normal tissue temperatures of 40–45°C are well tolerated and do not lead to an increase in radiotherapy- or chemotherapy-related side-effects in the surrounding normal tissue. Temperatures exceeding 45°C should be avoided as these can lead to pain and normal tissue damage [9].

Superficial malignancies, such as chest wall recurrences of breast cancer or melanoma, extend less than 4 cm from the skin surface [10] and are generally treated with MW antennas placed onto the lesion. The 915 MHz antennas of the BSD-500 system [11–13] and the 434 MHz microstrip applicators of the ALBA-4000 system [14–19] are the applicators used in the present clinically available superficial systems. Deep-seated malignancies, such as cervix, prostate, bladder, and rectum tumors, are usually heated with a phased array of RF antennas, organized in one or multiple rings around the pelvis of the patient [20, 21]. Clinical locoregional devices include the AMC-4 system [22], AMC-8 system [23], ALBA-4D system [24], and BSD-2000 series [25, 26], which all operate at frequencies between 70 and 150 MHz. These phased array systems provide spatial steering of the energy deposition [21, 23], which proved instrumental in achieving good and therapeutic temperatures and good clinical results in a range of tumor sites including rectum, bladder, cervix, and soft-tissue sarcoma [27–31].

However, not all tumor sites can be optimally heated with the commercially available devices listed in the previous paragraph. This paper reports on the development of three novel dedicated RF-based hyperthermia systems capable of delivering hyperthermia to three different challenging semi-deep-seated tumor sites: the leg, the breast, and the upper thorax (Fig. 1). Each system design is described, including clinical tumor temperature measurement methods, followed by examples of the actual clinical application.

Methods

All systems are intended for deep/semi-deep-seated tumors, extending more than 4 cm from the skin surface. Therefore, we use the 70 MHz waveguides designed for the AMC-4, AMC-8, and ALBA-4D systems used at our department, as these have a 50% larger penetration depth than 434 MHz antennas [32]. The water-filled waveguides have a length of 12 cm ($\frac{1}{4}\lambda$), apertures of 34 × 21 cm, 34 × 15 cm, or 34 × 8.5 cm, and effective penetration depths of 3.5, 3.1, and 2.7 cm, respectively (Fig. 1(d)) [33]. The effective penetration depth is the depth at which specific absorption rate (SAR) is 50% of the value at 1 cm depth, as defined in the European Society of Hyperthermia (ESHO) Quality Assurance (QA) guidelines [10, 34].

The 70 MHz generator system of the AMC-8 system shown in Fig. 2 is used [23]. This is an eight channel DDS-based phase and amplitude controlled RF generator system with a phase

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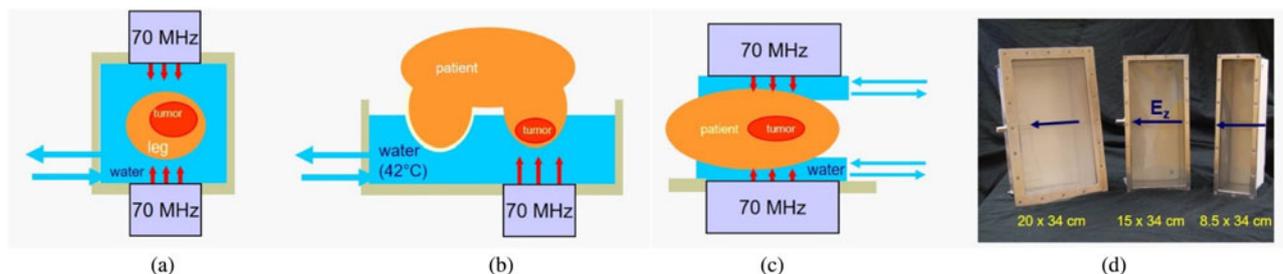


Fig. 1. The three dedicated systems presented in this paper. (a) Double-waveguide set-up for leg tumors with open water bolus. (b) Single-waveguide set-up with open water bolus for deep-seated breast tumors. (c) Double-waveguide set-up for tumors in the upper thorax, which uses three different aperture sizes. (d) Dominant field component E_z indicated by the blue arrow.

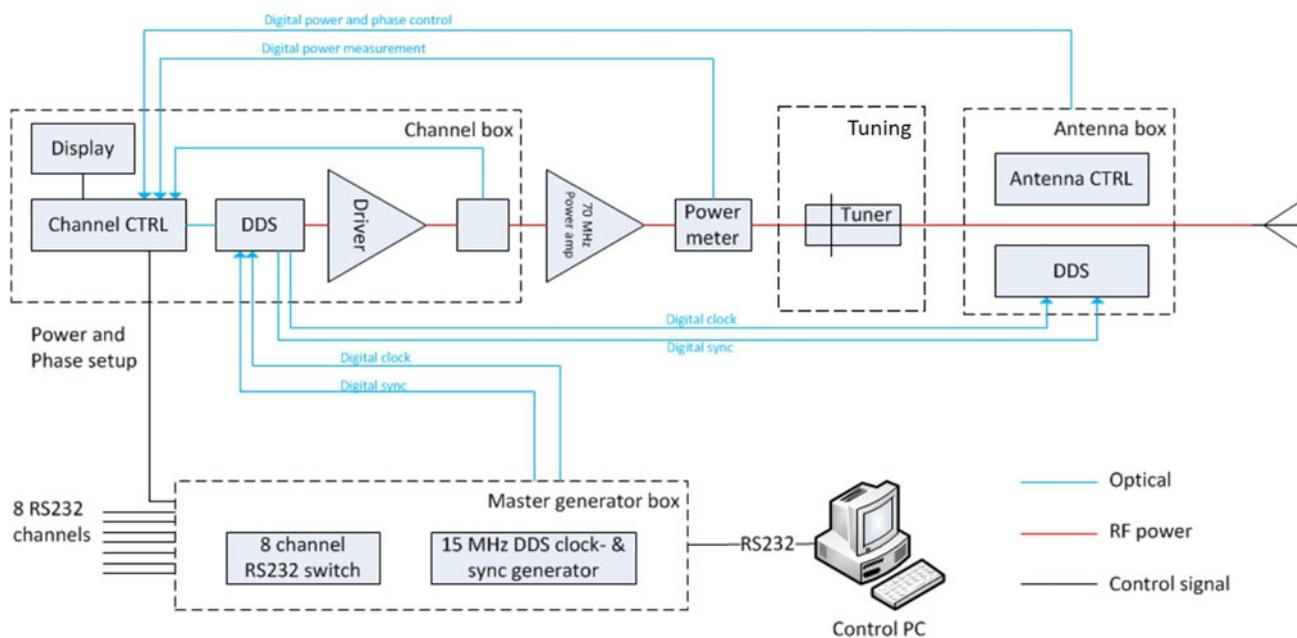


Fig. 2. The eight channel DDS phase and amplitude controlled 70 MHz generator system used for all three systems shown in Fig. 1. Each channel has a tuner and 500 W maximum output power [23].

accuracy of 3° and an output power accuracy of 10 W (SSB Electronic, Iserlohn, Germany). A double-slug tuner is placed between the 70 MHz power amplifier and the antenna. This tuner is used for tuning of each channel. The solid state amplifiers used (Restek, Rome, Italy) provide 500 W maximum output power for each channel.

Two systems presented in this paper use the principle of a phased antenna array and phase steering. This principle is also applied for instance in the AMC4 and ALBA4D phased array systems for pelvic and abdominal tumors, which both use a ring of four waveguides positioned around the patient as shown in Fig. 3 [22, 24]. The four waveguides operate in the TE₁₀ mode and are positioned in such a way that the dominant E -field component E_z of each antenna is parallel to the longitudinal axis of the body. Thus, the $E_z(i)$ contributions of each waveguide i add up, which allows to realize a central E -field focus at the tumor, with a local power deposition expressed as SAR in W/kg proportional to the square of the total E -field:

$$SAR \sim E^2 \approx \sum_{i=1}^4 E_z^2(i) \quad (1)$$

Phase steering of the four waveguides is utilized to position the E -field focus onto the desired tumor target location [22, 24]. Similar phase steering principles are applied in the two double-waveguide dedicated systems for the leg and upper thorax described in this paper. The optimal phase difference between the two waveguides yielding best focalization onto the tumor is established by performing a ΔT test. This involves measuring at the start of each clinical treatment the temperature rise ΔT in the tumor after 60 s of power on, and comparing the resulting ΔT for three different phase settings, e.g. -40° , 0° , and $+40^\circ$. The phase setting yielding the best temperature increase in the tumor will be selected [35].

A water bolus is positioned between the antennas and the patient to ensure that the electromagnetic energy emitted by the antennas is coupled effectively into the patient, and to provide either warming or cooling of the skin to ensure that the entire tumor is heated to the therapeutic temperature range. This water bolus is either a plastic bag containing distilled water (system 1C is an example) or an open tank with tap water or distilled water (as used for systems 1A and 1B). The open tank is used to optimize energy coupling to irregularly shaped body

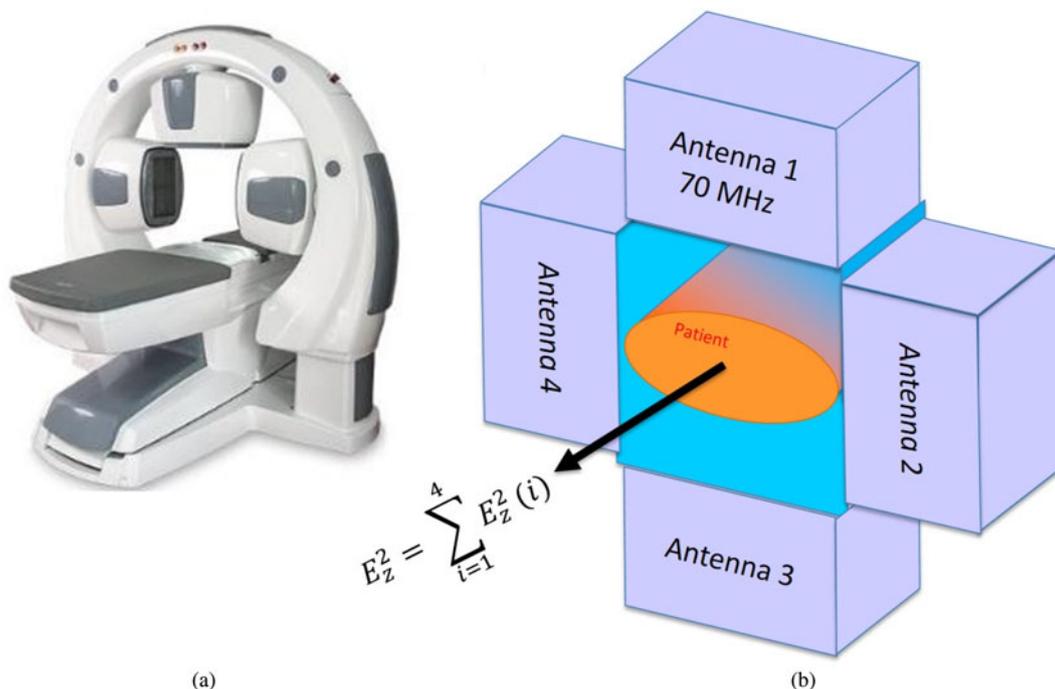


Fig. 3. Principle of phased array systems. (a) Four antenna ALBA4D system. (b) A central E -field focus can be realized by superposition of the $E_z(i)$ of antennas 1 through 4 parallel to the longitudinal axis of the patient body in the ALBA4D system.

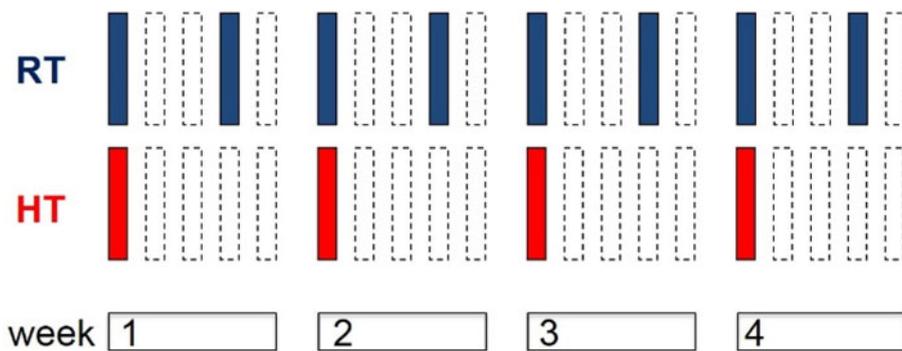


Fig. 4. Hypofractionated 8×4 Gy schedule giving radiotherapy twice a week, once a week hyperthermia is performed, ~ 1 h after the radiotherapy fraction.

surfaces. Distilled water has the advantage of negligible power loss in the water bolus, ensuring optimal energy transfer to the tumor.

Tumor and skin temperature measurements are performed using multi-sensor copper constantan thermocouple probes (ELLA-CS, Hradec Králové, Czech Republic) placed in catheters inserted in the tumor. An in-house developed 196 channel thermometry system is used to measure undisturbed tumor temperatures during brief power-off intervals. Tumor temperatures during treatment are reported as T_{10} , T_{50} , and T_{90} , i.e. the temperature at least achieved in 10, 50, and 90% of the tumor during the 1 h steady state period of the treatment. Invasive normal tissue temperature measurements are clinically nearly impossible for ethical reasons. Incidence of normal tissue hot spots is therefore generally monitored by responding to patient complaints, which occur when a pain threshold of 45°C is exceeded [9].

All treatments in this paper combined hyperthermia with radiotherapy, typically in a hypo-fractionated schedule of 8×4 Gy as shown in Fig. 4, with radiotherapy given twice a week and once a week the radiotherapy fraction was followed by 1 h of

hyperthermia with a time interval of 1 h or less between the two treatments to achieve maximum thermal sensitization of the effectiveness of radiotherapy by the addition of hyperthermia [36].

Hyperthermia of a leg

The leg system consisted of two opposing waveguides with an aperture of 34×21 cm placed on either side of the leg immersed in an open, temperature-controlled water bolus. The open water bolus serves to optimize coupling of energy into the leg without inducing local hot spots in the skin (Figs 1(a) and 5). The waveguides operate in the TE₁₀ mode and are placed with the long side in the axial direction of the leg to cover a ~ 35 cm section of the leg. The dominant E -field component E_z is thus perpendicular to the longitudinal axis of the leg (Figs 1(a) and 5). Phase steering of the two waveguides is utilized to move the E -field focus onto the tumor target location. The water bolus temperature is set to fairly high values ($\sim 40^\circ\text{C}$) as the tumors in the leg generally already start quite close to the skin surface; low water

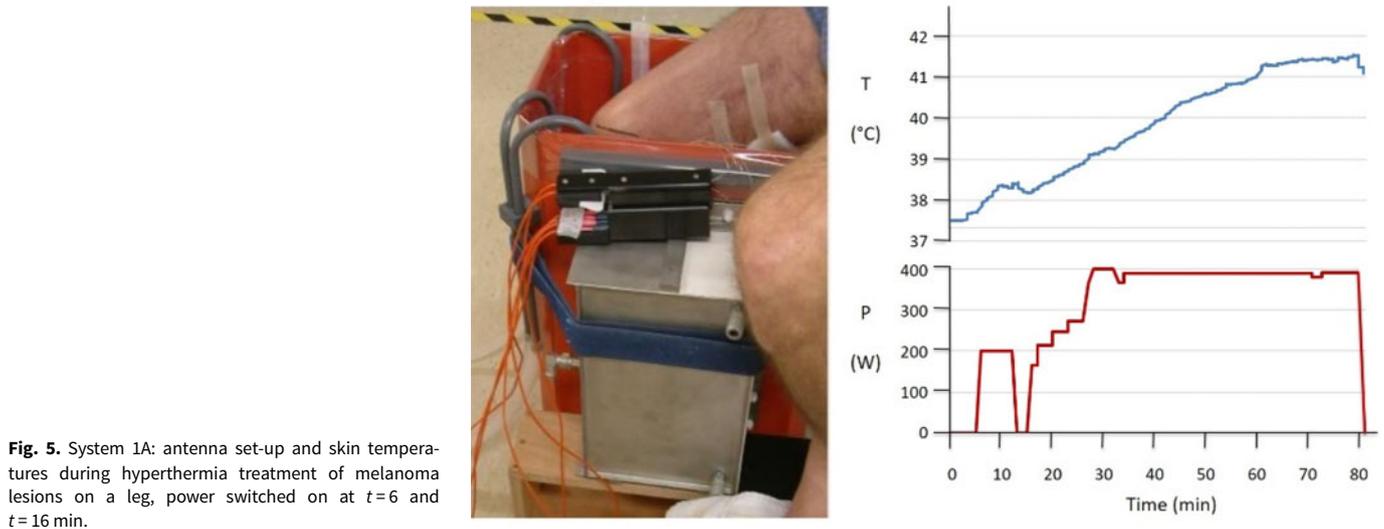


Fig. 5. System 1A: antenna set-up and skin temperatures during hyperthermia treatment of melanoma lesions on a leg, power switched on at $t=6$ and $t=16$ min.

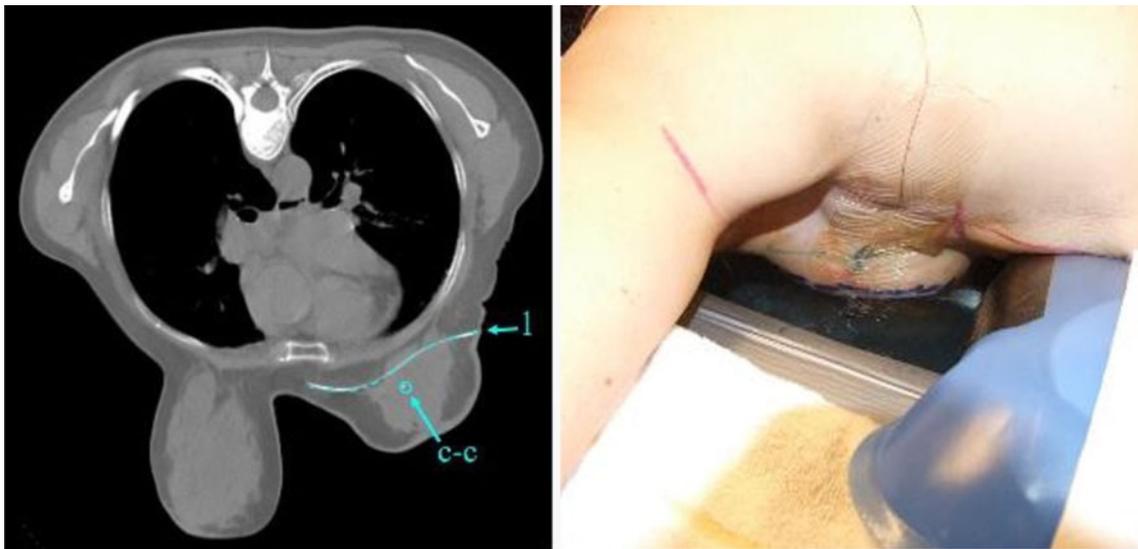


Fig. 6. System 1B: location of lateral (*l*) and crano-caudal (*c-c*) invasive thermometry probes during hyperthermia. Right: position of the breast in the open water bolus.

temperatures would lower the tumor temperature near the skin. More technical details can be found in [37].

Hyperthermia of an intact breast

This set-up uses an open water bolus into which the breast is hanging to ensure optimal coupling of energy into the breast without inducing local hot spots in the skin. Heating is achieved using a single waveguide with an aperture of 34×21 cm placed at the bottom of a temperature-controlled water bath (Fig. 1(b)). The waveguide aperture orientation is with its long side in the axial direction of the patient. To avoid unwanted field deposition in the non-tumor breast, the skin of that breast is covered with a water-tight cloth to prevent any SAR deposition in the healthy breast.

The water temperature is in the higher temperature range (~ 40 – 43°C) as the skin of the breast is part of the tumor target volume. Thermocouple temperature probes are placed onto the

skin and invasively in the tumor (Fig. 6). Prior to treatment both tap water and distilled water have been tested. Tap water leads to significant absorption in the water bolus, and requires relatively high power to ensure sufficient SAR in the tumor. We did choose tap water for hygiene, as distilled water required continuous recirculation of water. For details see [38].

Hyperthermia of semi-deep-seated tumors in the thorax

This system consists of two waveguides operating in the TE₁₀ mode; these are placed to the ventral and dorsal side of the thorax. The set-up shown in Fig. 1(c) has a dominant *E*-field component along the longitudinal axis of the body, similar to the orientation in the four waveguide phased array used for heating pelvic and abdominal tumors (Fig. 3). The two waveguide system allows both waveguides to rotate to accommodate the optimal position in view of the actual anatomical location (Fig. 7). Phase steering

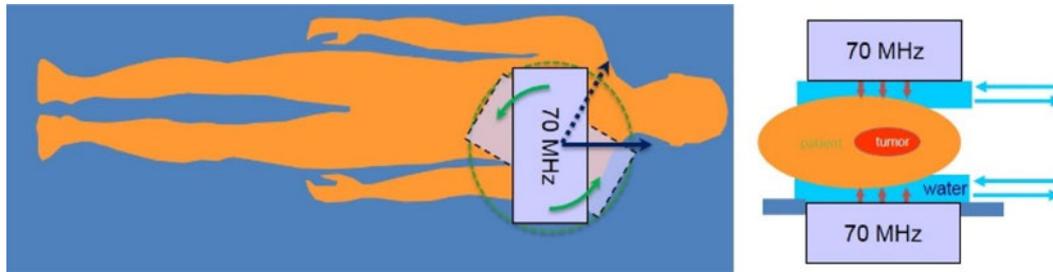


Fig. 7. System 1C: placement and rotation of the ventral 70 MHz waveguide on the thorax. Blue arrows indicate dominant E -field direction for different antenna directions.

is utilized to move the E -field focus onto the tumor target location. The dorsal waveguide is always the largest size with an aperture of 21×34 cm, the ventral waveguide is selected based on the exact anatomical site. Locations close to the head generally require the use of the smaller-sized waveguide models to ensure sufficient distance to the head of the patient. Thermocouple temperature probes are placed invasively in the tumor (Fig. 11). The water bolus temperature can range between room temperature ($\sim 21^\circ\text{C}$) and 43°C and can be set separately for each waveguide. This temperature is selected based on the tumor location. More details can be found in [33].

Results

Hyperthermia of a leg

Figure 5 shows patient set-up and temperature results for a patient with multiple large melanoma on his leg. The patient is treated in sitting position with the leg immersed in the double-waveguide hyperthermia system. All treatment sessions were performed with both waveguides operating at the same amplitude and with a 0° phase difference. High power (400 W) in combination with a low water temperature of 39.5°C resulted in better median temperatures exceeding 40°C , than high water temperature (42°C) and low power (200 W). The treatment was tolerated with no hot-spot-related pain complaints. At 7 weeks after treatment, the sizes of the largest tumor volume had decreased significantly and necrotic regions in the tumor were observed (Fig. 8). Therefore, local tumor control was achieved, but unfortunately the disease progressed outside the leg.

Hyperthermia of an intact breast

A series of six consecutive breast cancer patients were treated with the single 70 MHz waveguide breast applicator, with each patient receiving a total of 4 weekly sessions. Figure 6 shows a computerized tomography (CT) image with the tumor location for one of our patients, along with an image of the breast immersed in the open water bolus during treatment. The water temperature was $\sim 42^\circ\text{C}$ and power was relatively high due to the use of tap water, and ranged between 300 W in the first patient and 925 W in the last patient. Treatment was well tolerated by all patients, no pain complaints due to SAR-related hot spots occurred, not even at 925 W. This can probably be attributed to the use of the open water bolus, combined with the effective heat removal by the high blood flow in the superficial vessels in the skin of the breast, which is greatly enhanced in response to the hyperthermic conditions.



Fig. 8. System 1A: regression and necrotization of melanoma on the lower leg 7 weeks after the last hyperthermia session, as compared to the status in the third week of treatment.

The invasive tumor temperatures measured during the 1 h steady-state period of treatment averaged over all six patients and all four sessions per patient were $T_{90} = 39.9^\circ\text{C}$, $T_{50} = 41.2^\circ\text{C}$, and $T_{10} = 42.3^\circ\text{C}$ (Fig. 9).

An example of typical temperature profiles during treatment shows that the skin temperature is fairly uniform at $\sim 42.5^\circ\text{C}$, and fairly high and uniform invasive tumor temperatures between 41.5 and 42°C are achieved at maximum depth in the central target zone (Fig. 10).

Hyperthermia of semi-deep-seated tumors in the thorax

Figure 11 shows a CT with the tumor site and temperature probe for one of our first patients with a supraclavicular tumor in the upper thorax, along with an image of the placement of the 70

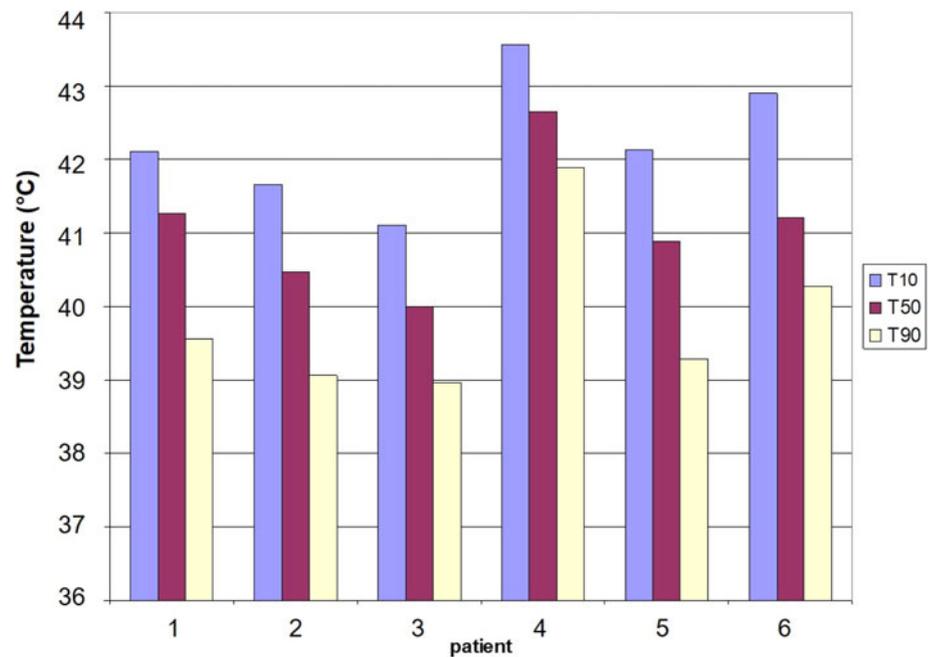


Fig. 9. System 1B: average tumor temperatures T10, T50, and T90 for six breast cancer patients.

MHz waveguide at the ventral side. The dorsal waveguide embedded in the table top is not visible. Both waveguides had an aperture size of 21×34 cm. The treatment series started with two sessions using only the ventral waveguide, followed by two sessions during which both waveguides were used. Output power was set at 100 and 250 W for the ventral and dorsal waveguides, respectively, this was based on patient tolerance for output power for each waveguide. The temperature in the water bolus was $\sim 30^\circ\text{C}$ for both waveguides to cool the skin moderately, and the resulting median tumor temperature T_{50} was $\sim 39^\circ\text{C}$ in the first sessions using one waveguide, increasing to $\sim 44^\circ\text{C}$ in the later sessions using both waveguides. Even the lower tumor temperature T_{90} exceeded 41°C in the last two sessions, indicating the entire tumor had reached therapeutic temperature levels (Fig. 12).

We presently treat 20–25 patients per year with this device. Patient tolerance varies, sometimes pain complaints occur due to unwanted hot spots close to bony structures. These are normally resolved by rotating the two waveguides to another angle to avoid the dominant E_z field component to point straight into bony structures, or by altering the power balance between dorsal and ventral waveguides to alleviate the pain complaint. More eccentric locations can pose issues with excessive water accumulation in the section of the water bag of the ventral waveguide extending outside the body. This can usually be resolved by modifying the shape of the water bag.

Conclusion

Clinical experience with heating of deep-seated pelvic tumors using phased array systems of RF antennas is based on large patient series around the globe starting already in the 1980s. We have demonstrated in this paper that the basic principles of this technology can be used to treat also more challenging deep-seated and semi-deep-seated tumor locations elsewhere in the body, presenting three dedicated systems for the intact breast, the upper thorax, and the limbs. We should also mention the development of dedicated phased array systems by other research

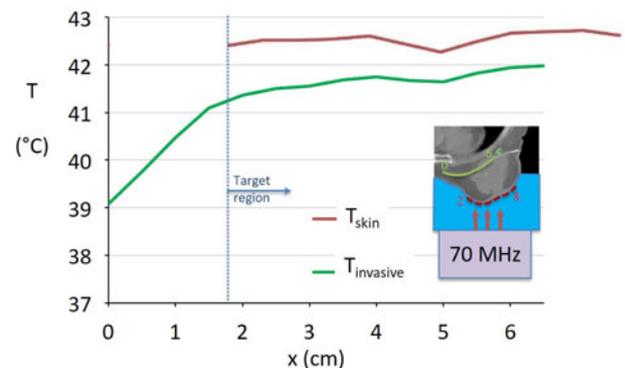


Fig. 10. System 1B: temperature profile measured with the skin probe (T_{skin}) and the lateral invasive probe ($T_{invasive}$) during treatment of the patient shown in Fig. 6. The inset shows location of tumor target and probes in the CT image of Fig. 6, including x -values for start and end of probe.

groups, using 140 MHz antennas for breast lesions [39], and 434 MHz antennas for head and neck tumors [40, 41]. The relatively low frequency of 70 MHz we have been using has as potential disadvantage that the focal volume is relatively large, but also a major advantage that the penetration depth is better than at higher frequencies. This resulted in adequate therapeutic temperatures in most of our patients, a good achievement in view of the fact that all presented systems used just one or two waveguides to achieve heating at depth. Another favorable feature is the stable phase control, which can also be partly be attributed to the use of robust waveguide technology. Arrays of other types of antennas can display crosstalk between antennas, this form of mutual interaction can cause unwanted and large phase shifts which can result in suboptimal focalization of the tumor target region [42, 43].

The tumor temperatures we achieved are in fact in a similar therapeutic range as the temperatures achieved in pelvic tumors using phased array systems with larger numbers of antennas.

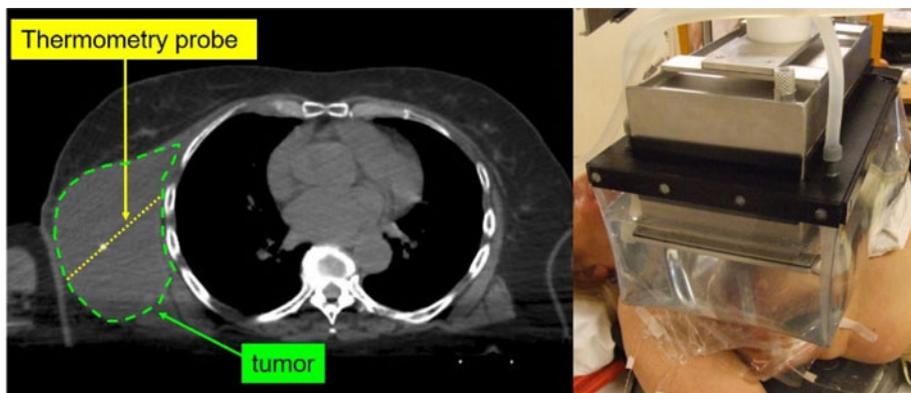


Fig. 11. System 1C: location of the temperature probe and position of the ventral waveguide for a patient with a supraclavicular tumor in the upper thorax.

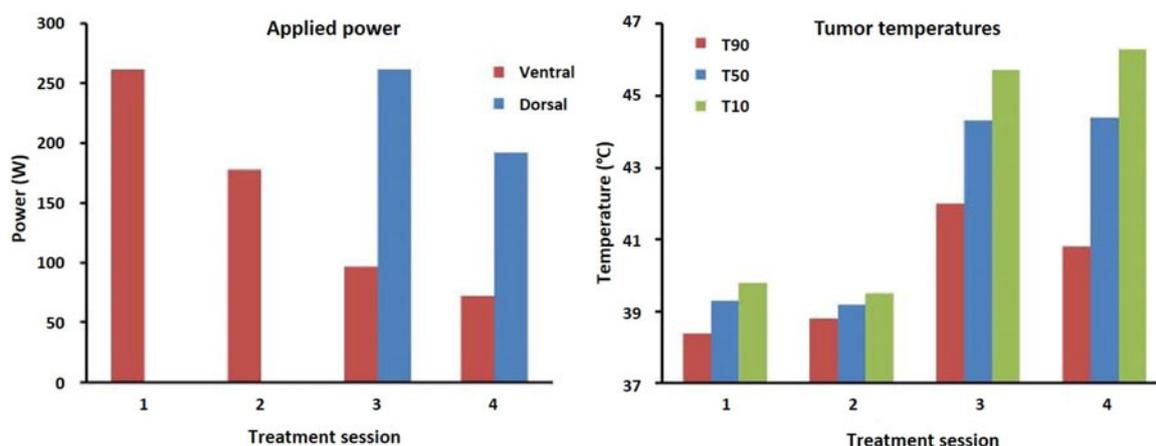


Fig. 12. System 1C: applied power and tumor temperature during treatment of the deep-seated supraclavicular tumor shown in Fig. 8. Sessions 1 + 2: ventral waveguide is used, sessions 3 + 4: both ventral and dorsal waveguides are used.

This is very important in view of the strong dose–effect relationship found for many tumors, e.g. as found in a recent review for recurrent breast cancer treated mainly with 434 MHz applicators [8] and for cervical tumors treated with phased array systems of RF antennas in Rotterdam [6, 7] and in Amsterdam [36].

The next step is to promote more wide clinical use of these solutions for challenging locations. This will require convincing manufacturers to include these solutions as an add-on with their phased array systems for deep-seated pelvic tumors.

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