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ORIGINAL ARTICLE

Temperature measurements in a capacitive system of deep loco-regional hyperthermia

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ABSTRACT

Hyperthermia has been shown to be a medically useful procedure applicable for different indications. For the connection between clinical effects and heat, it is important to understand the actual temperatures achieved in the tissue. There are limited temperature data available when using capacitive hyperthermia devices even though this is worldwide the most widespread method for loco-regional heating. Hence, this study examines temperature measurements using capacitive heating. Bioequivalent phantoms were used for the measurements, which, however, do not consider perfusion in live tissue. In general, the required temperature impact for an effective cancer therapy should need an increase of 0.2°C/min, which has been achieved. In the described tests on the non-perfused dummy, on average, the temperature increases by approximately 2°C in the first 12 min. The temperature difference relative to the starting temperature was 10–12°C within a therapy time of 60 min (rising from the initial room temperature between 20–24°C and 32–34°C). The average deviation with three individual measurements each on different days in a specified localization was 2°C. The minimum temperature difference was 4.2°C, and the maximum value was reached in the liver with 10.5°C. These values were achieved with a moderate energy input of 60–150 watts, with much higher performance outputs still available.

These results show that the tested capacitive device is capable of achieving quick temperature increase with a sufficient impact into the depth of a body.

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KEYWORDS
Hyperthermia; deep hyperthermia; temperature measurement; capacitive system; specific absorption rate (SAR)

Introduction

The effect of heat on the human body has been used for thousands of years in the medical field. Specifically in oncology, new thermo-biological research has shown heat to be a strong sensitizer for radiotherapy (RT) and chemotherapy (CT) that can have measurable advantages for the patient (Seegenschmiedt et al., 1995). The effects of hyperthermia on biological structures are in itself pleiotropic and complex. The effectiveness of achieving a desired temperature impact depends on many factors such as the technology used, the applied structure of power output, heating-up time, and other factors, including shape, type and size of the tissue, circulation and the homogeneity of temperature distribution, and range from the denaturation of cellular and sub-cellular elements to influencing the entire tumor tissue and the tumor's surroundings. Numerous studies about the use of hyperthermia combined with radiation therapy and/or chemotherapy have been partially able to confirm the effects of significantly contributing to tumor regression. Horsmann and Overgaard's (2007) reviews reach the conclusion that hyperthermia could be one of the most effective procedures in support of radiation/chemotherapy. Randomized phase III trials support this effect (van der Zee et al., 2000; Vernon et al., 1996; Issels et al., 2010). Therefore, in 2007, the National Comprehensive Cancer Network (NCCN) has included the combination treatment of radiotherapy (RT) and hyperthermia (HT) in its guidelines for breast cancer recurrence for the first time.

Even though the mechanisms *in vivo* have not been conclusively understood yet, experts agree that the temperature required to treat tumors must be between 39°C (Reparsky et al., 2013) and 42–44°C (Jones et al., 2005) in the tissue. For quality control, this temperature range should be achievable for each patient. Since invasive temperature measurements are difficult to perform, most loco-regional hyperthermia treatments worldwide are applied without measuring temperatures. Predominantly, only recommendations of power impacts are made available

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that users have to rely on. This study investigates the ability of one commercially available capacitative device to achieve temperatures in depth in various models.

Materials and methods

We used a commercially available device for the temperature measurement based on the capacitive heating technology (Figures 1 and 2).

Temperature probes

Company: TempSens Canada, fiber optic four-channel sensor measurement.

Sensors compatible to MRI/EMI/RFI & microwaves, CT scanning and X-ray, PVC coated (see images below); Accuracy: ±0.3°C; Diameter: 1) 0.9 mm, 2) 1.8 mm

Length of the active measuring probe: 20 mm

Description of the therapy device: Operation of the system

In capacitive-coupled hyperthermia, two plates are placed on the patient's affected body part. Placed directly below the electrodes are water bags with de-ionized water exchange for better adaptation to the body's surface. The polarities in these plates are now reversed at a high rate of speed (13.56 million per second (Figures 3 and 4). The tissue below represents the dielectric and is heated based on the adaptive orientation of the ions in the cells and in the inter-cellular space (Figure 5). Significant temperature gradients can be achieved depending on the location and output. Based on this technology and the underlying base frequency, it is also possible to reach deeper areas in the body tissue and virtually heat from inside out. Polyurethane-covered water bags are located below the electrodes for improved adaptation to the body's unevenness. The contained deionized water is cooled via a cooling circuit. Cooling the thermo receptors on the skin surface and subcutan fat areas contributes to preventing the patient from experiencing pain caused by the heat, allowing for increased heat inputs. The carrier frequency is 13.56 MHz with a performance of up to 600 watts. Different electrode sizes below and on top guarantee a selective local impact. Changes in temperature were continuously documented manually as well as with the temperature measurement unit connected to the therapy device. The room temperature was steady at 22–24°C.

Description of materials for temperature measurement: Temperature measurement in muscle-equivalent agar phantom

The phantom consisted of 4% agar–agar (a polysaccharide derived from algae) in a physiological saline solution (0.9% NaCl). The resulting jelly can be used as a phantom, equivalent to muscle tissue for temperature measurements (Figure 6). It must be noted that fat tissue or tissue of internal organs, for example, the liver, reacts more sensitively to energy inputs and temperature increases in comparison with the muscle tissue. The agar phantom is also recommended for research purposes in the ESHO guidelines (Lagendijk et al., 1998). This phantom technology also allows generation of infrared heat images.

Temperature measurements in bioequivalent radiation dummy

For their simulation purposes, radiation therapy uses radiobiological phantoms (tissue equivalent) that attempt to replicate the tissue structure of humans. A dummy (Figure 7) was used for a hyperthermia

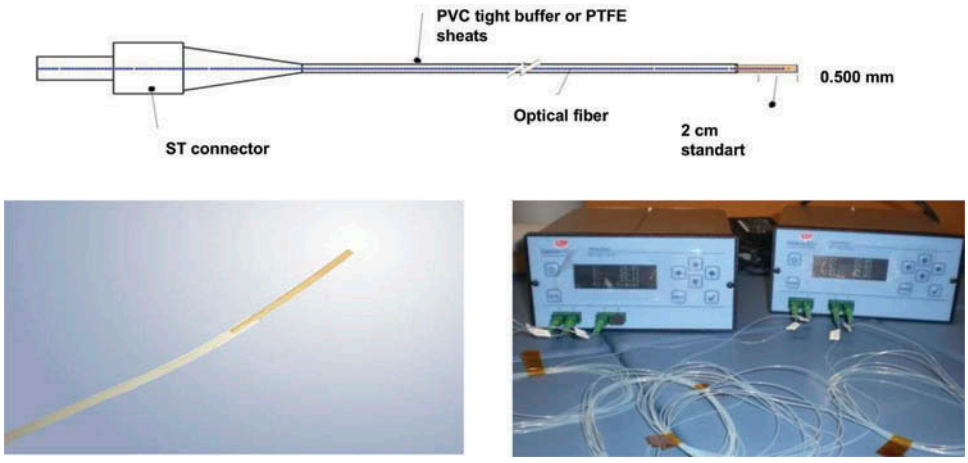

Figure 1. Temperature sensors, dimensions and data.

Figure 2. The Celsius+TCS made by Celsius 42 GmbH in Germany.

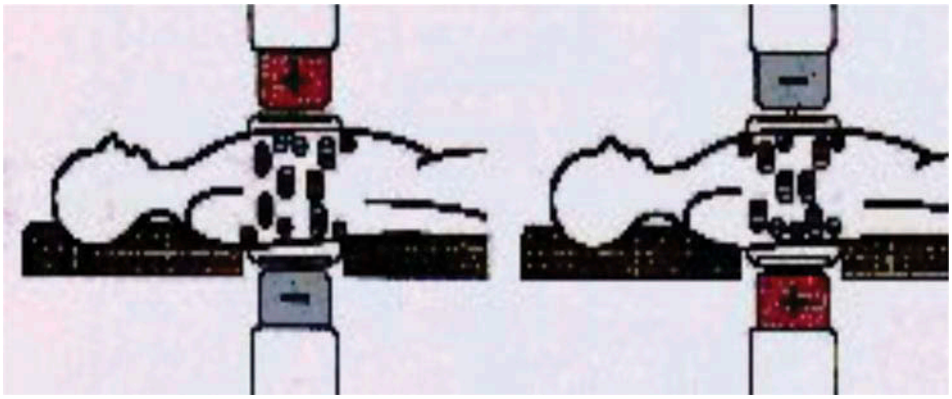

Figure 3. Capacitive coupling, mode of operation, and mechanism of action.

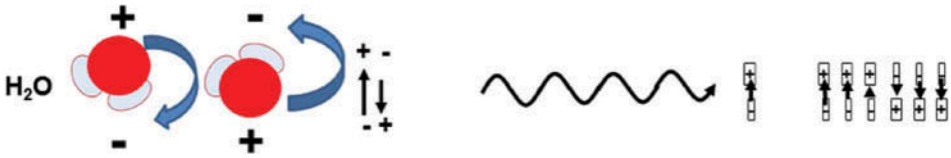

Figure 4. Due to bipolar structure of water molecules, ions in the cells and in inter-cellular space are heated up.

treatment in the area of the lungs and the pancreas. The objective of the trials was to find the proper power input need to achieve a temperature increase of 0.2°C/min and 10–12°C in 1 h.

We used an Alderson radiation therapy phantom (ART) for the measurements, Radiology Support Devices lnc., Long Beach, CA, USA (www.rsdphantoms.com).

The male ART is 175 cm tall and weighs 73.5 kg. The ART phantom is divided into 2.5-cm-thick slices. Each slice is perforated. The body areas conform to the biological tissue, that is, soft tissue-equivalent or lung tissue-equivalent or bone-equivalent, which can be replaced via TLD holder pins.

Measurements were performed 3 times, and the indicated numbers represent the temperature in °C.

Heat generation

A second characteristic for quality assurance in a temperature dose is found in the technical implementation of its application. The following applies for a passive loco-regional hyperthermia with deep impact in the body:

- It is passive because it is generated by a device.
- It is loco-regional because a more or less large target area is defined (e.g., right lobe of the lung, or liver).

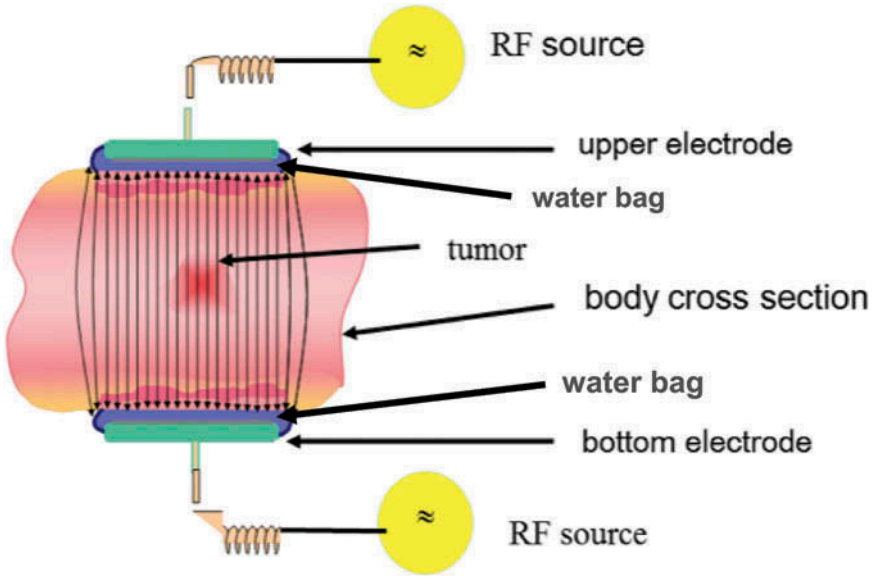

Figure 5. Schema of capacitive heating technology (two identical electrodes, polyurethane-covered water bags).

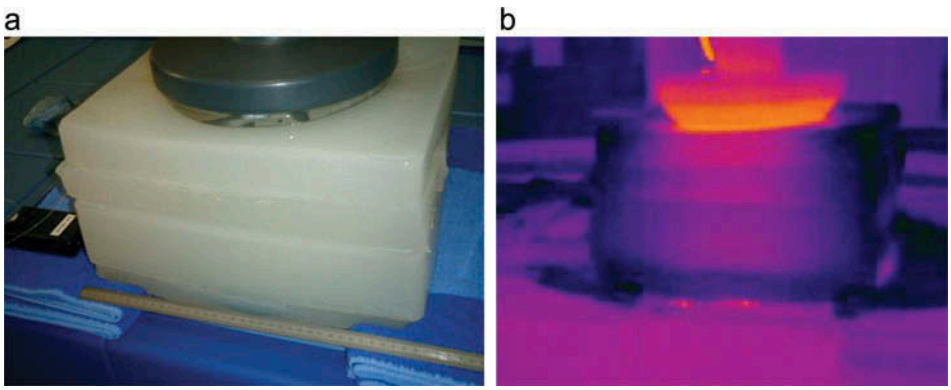

Figure 6. Agar–agar phantom as muscle-equivalent temperature model.

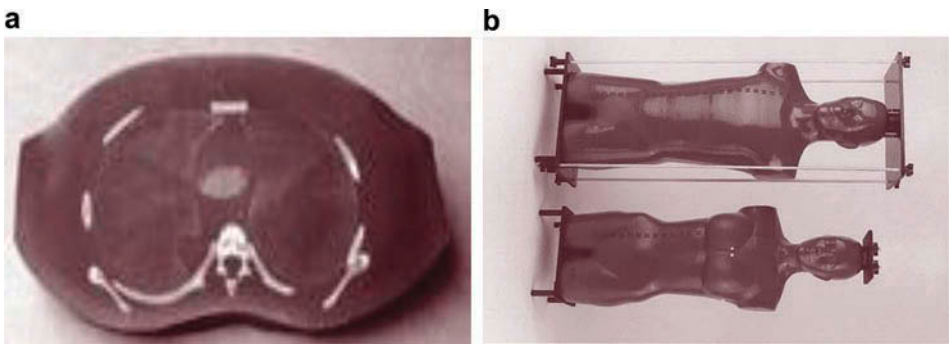

Figure 7. Alderson radiation therapy phantom (ART): The male ART is 175 cm tall and weighs 73.5 kg.

- The depth effect stands in contrast to mere surface hyperthermia of the skin and subcutaneous tissue.

Basically, there are three different noninvasive procedures on the market: Introducing the energy via radiating antennas as well as capacitive coupling. Depth-penetration into water-dominated tissue is not achievable with frequencies >150 MHz. Hence, commercially available devices with higher frequencies are generally designed for surface hyperthermia.

At present, there are three techniques or principles available to introduce external (passive) deep hyperthermia:

- Energy transmission via electrical field (capacitive coupling)
- Energy transmission via magnetic field (inductive coupling)
- Energy transmission via electromagnetic radiation (antenna system)

Capacitive procedures

Capacitive procedures use the patient's body as dielectricum between two electrodes that are fed with quickly alternating polarities. The following configurations influence heat generation, which results in substantial difference between various types of devices:

- The size of the electrodes (individually and in relation to each other)
- The underlying carrier frequency (offered devices feature 8 MHz, 13.56 MHz, or 27 MHz)
- Input power (devices with 150, 600, 800 watt up to 1600 watts)
- Structural conditions (number of active therapy electrodes: 1–2 electrode pairs)

Even in earlier trials with capacitively coupled energy transmission, especially with devices made in Japan, it was shown that this device technology is basically capable of achieving sufficient temperatures at depth. There, certain criteria were discussed, performance characteristics were determined (Kato et al., 2008; Song et al., 1986; Kotsuka, 1990; Fujita et al., 1993), and temperature measurements were performed (Paliwal et al., 1982).

In an energy transmission via an electrical field (capacitive coupling), electrodes function as capacitors. This means the patient's body basically becomes an "insulating material" in the capacitor. The effect of quickly rotating fields on the bipolar structure of water molecules creates heat in the body.

If, as suggested by Nordenström (1983), the conductivity and the dielectricity in tumor tissue are significantly higher and the electrical resistance lower compared with healthy tissue, then this results in an additional focusing effect on the tumor tissue. However, this is not uniformly supported by all data (Gabriel et al., 1996). The carrier frequency of the capacitive coupling should be low (8–27 MHz) to be able to penetrate into the depth of a body. The higher the applied energy, the higher is the basic energy impact into the tissue.

Inductive coupling

In inductive coupling, a high frequency field is generated via a magnetic coil and applied around the patient's entire body. In general, ferromagnetical nanoparticles or seeds are inserted into the tumor to draw the absorption of the energy in the target tissue. In this respect, this is actually not a noninvasive method in the traditional sense. This method is still in an experimental phase due to concerns over location constancy of the inserted nanoparticles and the long-term effects, but it has reached a certain status for treating brain tumors (Maier-Hauff et al., 2010).

Antennas

For transferring energy via electromagnetic radiation (antenna system), a ring of antennas is arranged around the body. The target area is focused on by adjusting the intensity, phase, and frequency of the transmitted waves. This mostly uses higher frequencies (80–160 MHz). The energy can be adjusted individually with regard to focus and depth by a different steering of the various antennas. Controlled clinical studies have shown the effectiveness of antenna arrays (Canters et al., 2009). Problems can be caused by so-called undesirable hot-spots of reflections and overlaps as well as time and personnel expenses for a session.

Temperature dose

According to the recommendations of the Interdisciplinary Working Group on Hyperthermia (Interdiszi-plinäre Arbeitsgemeinschaft für Hyperthermie (IAH), now Atzelsberger Kreis, under the umbrella of the German Cancer Society, the European Society of Hyperthermic Oncology (ESHO), as well as the German Society for Hyperthermia (Deutsche Gesellschaft für Hyperthermie e.V. (DGHT), new standards are developed constantly, which must be complied with to gain comparable therapy results (Lagendijk et al., 1998; Bruggmoser, 2012). Latest comments on guidelines that standardizes the rules for regional deep hyperthermia were released in 2012 (Bruggmoser et al., 2012) and 2013 (Hirokazu et al., 2013).

One of the requirements of IAH and ESHO is that the SAR (specific absorption rate) should be as follows (Lagendijk et al., 1998):

∞ Increase of 0.2 °C/min, that is, 1°C in 5 min (without perfusion). This means in a non-perfused

dummy, as it is used in radiation therapy for therapy planning, the temperature should increase by 2°C in the first 10 min, and the total temperature increase in 60 min should be 10–12°C. This is a reference value.

Results

Temperature measurement in muscle-equivalent agar phantoms

The first experimental measurement with a reduced power output of only 150 Watts (considering the device's capacity of up to 600 watts) shows an average temperature gradient of 6.6°C and a peak temperature rise of 14.5°C in the top one-third of the 16 cm agar phantom (Figure 8a and 8b). The Celsius+ TCS device allows for different sizes of the electrodes on top and bottom, enabling to focus the temperature effect in the dielectric space in between. Using varying electrode sizes allow for a relatively stronger temperature gradient to be achieved toward the part of the electrode with the smaller surface.

A test was performed with an agar phantom dimensioned 18 × 35 × 30 cm to examine this effect (Figure 9). The temperature sensors were inserted in different places in the model. As shown in earlier trials, there is no significant temperature effect directly below the electrodes due to the cooling water bolus. The assumed region of interest in this setting was to be located in the center of the lower third of the model. Therefore, a smaller electrode was selected for the bottom side (150 mm) versus the top side (250 mm). A selective introduction of heat into this region was expected, even though exact focusing is not possible due to technical limitations. In the first phase of the trial, 150 watts were applied over the course of 25 min, which was then increased to 300 watts for 25 min in the second phase of the trial.

When examining SAR (specific absorption rate), sensor no. 8, which is assumed to be in the target area, shows in this first phase an identical increase compared to the reference line of 0.2°C/min, as mentioned above. The combination of all sensors, on the other hand, shows a lower SAR then the reference line (see Figure 10 and Table 1). Note that SAR is actually measured in W/kg; however, we use its consecutive effect measured in °C/min as this is the clinically

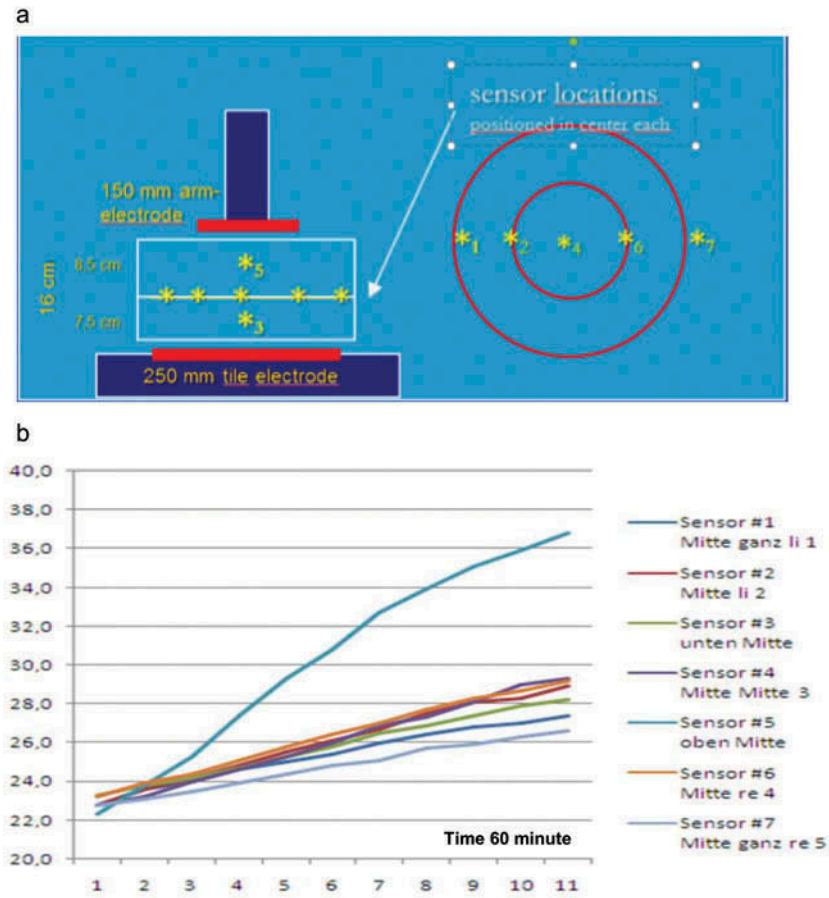

Figure 8. Location of sensors in the agar phantom and according temperature measurements (Time 60 min).

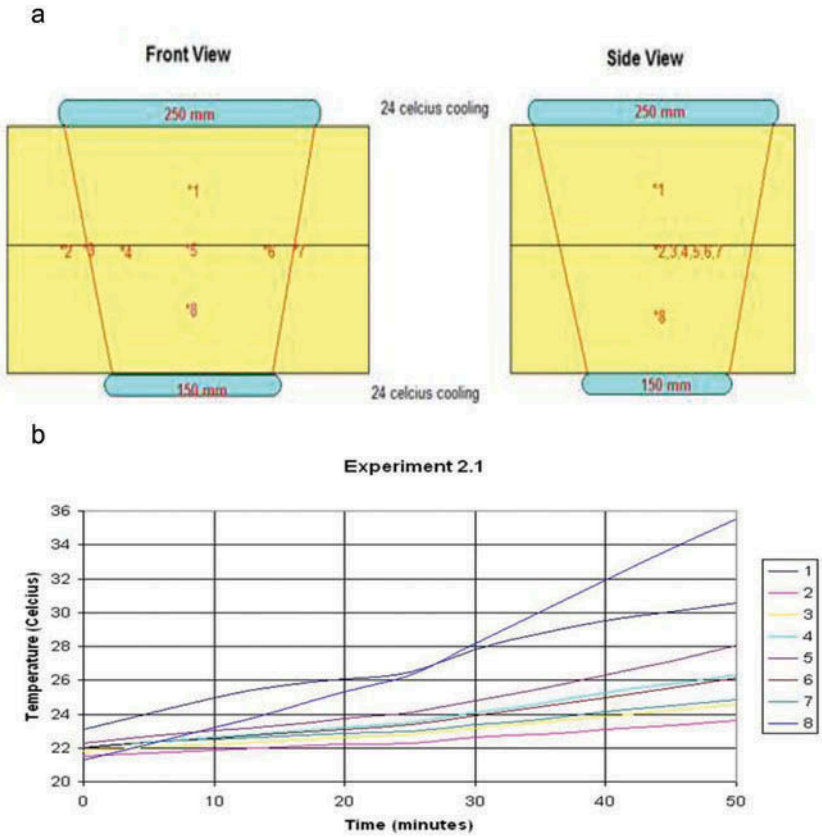

Figure 9. Location of sensors in the agar phantom and according temperature measurements.

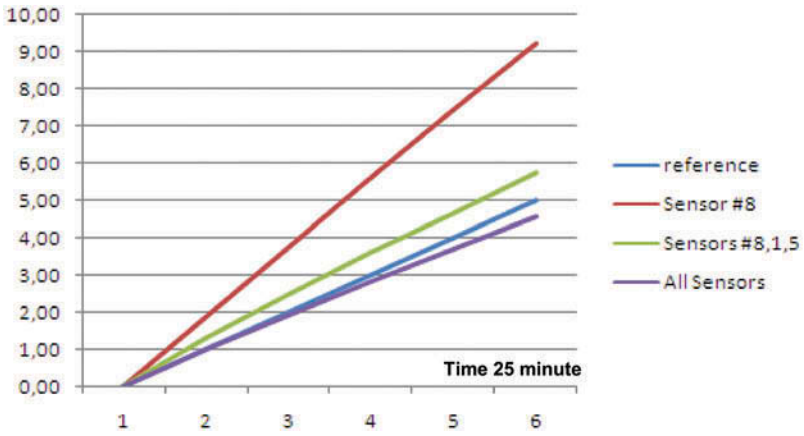

Figure 10. SAR rate for first 25 min at 150 Watt power application.

relevant dimension. In the second phase with an output of 300 watts, however, sensor eight shows a much higher SAR than the reference line. The SAR of the central region below the electrodes was also slightly higher in comparison with the reference (Figure 11 and Table 2). These results prove that the Celsius +TCS device achieves a better heat input in the assumed target region compared to the specified increase of 0.2°C/min.

Temperature measurements in bioequivalent radiation dummy

For the first trial, the temperature sensors were placed in the area that corresponds to the human pancreatic head. This position provides for the largest possible distance between the sensors and the electrodes. This trial was performed for 60 min with 180 watts with two 250 mm electrodes on top and bottom and with a

Table 1. SAR rate for first 25 min at 150 Watt power application.

At 150 W	Rise of 0.2°C/min			
time	reference	Sensor #8	Sensor #8, 1, 5	All sensors
0	0.00	0.00	0.00	0.00
5	1.00	0.96	0.75	0.59
10	2.00	1.94	1.51	1.16
15	3.00	2.95	2.18	1.67
20	4.00	4.03	2.81	2.16
25	5.00	5.04	3.40	2.62

capacitive coupling therapy device. This corresponds to an energy input that is well tolerated by patients according to clinical experience.

The average temperature increase was 0.83°C or 1.2° C per 5 min, a cumulated 10°C or 12°C, respectively. The values of the sensors are, therefore, in line with the reference, that is, the SAR matches the reference line. The deep region in the center of the body or dummy therefore exhibits a SAR that is equivalent to a temperature increase of almost 1°C/min with regard to the first 5 min.

Heat propagation and environmental influences were still minor in the first trial phase over 12 min. The average temperature increase for this phase was approx. 0.17°C/min and cumulated approximately 2°C in the first 12 min. This means that the sensors are matching the reference line.

In the second trial series of treatments of the lung, liver, and pelvic region, the therapy was simulated and documented repeatedly over three separate days. The duration of therapy was 60 min, and power input was 60–150 watts, with a cumulated energy input of 340 kJoule. Two 250 mm electrodes were used, and four sensors were placed with the same distance to the measured body part (lung, liver, and pelvis). The results were almost identical (see Figure 12a–Figure 12c). The room temperature was between 20°C and 24°C.

Figure 12 shows that a temperature gradient of 4.3–6.0°C was achieved. The power inputs ranging from 60 to 150 watts are very conservative and can be increased for many patients without reaching the heat-tolerance limit.

Discussion

Quality assurance in the form of validation of the achieved temperature is the major issue with this methodology. One of the questions for temperature measurements is whether a point, surface, or volume measurement should be conducted. The latter would certainly be desirable, but the effort to do so is immense (see below). Second, the physiological particularities are different from patient to patient, and there are even intra-individual differences in patients at different times of treatment.

Physiologically, perfusion is highly irregular, especially in tumor tissue (Vaupel, 2008). Thermal development is highly dependent on the location and size of blood vessels in the region of interest (ROI) as well as the intensity of blood perfusion, which is acting as a cooling circuit. This effect was observed multiple times (van der Zee et al., 1999).

Finally, there is a fundamental problem in defining a heat dose. Is a high temperature for a short period equivalent to a low temperature for a longer period of time? How does this relate to the body temperature and room temperature and what limit values should be used? It is generally accepted that a treatment of 60 min at 41°C is supposedly equivalent to a treatment of 30 min at 42°C (Gabriel et al., 1996; Paliwal et al., 1982; Stogryn, 1971; ESHO Taskgroup Committee, 1992).

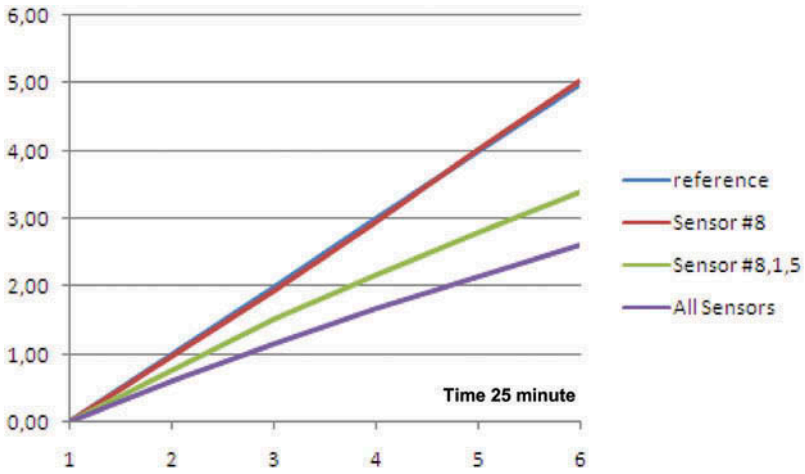

Figure 11. SAR rate for subsequent 25 min at 300 Watt power application.

Table 2. SAR rate for subsequent 25 min at 300 Watt power application.

At 300 W	Rise of 0.2°C/min			
time	reference	Sensor #8	Sensor #8, 1, 5	All sensors
0	0.00	0.00	0.00	0.00
5	1.00	1.86	1.29	1.00
10	2.00	3.73	2.46	1.92
15	3.00	5.60	3.59	2.83
20	4.00	7.44	4.66	3.69
25	5.00	9.23	5.74	4.57

Besides, different technical methods have been described for temperature measurement.

Infrared images of the skin surface can be taken and compared before and after a local hyperthermia. They do not work well for quality assurance in deep tissue because they only show the temperature on the surface.

Ultrasound, Moros (2012) illustrates the basic feasibility of temperature-equivalent measurements using ultrasound. This is not, however, suitable for everyday use.

Spectroscopy, with light from the near-infrared range, sounds promising at first and would also be capable of measuring in deep tissue at a reasonable cost. However, this technique is not yet feasible for everyday use because of insufficient differentiation between temperature and pressure differences.

Invasive measurement with fiber optic sensors has two disadvantages: It is invasive for deep regions of interest (ROI), and it is only a point measurement. It is cheap, however, and, once calibrated, there is little room for interpretation when analyzing the measured temperatures. Different temperatures can also be measured in a guide tube when the sensor is moved along the path.

Magnetic resonance tomography (MRT), even though an indirect method, is basically suited for temperature representation (Rieke and Butts, 2008) The possibility of having a 3D representation is a plus, but it is limited by its high financial costs to dedicate an MRT to this task. The devices (MRT and hyperthermia device) would have to be calibrated to each others to be able to measure temperatures during a treatment. This results in an MRT device that can now be used for these temperature identifications only.

These are the Invasive measurement with fiber optic sensors used for the trials conducted in this study. Temperature measurements in both phantoms showed a promising temperature increase in the specified time frame.

The temperature of the human body fluctuates between 35.8°C and 36.9°C under normal conditions. Older patients tend to have a lower temperature compared with younger patients.

If the therapeutic objective is to achieve a temperature of 40–41.5°C in the tissue, then this would require an increase of 4.6–6.1°C.

When examining the values achieved in the phantom, we have determined that these values are very much attainable with a well-tolerated power input (up to 150 watt max. in this case). Similar results achieved with capacitive devices are found in the literature (Paliwal et al., 1982; Lagendijk et al., 1998). One disadvantage of

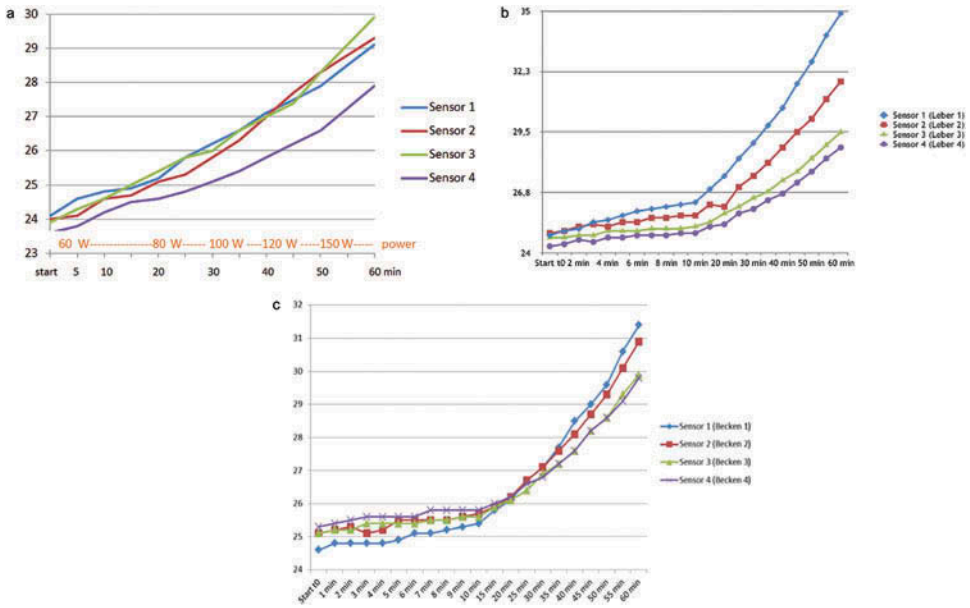

Figure 12. (a) Temperatures on the four sensors placed in the lung area (bifurcation) of phantom; (b) Temperatures on the four sensors placed in the liver area of phantom; (c) Temperatures on the four sensors placed in the pelvic area of phantom.

these measurements is the absence of perfusion in the tissue when transferring this data to a living human being. The significance of perfusion was shown in experiments by several authors and in *in vivo* measurements (van der Zee et al., 2000; Stogryn, 1971). Some authors refer to a local cooling effect of 1.5°C (Osinky et al., 2011). This needs to be considered in the therapeutic setting.

A comparison of temperature distribution in the phantom between capacitive and other techniques does not show relevant differences. Some authors showed testing and implementation in their work (Kato et al., 2008; Canters et al., 2009; Lagendijk et al., 1998; Bruggmoser et al., 2012; Paliwal et al., 1982) as well as the results of their work with regard to quality control and planning-safety for loco-regional deep hyperthermia. The results of these works seem rather comparable to our results, and they appear plausible.

This study illustrated trials on the agar block as well as the radiation dummy in the areas of the lung, the liver/pancreas, and the pelvic region. All measurements have indicated that the temperature also increases deep inside the phantoms. In general, a temperature increase of 0.2°C/min or 10–12°C in 60 min is required for an effective therapeutic cancer treatment. In the described trials on the unperfused dummy, the temperature gradient with regard to the starting temperature was 10–12°C. This study has, therefore, shown that the tested a capacitive device was capable of achieving the required temperature, even in deep tissue.

Further measurements on the skull, neck region, abdomen, as well as the pelvic and femoral regions, which have not been elaborated here, indicate comparable and repeatable results. Tests on animals with invasive measurements on liver, lung, nose/throat area, and esophagus were already conducted. These results will be published together with the first series of measurements in patients after a further phase of the trial is completed.

Conclusion

As mentioned before, a variety of different studies have proven that capacitive hyperthermia can be a positive addition to cancer therapy. There seem to be no or only minor problematic side effects. One question with regard to quality assurance is the aspect of the achieved temperature during treatment. Regular temperature controls at a reasonable cost (without MRI) are currently possible with invasive point measurements only (sensor on the tip of fiber optic lines). However, a regular invasive temperature measurement is ethically not acceptable. The creation and validation of protocols that are capable of achieving certain temperatures with a high probability could replace such measurements.

The TCS device made by Celsius42+ was used in the context of these trials. It has an overall performance of 600 watts, features two opposing applicators (therapy electrodes) and uses a carrier frequency of 13.25 MHz capable of penetrating deeper layers of a water dominated human body. By using two actively adjustable electrodes (in size, performance, and cooling) for individual target areas, it is possible to effectively reach deeper tissue areas for heating.

The temperature reached in specific individual cases significantly depends on blood perfusion, which acts like a cooling circuit. This cooling effect is not predictable, especially in tumor tissue, and it is intra-individually highly variable as well. Thus, measurements on phantoms are still useful because warming effects can be observed without having to account for irregularities in blood perfusion, respiratory cooling, etc. The results gained from the agar phantom as well as from the bioequivalent radiation dummy unequivocally prove that the tested device operating with capacitive-coupled technology and 13.56 MHz frequency is capable of achieving a temperature impact of 5°C or more deep in the body. Such a device is capable of reaching the so-called SAR (specific absorption rate) of 0.2°C/min (or 1°C/5 min) required by the hyperthermia societies.

In-house *in-vivo* measurements in patients with similar protocols also show temperature gradients of 5–6°C in individual measurements. It is rather evident that temperatures of 39–42°C can be reached with commonly tolerable performance protocols, and this is helpful in the planning and implementation of hyperthermia applications.

Declaration of interest

The authors do not have any declarations of interest.

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